SEATING LIST

Centennial Banquet of the

National Academy of Sciences

Presidential Ballroom

Statler Hilton Hotel, Washington, D. C.

October 23, 1963

ALPHABETICAL LIST

SEATING ARRANGEMENT

Head Table

Dr. L. V. Berkner
Dr. and Mrs. Detlev W. Bronk
Dr. Harrison Brown
Sir Howard Florey
Dr. Sven Hörstadius
Dr. and Mrs. G. B. Kistiakowsky
Dr. and Mrs. Henry Allen Moe
Dr. Nathan M. Pusey
Dr. and Mrs. Alfred N. Richards
Dr. and Mrs. Frederick Seitz
Dr. and Mrs. J. A. Stratton
Dr. and Mrs. Jerome B. Wiesner
Dr. Edwin B. Wilson

Table 1

Dr. and Mrs. C. B. Anfinsen
Dr. and Mrs. S. T. Coulter
Dr. David P. Cuthbertson
Dr. Karl Folkers
Dr. and Mrs. C. G. King
Mrs. Anton Leb
Dr. and Mrs. Oskar Wintersteiner

Table 2

Dr. and Mrs. H. B. Andervont
Dr. W. Mansfield Clark
Dr. Joseph S. Fruton
Dr. and Mrs. Hudson Hoagland
Dr. and Mrs. T. M. Sonneborn
Dr. and Mrs. Luther L. Terry

Table 3

Dr. and Mrs. Robert B. Brode
Dr. Joel H. Hildebrand
Dr. and Mrs. G. Evelyn Hutchinson
Dr. and Mrs. Roger Revelle
Dr. and Mrs. Ragnar Rollefson
Hon. James H. Wakelin, Jr.
Dr. John A. Wheeler

Table 4

Dr. and Mrs. Melvin Calvin
Dr. and Mrs. Leonard Carmichael
Hon. Emilio Q. Daddario
Mr. Robert B. Eddy
Dr. and Mrs. A. L. Lehninger
Dr. and Mrs. S. Dillon Ripley, II
Dr. William H. Taliaferro

Table 5

Dr. Carl W. Borgmann
Dr. L. A. DuBridge
Prof. Roger Heim
Dr. and Mrs. Edwin M. McMillan
Dr. John S. Millis
Dr. Robert S. Mulliken
Dr. and Mrs. J. R. Oppenheimer
Lord Todd
Academician V. I. Veksler

Table 6

Dr. and Mrs. C. H. Best
Dr. L. C. Dunn
Dr. and Mrs. Wallace O. Fenn
Dr. Leland J. Haworth
Dr. and Mrs. Kenneth B. Raper
Dr. and Mrs. E. L. Tatum
Dr. C. S. Wu

Table 7

Lord Adrian
Dr. Edoardo Amaldi
Dr. and Mrs. Robert H. Cole
Dr. J. C. Hunsaker
Dr. and Mrs. Alfred S. Romer
Dr. and Mrs. Merle A. Tuve
Dr. and Mrs. Paul Weiss

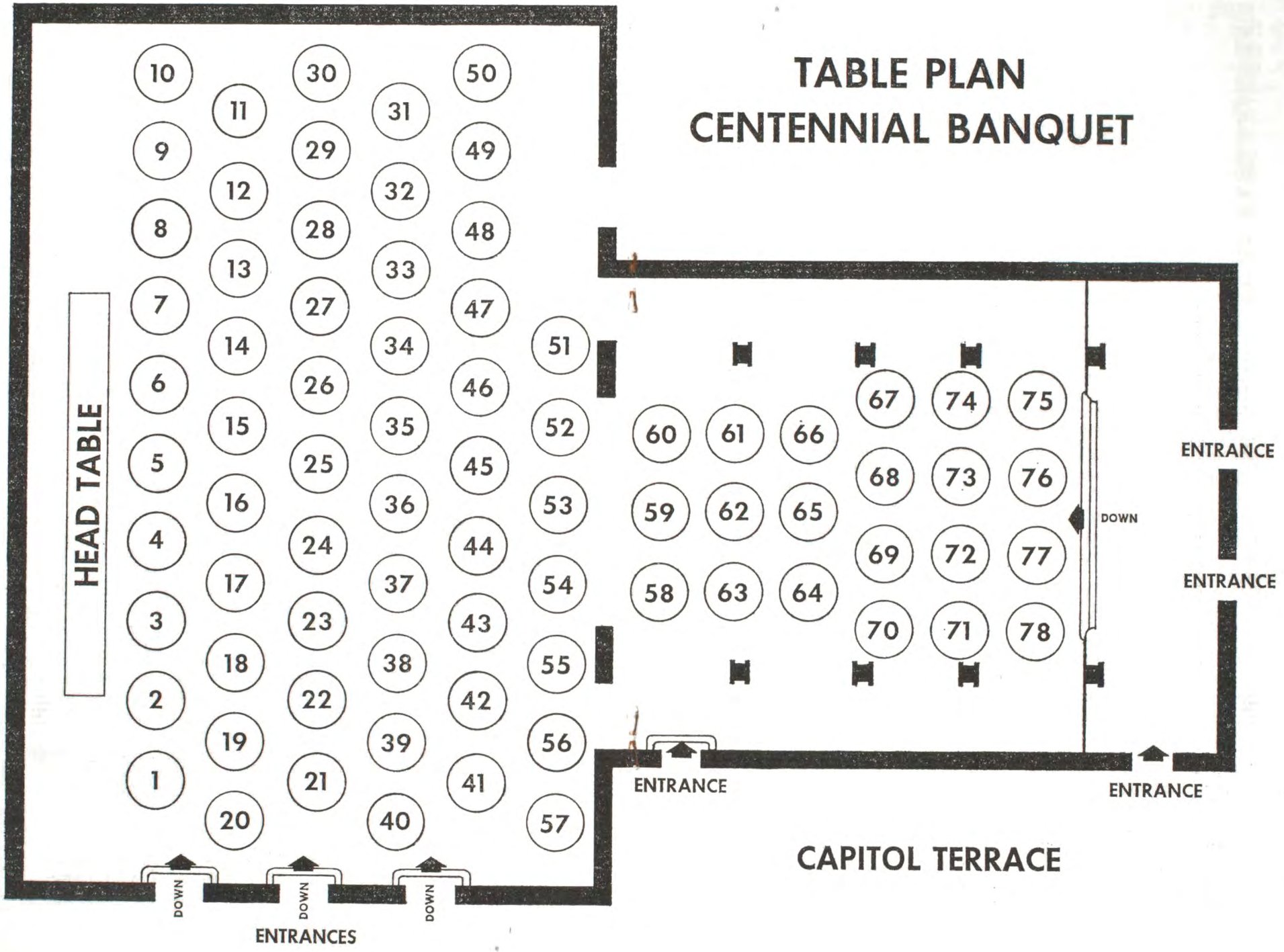
Table 8

Dr. and Mrs. David M. Bonner
Dr. T. M. Cherry
Dr. Augustus B. Kinzel
Miss Martinek
Dr. and Mrs. Albert C. Smith
Dr. and Mrs. Ernst Weber
Dr. and Mrs. John T. Wilson

Table 9

Dr. Justin M. Andrews
Dr. and Mrs. Rudolf L. Baer
Dr. and Mrs. W. B. Castle
Dr. and Mrs. G. Dalldorf

TABLE PLAN
CENTENNIAL BANQUET



Dr. Herbert M. Evans
Dr. and Mrs. Teru Hayashi
Dr. Berwyn F. Mattison

Table 10

Dr. Carl O. Dunbar
Dr. and Mrs. C. Lewis Gazin
Mr. and Mrs. William Laurence
Mr. and Mrs. Howard J. Lewis
Dr. and Mrs. P. F. Scholander
Dr. and Mrs. William Thurston

Table 10A

Dr. Raymond B. Allen
Miss Dorothy T. Allen
Dr. and Mrs. Christopher E. Barthel
Dr. Felix L. Haas
Dr. B. W. Hogan
Dr. and Mrs. Samuel Silver
Mr. Tun Thin
Dr. Clark D. West
Mrs. Josephine A. Williams

Table 11

Dr. and Mrs. S. S. Ballard
Dr. and Mrs. Raymond T. Birge
Dr. C. P. Boner
Dr. and Mrs. Walter H. Brattain
Dr. R. C. Gibbs
Dr. and Mrs. Elmer Hutchisson
Mrs. Charles W. Jones
Dr. Walter D. Lambert

Table 12

Dr. and Mrs. Paul J. Kramer
Dr. and Mrs. Feodor Lynen
Dr. and Mrs. Severo Ochoa
Dr. and Mrs. Edward Wenk
Dr. and Mrs. Harland G. Wood
Dr. J. Yanney-Wilson

Table 13

Dr. William A. Fowler
Hon. and Mrs. Najeeb E. Halaby
Dr. and Mrs. H. H. Hess
The Reverend Francis J. Heyden
Dr. and Mrs. John Katili
Dr. Jacinto Steinhardt
Dr. and Mrs. Fred L. Whipple

Table 14

Mrs. Mabel H. Bright
Dr. and Mrs. Frank Brink, Jr.
Dr. and Mrs. Ragnar Granit
Dr. and Mrs. H. Keffer Hartline
Dr. and Mrs. A. Baird Hastings
Dr. Leonard M. Rieser, Jr.
Mrs. Rose F. Schmidt

Table 15

Dr. and Mrs. Robert F. Bacher
Dr. and Mrs. H. E. Carter
Dr. and Mrs. Bentley Glass
Sir William and Lady Penney
Dr. and Mrs. Athos Silveira Ramos
Dr. Robert E. Wilson

Table 16

Dr. and Mrs. T. Dobzhansky
Dr. William Doering
Dr. and Mrs. Edward A. Doisy
Dr. Paul M. Gross
Dr. Gerard Pomerat
Dr. and Mrs. William J. Robbins
Dr. and Mrs. Alan T. Waterman

Table 17

Dr. Paul Doty
Dr. and Mrs. Donald F. Hornig
Academician V. A. Kirillin
Hon. and Mrs. John G. Palfrey
Dr. and Mrs. Theodore Shedlovsky
Dr. and Mrs. John Verhoogen
Academician A. P. Vinogradov

Table 18

Dr. Vernon Bryson
Dr. and Mrs. Carl F. Cori
Dr. and Mrs. Harry Eagle
Dr. L. L. Hammerich
Dr. Herman M. Kalckar
Mrs. A. Laursen
Dr. and Mrs. M. H. Trytten
Dr. George Wald

Table 19

Dr. Roger Adams
Dr. E. K. Bolton
Dr. Robert W. Cairns

Dr. Bryce Crawford, Jr.
Dr. W. O. Lundberg
Dr. and Mrs. John D. Roberts
Dr. and Mrs. F. H. Spedding
Dr. and Mrs. Edward Wichers

Table 20

Dr. and Mrs. C. G. Abbot
Dr. and Mrs. Allen V. Astin
Dr. Leona Baumgartner
Mr. and Mrs. G. D. Meid
Dr. and Mrs. Nathan Reingold
Dr. and Mrs. Alexander Wetmore

Table 21

Dr. and Mrs. Frank L. Horsfall
Dr. and Mrs. Robert J. Huebner
Dr. and Mrs. George E. Judd
Dr. and Mrs. John Kidd
Dr. and Mrs. Julius Sendroy, Jr.
Prof. Arne Tiselius

Table 22

Dr. Alan Cartter
Dr. Pradisth Cheosakul
Dr. and Mrs. Francois N. Frenkiel
Dr. Edwin C. Kemble
Dr. and Mrs. Donald H. Menzel
Dr. Marcos Moshinsky
Dr. Phya Salvidhan Nides
Dr. and Mrs. J. C. Warner

Table 23

Dr. and Mrs. Charles A. Anderson
Dr. Walter H. Bucher
Dr. and Mrs. Ernst Cloos
Dr. and Mrs. J. M. Harrison
Dr. Jorge Muñoz-Reyes
Dr. and Mrs. Thomas B. Nolan
Prof. C. Troll

Table 24

Dr. and Mrs. Joseph C. Aub
Dr. Erling Christophersen
Dr. and Mrs. Clyde A. Hutchison, Jr.
Dr. and Mrs. Linus Pauling
Dr. and Mrs. Emilio Segrè
Dr. and Mrs. Esmond E. Snell

Table 25

Dr. and Mrs. Thomas Henry Carroll, II
Dr. and Mrs. Farrington Daniels
Dr. and Mrs. C. A. Fleming
Dr. Viktor Hamburger
Dr. and Mrs. Ernst Mayr
Dr. and Mrs. Gregorio Y. Zara

Table 26

Academician Victor Ambartsumian
Dr. Dirk Brouwer
Dr. and Mrs. G. M. Clemence
Dr. and Mrs. Leo Goldberg
Dr. and Mrs. Jesse L. Greenstein
Dr. G. C. McVittie
Hon. and Mrs. Gerald F. Tape

Table 27

Dr. Preston Cloud
Dr. and Mrs. James Gilluly
Dr. and Mrs. Arthur Roe
Dr. and Mrs. J. F. Schairer
Dr. and Mrs. B. D. Van Evera
Dr. Wang Chi-wu
Dr. Wang Shi-chieh

Table 28

Dr. and Mrs. Karl K. Darrow
Dr. and Mrs. Raymond Fuoss
Dr. and Mrs. C. J. Gorter
Dr. and Mrs. W. V. Houston
Mrs. J. G. Kirkwood
Dr. Victor F. Weisskopf
Dr. Eugene P. Wigner

Table 29

Dr. and Mrs. Alfred Jay Bollet
Dr. Thomas P. Carney
Dr. and Mrs. Lester R. Dragstedt
Dr. and Mrs. C. de Duve
Dr. and Mrs. Walther F. Goebel
Dr. and Mrs. James P. Hollers

Table 30

Dr. and Mrs. Samuel K. Allison
Dr. V. Boekelheide
Dr. and Mrs. John C. Slater
Dr. and Mrs. Leo Szilard

Dr. and Mrs. George E. Uhlenbeck
Dr. and Mrs. V. K. Zworykin

Table 31

Dr. Philip H. Abelson
Dr. Carl D. Anderson
Prof. J. W. Duyff
Dr. and Mrs. Ralph W. Gerard
Dr. and Mrs. Samuel A. Goudsmit
Dr. and Mrs. Colin M. MacLeod
Dr. and Mrs. Clinton N. Woolsey

Table 32

Mr. and Mrs. Nathan Cohn
Dr. and Mrs. W. A. Heiskanen
Dr. Richard C. Jordan
Mr. and Mrs. Waldo E. Smith
Dr. and Mrs. Frederick T. Wall
Dr. and Mrs. Abel Wolman

Table 33

Dr. and Mrs. Harve J. Carlson
Dr. and Mrs. Britton Chance
Dr. and Mrs. A. Engstrom
Dr. Janusz Groszkowski
Dr. and Mrs. J. L. Oncley
Dr. and Mrs. Francis O. Schmitt

Table 34

Dr. and Mrs. A. Adrian Albert
Dr. Norman Hackerman
Dr. and Mrs. William D. McElroy
Dr. and Mrs. E. J. McShane
Dr. and Mrs. Wilson S. Stone
Dr. Oswald Tippo
Dr. Ahmed Riad Tourky

Table 35

Dr. George A. Jeffrey
Dr. and Mrs. Marston Morse
Dr. and Mrs. I. G. Murgulescu
Dr. and Mrs. K. S. Pitzer
Dr. and Mrs. Frederick D. Rossini
Dr. William G. Shepherd
Sir Geoffrey Taylor

Table 36

Dr. and Mrs. Herbert Friedman
Dr. and Mrs. Geoffrey Keller
Dr. Morris Neiburger
Dr. and Mrs. F. W. Reichelderfer
Dr. and Mrs. Harold C. Urey
Dr. and Mrs. Robert M. White

Table 37

Dr. and Mrs. Percival Bailey
Dr. and Mrs. R. Keith Cannan
Dr. and Mrs. E. H. Christopherson
Dr. and Mrs. Charles L. Dunham
Dr. Irving M. London
Dr. and Mrs. Cecil James Watson

Table 38

Dr. and Mrs. Leopold Brahdy
Dr. and Mrs. W. Z. Hassid
Dr. and Mrs. Nathan Jacobson
Mr. Markus Reiner
Dr. and Mrs. John W. Tukey
Dr. and Mrs. F. Joachim Weyl

Table 39

Dr. and Mrs. Glen Finch
Dr. and Mrs. Richard H. Holton
Dr. Heinrich Klüver
Dr. and Mrs. Neal E. Miller
Dr. and Mrs. Archie M. Palmer
Dr. and Mrs. Carl Pfaffmann

Table 40

Dr. and Mrs. David M. Dennison
Dr. William M. Fairbank
Dr. and Mrs. Crawford H. Greenewalt
Dr. and Mrs. Hoyt C. Hottel
Dr. and Mrs. Harry F. Olson
Dr. and Mrs. E. R. Piore

Table 41

Dr. and Mrs. J. W. Beams
Dr. and Mrs. Nicolaas Bloembergen
Dr. and Mrs. J. P. Den Hartog
R. Adm. H. Arnold Karo
Dr. Robert E. Marshak
Dr. A. R. Olpin
Dr. Jaroslav Pluhar
Dr. G. Temple

Table 42

Dr. and Mrs. John C. Ayers
Dr. R. Courant
Dr. and Mrs. Ross Gunn
Dr. Bernhard Haurwitz
Dr. and Mrs. Carl L. Hubbs
Dr. Wendell A. Mordy
Prof. Tatsuo Morito
Dr. J. L. Synge

Table 43

Dr. and Mrs. David Bodian
Dr. and Mrs. Alfred E. Emerson
Dr. and Mrs. Arthur W. Galston
Dr. and Mrs. Robert K. S. Lim
Dr. Maclyn McCarty
Dr. and Mrs. A. Poldervaart

Table 44

Dr. and Mrs. Henry G. Booker
Dr. Sydney Chapman
Dr. and Mrs. George V. Cohee
Dr. Joseph Kaplan
Dr. and Mrs. Hugh Odishaw
Dr. and Mrs. Louis B. Slichter
Dr. György Szigeti

Table 45

Dr. Ralph E. Cleland
Dr. and Mrs. Samuel L. Emsweller
Dr. and Mrs. Alexander Hollaender
Dr. and Mrs. A. E. Kehr
Dr. R. N. Robertson
Dr. and Mrs. Kenneth V. Thimann
Dr. Yi Pyeng-do

Table 46

Dr. and Mrs. Edwin H. Colbert
Dr. and Mrs. Caryl P. Haskins
Dr. Johannes Holtfreter
Dr. and Mrs. P. C. Mangelsdorf
Dr. and Mrs. Benjamin H. Willier
Dr. and Mrs. Sewall Wright

Table 47

Dr. Theodore H. Bullock
Dr. and Mrs. T. C. Byerly
Dr. and Mrs. J. Clyde Driggers
Dr. and Mrs. James D. Ebert
Dr. and Mrs. Colin S. Pittendrigh
Mr. and Mrs. Paul A. Scherer

Table 48

Dr. and Mrs. Harold J. Coolidge
Dr. Fred G. Evenden
Dr. and Mrs. A. Irving Hallowell
Dr. Emil W. Haury
Mr. and Mrs. Edward K. Kaprelian
Dr. and Mrs. T. S. Ronningen
Dr. Gordon R. Willey

Table 49

Dr. Manson Benedict
Dr. Walker Bleakney
Mr. and Mrs. Leon Chatelain, Jr.
Dr. Donald E. Marlowe
Dr. and Mrs. Stephen G. Petersen
Dr. and Mrs. W. H. Pickering
Dr. and Mrs. C. Richard Soderberg

Table 50

Dr. and Mrs. Charles Armstrong
Dr. and Mrs. Paul R. Cannon
Dr. and Mrs. Floyd S. Daft
Dr. and Mrs. James G. Horsfall
Dr. and Mrs. C. N. H. Long
Dr. Alden H. Miller

Table 50A

Dr. and Mrs. Bowen C. Dees
Dr. and Mrs. Paul Herget
Dr. Dwight J. Ingle
Mr. and Mrs. M. Bryce Leggett
Dr. and Mrs. Carl F. Sierk
Mr. and Mrs. R. G. W. Willcocks

Table 51

Dr. and Mrs. Wallace W. Atwood, Jr.
Dr. and Mrs. David R. Goddard
Mr. and Mrs. Walter M. Rudolph
Dr. and Mrs. Ralph H. Wetmore
Mr. George W. Wood
Dr. and Mrs. W. J. Zaumeyer

Table 52

Dr. and Mrs. Wallace R. Brode
Dr. and Mrs. John D. Ferry

Dr. and Mrs. H. S. Gutowsky
Dr. and Mrs. Paul W. McDaniel
Dr. Grga Novak
Dr. and Mrs. M. L. Wolfrom

Table 53

Dr. Karl H. Beyer, Jr.
Dr. and Mrs. Alfred Blalock
Dr. Ray G. Daggs
Dr. Alexander Forbes
Dr. and Mrs. Esmond R. Long
Dr. J. R. Porter
Dr. Jack Schultz
Dr. and Mrs. Harold L. Stewart

Table 54

Dr. and Mrs. R. H. Bing
Dr. Chern Shiing-shen
Dr. Merrill M. Flood
Dr. and Mrs. K. O. Friedrichs
Dr. and Mrs. Abe Gelbart
Dr. and Mrs. Einar Hille
Dr. Jerzy Neyman

Table 55

Dr. C. J. Alexopoulos
Dr. Daniel I. Arnon
Dr. and Mrs. Lawrence R. Blinks
Dr. and Mrs. A. G. Norman
Dr. and Mrs. Alex B. Novikoff
Dr. and Mrs. Karl Sax
Dr. Ira Wiggins

Table 56

Dr. André Cournand
Dr. and Mrs. Walter R. Miles
Dr. and Mrs. John A. Moore
Dr. Marvin L. Niehuss
Dr. Morris E. Opler
Dr. and Mrs. Curt P. Richter
Dr. and Mrs. Lorrin A. Riggs

Table 57

Dr. A. Allan Bates
Mr. and Mrs. John S. Coleman
Mr. W. Leighton Collins
Dr. and Mrs. Lawrence S. Darken
Dr. and Mrs. Paul D. Foote
Dr. M. L. Goldberger
Mr. and Mrs. Louis Jordan

Table 58

Dr. and Mrs. R. Alexander Brink
Dr. and Mrs. C. Stacy French
Dr. and Mrs. Seymour S. Kety
Dr. and Mrs. J. Charles Walker
Dr. and Mrs. Perry W. Wilson

Table 59

Dr. and Mrs. Martin Deutsch
Dr. and Mrs. Harvey Fletcher
Dr. and Mrs. Karl F. Herzfeld
Dr. and Mrs. Charles H. Townes
Dr. and Mrs. Alvin M. Weinberg

Table 60

Dr. and Mrs. Arnold Kent Balls
Dr. and Mrs. Lyman C. Craig
Dr. and Mrs. Hans Neurath
Dr. and Mrs. Donald D. Van Slyke
Dr. and Mrs. H. B. Vickery

Table 61

Dr. and Mrs. Louis P. Hammett
Dr. and Mrs. Herbert S. Harned
Dr. and Mrs. Lars Onsager
Dr. and Mrs. George Scatchard
Dr. and Mrs. D. Stanley Tarbell

Table 62

Dr. and Mrs. Perry Byerly
Mr. and Mrs. Scott E. Forbush
Dr. and Mrs. David T. Griggs
Dr. and Mrs. Hollis D. Hedberg
Dr. and Mrs. M. King Hubbert

Table 63

Dr. and Mrs. Fred Eggan
Dr. and Mrs. B. L. Horecker
Dr. and Mrs. Edward C. Kendall
Dr. and Mrs. David Rittenberg
Dr. and Mrs. Carl F. Schmidt

Table 64

Dr. and Mrs. C. C. Lin
Dr. and Mrs. George W. Mackey
Dr. and Mrs. N. E. Steenrod
Dr. and Mrs. J. J. Stoker

Table 65

Dr. and Mrs. R. L. Wilder
Dr. and Mrs. M. Goldhaber
Dr. and Mrs. Mark Inghram
Dr. and Mrs. Bruno B. Rossi
Dr. and Mrs. Robert Serber
Dr. and Mrs. John A. Simpson

Table 66

Dr. and Mrs. M. R. Irwin
Dr. Knut Schmidt-Nielsen
Dr. and Mrs. T. D. Stewart
Dr. and Mrs. William L. Straus, Jr.
Dr. Shields Warren
Dr. and Mrs. Carroll M. Williams

Table 67

Dr. and Mrs. David Shemin
Dr. and Mrs. Emil L. Smith
Dr. and Mrs. Wendell M. Stanley
Dr. and Mrs. William H. Stein
Dr. and Mrs. Selman A. Waksman

Table 68

Dr. and Mrs. Joseph E. Mayer
Dr. and Mrs. John C. Sheehan
Dr. and Mrs. Charles P. Smyth
Dr. and Mrs. L. H. Thomas
Dr. and Mrs. Richard Tousey

Table 69

Dr. and Mrs. Bryan Patterson
Dr. and Mrs. Charles S. Piggot
Dr. and Mrs. William S. Tillet
Dr. and Mrs. Francis J. Turner
Dr. and Mrs. Hatten S. Yoder, Jr.

Table 70

Colonel and Mrs. Robert A. Cliffe
Dr. S. D. Cornell
Mr. and Mrs. Robert E. Green
Dr. and Mrs. Monroe H. Martin

Table 71

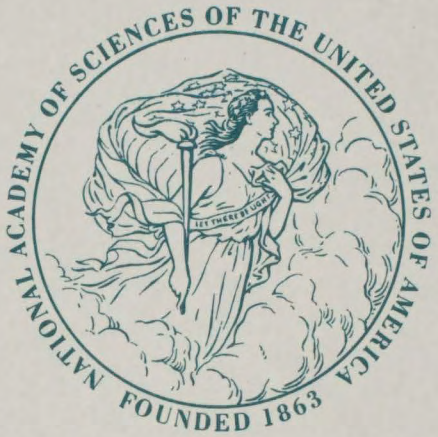
Dr. and Mrs. Frank L. Campbell
Miss Ann Ewing
Dr. and Mrs. Linn Hoover
Mr. and Mrs. W. Murray Todd

Address

National Academy of Sciences

of the United States of America

★ ★ ★ ★ ★



★ ★ ★ ★ ★

MEMBERSHIP

July 1, 1962

NATIONAL ACADEMY OF SCIENCES

July 1, 1962

OFFICERS

	Term expires
President—Frederick Seitz	June 30, 1966
Vice President—J. A. Stratton	June 30, 1965
Home Secretary—Hugh L. Dryden	June 30, 1963
Foreign Secretary—Harrison Brown	June 30, 1966
Treasurer—L. V. Berkner	June 30, 1964

Executive Officer
S. D. Cornell

Business Manager
G. D. Meid

COUNCIL

*Berkner, L. V.	(1964)	*Revelle, Roger	(1965)
*Brown, Harrison	(1966)	*Seitz, Frederick	(1966)
*Dryden, Hugh L.	(1963)	*Stratton, J. A.	(1965)
Hutchinson, G. Evelyn	(1963)	Williams, Robley C.	(1963)
*Kistiakowsky, G. B.	(1964)	Wood, W. Barry, Jr.	(1965)
Raper, Kenneth B.	(1964)		

MEMBERS

The number in parentheses, following year of election, indicates the Section to which the member belongs, as follows:

(1)	Mathematics	(8)	Zoology and Anatomy
(2)	Astronomy	(9)	Physiology
(3)	Physics	(10)	Pathology and Microbiology
(4)	Engineering	(11)	Anthropology
(5)	Chemistry	(12)	Psychology
(6)	Geology	(13)	Geophysics
(7)	Botany	(14)	Biochemistry

Abbot, Charles **G**reeley, 1915 (2), Smithsonian Institution, Washington 25, D. C.

Abelson, Philip Hauge, 1959 (6), Geophysical Laboratory, Carnegie Institution of Washington, 2801 Upton Street, N. W., Washington 8, D. C.

Adams, Leason **H**eberling, 1943 (13), Institute of Geophysics, University of California, Los Angeles 24, California

Adams, Roger, 1929 (5), Department of Chemistry and Chemical Engineering, University of Illinois, Urbana, Illinois

Ahlfors, Lars Valerian, 1953 (1), Department of Mathematics, Harvard University, 2 Divinity Avenue, Cambridge 38, Massachusetts

Albert, Abraham **A**drian, 1943 (1), 111 Eckhart Hall, University of Chicago, 1118 East 58th Street, Chicago 37, Illinois

Albright, William **F**oxwell, 1955 (11), Oriental Seminary, Johns Hopkins University, Baltimore 18, Maryland

---

* Members of the Executive Committee of the Council of the Academy.

Alexander, James Waddell, 1930 (1), 29 Cleveland Lane, Princeton, New Jersey

Allen, Eugene Thomas, 1930 (6), 135 Pleasant Street, Arlington 74, Massachusetts

Aller, Lawrence Hugh, 1962 (2), The Observatory of the University of Michigan, Ann Arbor, Michigan. After September 1, 1962: Department of Astronomy, University of California, Los Angeles 24, California

Allison, Samuel King, 1946 (3), The Enrico Fermi Institute for Nuclear Studies, University of Chicago, Chicago 37, Illinois

Alvarez, Luis Walter, 1947 (3), Lawrence Radiation Laboratory, University of California, Berkeley 4, California

Anderson, Carl David, 1938 (3), California Institute of Technology, Pasadena 4, California

Anderson, Charles Alfred, 1957 (6), United States Geological Survey, Department of the Interior, Washington 25, D. C.

Anderson, Edgar, 1954 (7), Missouri Botanical Garden, 2315 Tower Grove Avenue, St. Louis 10, Missouri

Anderson, Herbert Lawrence, 1960 (3), The Enrico Fermi Institute for Nuclear Studies, University of Chicago, Chicago 37, Illinois

Armstrong, Charles, 1944 (10), National Institutes of Health, Bethesda 14, Maryland

Arnold, William Archibald, 1962 (7), Biology Division, Oak Ridge National Laboratory, P. O. Box Y, Oak Ridge, Tennessee

Arnon, Daniel Israel, 1961 (7), 251 Hilgard Hall, University of California, Berkeley 4, California

Astin, Allen Varley, 1960 (4), National Bureau of Standards, Washington 25, D. C.

Astwood, Edwin Bennett, 1957 (9), New England Center Hospital, Harrison Avenue and Bennet Street, Boston 11, Massachusetts

Aub, Joseph Charles, 1957 (9), Massachusetts General Hospital, Fruit Street, Boston 14, Massachusetts

Babcock, Harold Delos, 1933 (2), 1820 Atchison Street, Pasadena, California

Babcock, Horace Welcome, 1954 (2), Mount Wilson and Palomar Observatories, 813 Santa Barbara Street, Pasadena 4, California

Bacher, Robert Fox, 1947 (3), California Institute of Technology, Pasadena, California

Badger, Richard McLean, 1952 (5), Gates and Crellin Laboratories of Chemistry, California Institute of Technology, Pasadena 4, California

Bailey, Percival, 1953 (10), Illinois State Psychiatric Institute, 1601 West Taylor Street, Chicago 12, Illinois

Bain, Edgar Collins, 1954 (4), 434 Maple Lane, Edgeworth, Sewickley, Pennsylvania

Bainbridge, Kenneth Tompkins, 1946 (3), Department of Physics, Harvard University, Cambridge 38, Massachusetts

Baker, William Oliver, 1961 (5), Bell Telephone Laboratories, Incorporated, Murray Hill, New Jersey

Ball, Eric Glendinning, 1948 (14), Department of Biological Chemistry, Harvard Medical School, 25 Shattuck Street, Boston 15, Massachusetts

Balls, Arnold Kent, 1954 (14), 1988 Thousand Oaks Boulevard, Berkeley 7, California

Bard, Philip, 1944 (9), School of Medicine, Johns Hopkins University, 725 North Wolfe Street, Baltimore 5, Maryland

Bardeen, John, 1954 (3), Department of Physics, University of Illinois, Urbana, Illinois

Barker, Horace Albert, 1953 (7), Department of Biochemistry, 337 Biochemistry and Virus Laboratory, University of California, Berkeley 4, California

Bartelmez, George William, 1949 (8), 224 Agnes Avenue, Missoula, Montana

Bartlett, Paul Doughty, 1947 (5), Department of Chemistry, Harvard University, 12 Oxford Street, Cambridge 38, Massachusetts

Beach, Frank Ambrose, 1949 (12), Department of Psychology, University of California, Berkeley 4, California

Beadle, George Wells, 1944 (7), University of Chicago, 5801 Ellis Avenue, Chicago 37, Illinois

Beams, Jesse Wakefield, 1943 (3), Physics Laboratory, University of Virginia, McCormick Road, Charlottesville, Virginia

Benedict, Manson, 1956 (4), Department of Nuclear Engineering, Massachusetts Institute of Technology, Cambridge 39, Massachusetts

Benioff, Victor **Hugo,** 1953 (13), Seismological Laboratory, California Institute of Technology, 220 North San Rafael Avenue, Pasadena 2, California

Benzer, Seymour, 1961 (7), Department of Biological Sciences, Purdue University, Lafayette, Indiana

Berkner, Lloyd Viel, 1948 (13), Graduate Research Center of the Southwest, P. O. Box 8478, Dallas 5, Texas

Bethe, Hans Albrecht, 1944 (3), Laboratory of Nuclear Studies, Cornell University, Ithaca, New York

Bigelow, Henry Bryant, 1931 (8), Museum of Comparative Zoology at Harvard College, Oxford Street, Cambridge 38, Massachusetts

Birch, Albert **Francis,** 1950 (6), Dunbar Laboratory, Harvard University, Cambridge 38, Massachusetts

Birge, Raymond Thayer, 1932 (3), University of California, Berkeley 4, California

Bjerknes, Jacob, 1947 (13), Department of Meteorology, University of California, Los Angeles 24, California

Blackwelder, Eliot, 1936 (6), P. O. Box 6506, Stanford, California

Blalock, Alfred, 1945 (10), Johns Hopkins Hospital, Baltimore 5, Maryland

Bleakney, Walker, 1959 (3), Palmer Physical Laboratory, Princeton University, P. O. Box 708, Princeton, New Jersey

Blinks, Lawrence Rogers, 1955 (7), Hopkins Marine Station of Stanford University, Pacific Grove, California

Bloch, Felix, 1948 (3), Department of Physics, Stanford University, Stanford, California

Bloch, Konrad Emil, 1956 (14), Department of Chemistry, Harvard University, 12 Oxford Street, Cambridge 38, Massachusetts

Bloembergen, Nicolaas, 1960 (3), Pierce Hall, Harvard University, Cambridge 38, Massachusetts

Blomquist, Alfred Theodore, 1960 (5), Department of Chemistry, Cornell University, Ithaca, New York

Bloom, William, 1954 (8), University of Chicago, 5640 South Ellis Avenue, Chicago 37, Illinois

Bochner, Salomon, 1950 (1), Department of Mathematics, Princeton University, P. O. Box 708, Princeton, New Jersey

Bode, Hendrik Wade, 1957 (4), Bell Telephone Laboratories, Incorporated, Whippany, New Jersey

Bodenstein, Dietrich H. F. A., 1958 (8), Department of Biology, University of Virginia, Charlottesville, Virginia

Bodian, David, 1958 (8), Department of Anatomy, School of Medicine, Johns Hopkins University, 725 North Wolfe Street, Baltimore 5, Maryland

Boekelheide, Virgil Carl, 1962 (5), Department of Chemistry, University of Oregon, Eugene, Oregon

Bolton, Elmer K., 1946 (5), 2310 West 11th Street, Wilmington, Delaware

Bonner, David Mahlon, 1959 (7), School of Science and Engineering, University of California, San Diego, 8602 La Jolla Shore Drive, La Jolla, California

Bonner, James Frederick, 1950 (7), Division of Biology, California Institute of Technology, Pasadena 4, California

Booker, Henry George, 1960 (13), School of Electrical Engineering, Cornell University, Ithaca, New York

Boring, Edwin Garrigues, 1932 (12), Memorial Hall, Harvard University, Cambridge 38, Massachusetts

Borthwick, Harry Alfred, 1961 (7), Plant Industry Station, United States Department of Agriculture, Beltsville, Maryland

Bowen, Ira Sprague, 1936 (2), Mount Wilson and Palomar Observatories, 813 Santa Barbara Street, Pasadena, California

Bradbury, Norris Edwin, 1951 (3), Los Alamos Scientific Laboratory, P. O. Box 1663, Los Alamos, New Mexico

Bradley, Wilmot Hyde, 1946 (6), United States Geological Survey, Department of the Interior, Washington 25, D. C.

Bramlette, Milton Nunn, 1954 (6), Scripps Institution of Oceanography, La Jolla, California

Brattain, Walter Houser, 1959 (3), Bell Telephone Laboratories, Incorporated, Murray Hill, New Jersey

Brauer, Richard Dagobert, 1955 (1), Department of Mathematics, Harvard University, 2 Divinity Avenue, Cambridge 38, Massachusetts

Braun, Armin Charles, 1960 (7), Rockefeller Institute, New York 21, New York

Breit, Gregory, 1939 (3), Sloane Physics Laboratory, Yale University, P. O. Box 2014, New Haven 11, Connecticut

Brewer, Leo, 1959 (5), Department of Chemistry, University of California, Berkeley 4, California

Briggs, Lyman James, 1942 (4), 3208 Newark Street, N. W., Washington 8, D. C.

Briggs, Robert William, 1962 (8), Department of Zoology, Indiana University, Bloomington, Indiana

Brillouin, Leon, 1953 (3), 88 Central Park West, New York 23, New York

Brink, Frank, Jr., 1959 (9), Rockefeller Institute, New York 21, New York

Brink, Royal Alexander, 1947 (7), Department of Genetics, University of Wisconsin, Madison 6, Wisconsin

Brode, Robert Bigham, 1949 (3), Department of Physics, University of California, Berkeley 4, California

Brode, Wallace Reed, 1954 (5), 3900 Connecticut Avenue, Washington 8, D. C.

Bronk, Detlev Wulf, 1939 (9), Rockefeller Institute, New York 21, New York

Brooks, Harvey, 1962 (4), 217 Pierce Hall, Harvard University, Cambridge 38, Massachusetts

Brouwer, Dirk, 1951 (2), Yale University Observatory, Box 2023, Yale Station, New Haven, Connecticut

Brown, Harrison Scott, 1955 (13), Division of Geological Sciences, California Institute of Technology, Pasadena, California

Brown, Herbert Charles, 1957 (5), Department of Chemistry, Purdue University, Lafayette, Indiana

Buchanan, John Machlin, 1962 (14), Division of Biochemistry, Department of Biology, Massachusetts Institute of Technology, Cambridge 39, Massachusetts

Bucher, Walter Hermann, 1938 (6), Department of Geology, Columbia University, New York 27, New York

Buddington, Arthur Francis, 1943 (6), Department of Geology, Princeton University, Princeton, New Jersey

Buerger, Martin Julian, 1953 (6), Department of Geology and Geophysics, Massachusetts Institute of Technology, Cambridge 39, Massachusetts

Burkholder, Paul Rufus, 1949 (7), Lamont Geological Observatory of Columbia University, Torrey Cliff, Palisades, New York

Burns, Robert Kyle, 1955 (8), Department of Biology, Bridgewater College, Bridgewater, Virginia

Burris, Robert Harza, 1961 (7), Department of Biochemistry, University of Wisconsin, Madison 6, Wisconsin

Bush, Vannevar, 1934 (4), Massachusetts Institute of Technology, Cambridge 39, Massachusetts

Byerly, Perry, 1946 (13), Seismographic Station, University of California, Berkeley 4, California

Byers, Horace Robert, 1952 (13), Department of Geophysical Sciences, University of Chicago, Chicago 37, Illinois

Calvin, Melvin, 1954 (5), Department of Chemistry, University of California, Berkeley 4, California

Cannon, Paul Roberts, 1946 (10), Department of Pathology, University of Chicago, Chicago 37, Illinois

Carmichael, Leonard, 1943 (12), Smithsonian Institution, Washington 25, D. C.

Carter, Herbert Edmund, 1953 (14), Department of Chemistry, University of Illinois, Urbana, Illinois

Castle, William Bosworth, 1939 (10), Boston City Hospital, Boston 18, Massachusetts

Chamberlain, Owen, 1960 (3), Department of Physics, University of California, Berkeley 4, California

Chance, Britton, 1954 (14), Eldridge Reeves Johnson Foundation for Medical Physics, University of Pennsylvania, Philadelphia 4, Pennsylvania

Chandler, William Henry, 1943 (7), 341 South Almont Drive, Beverley Hills, California

Chandrasekhar, Subrahmanyan, 1955 (2), Yerkes Observatory, University of Chicago, Williams Bay, Wisconsin

Chaney, Ralph Works, 1947 (6), Department of Paleontology, University of California, Berkeley 4, California

Chern, Shiing-shen, 1961 (1), Department of Mathematics, University of California, Berkeley 4, California

Chew, Geoffrey Foucar, 1962 (3), Department of Physics, University of California, Berkeley 4, California

Chipman, John, 1955 (4), Department of Metallurgy, Massachusetts Institute of Technology, Cambridge 39, Massachusetts

Clark, William **Mansfield,** 1928 (14), Department of Chemistry, Johns Hopkins University, Baltimore 18, Maryland

Clarke, Hans Thacher, 1942 (14), Department of Biochemistry, Yale University School of Medicine, 333 Cedar Street, New Haven 11, Connecticut

Clausen, Jens Christian, 1959 (7), Department of Plant Biology, Carnegie Institution of Washington, Stanford, California

Cleland, Ralph Erskine, 1942 (7), Department of Botany, Indiana University, Bloomington, Indiana

Clemence, Gerald **Maurice,** 1952 (2), United States Naval Observatory, Washington 25, D. C.

Cleveland, Lemuel **Roscoe,** 1952 (8), Department of Zoology, University of Georgia, Athens, Georgia

Cloos, Ernst, 1950 (6), Department of Geology, Johns Hopkins University, Baltimore 18, Maryland

Cloud, Preston Ercelle, **Jr.,** 1961 (6), Department of Geology, University of Minnesota, Minneapolis 14, Minnesota

Coblentz, William **Weber,** 1930 (3), 2737 Macomb Street, N. W., Washington 8, D. C.

Coggeshall, Lowell **Thelwell,** 1949 (10), University of Chicago, Chicago 37, Illinois

Colbert, Edwin Harris, 1957 (8), American Museum of Natural History, Central Park West at 79th Street, New York 24, New York

Cole, Kenneth Stewart, 1956 (9), Biophysics Laboratory, NINDB, National Institutes of Health, Bethesda 14, Maryland

Comroe, Julius Hiram, **Jr.,** 1961 (9), Cardiovascular Research Institute, University of California Medical Center, San Francisco 22, California

Conant, James Bryant, 1929 (5), 588 Fifth Avenue, New York 36, New York

Condon, Edward **Uhler,** 1944 (3), Department of Physics, Oberlin College, Oberlin, Ohio

Coon, Carleton Stevens, 1955 (11), The University Museum, University of Pennsylvania, 33rd and Spruce Streets, Philadelphia 4, Pennsylvania

Coons, Albert Hewett, 1962 (10), Department of Bacteriology and Immunology, Harvard Medical School, 25 Shattuck Street, Boston 15, Massachusetts

Cope, Arthur Clay, 1947 (5), Department of Chemistry, Massachusetts Institute of Technology, Cambridge 39, Massachusetts

Cori, Carl Ferdinand, 1940 (14), School of Medicine, Washington University, Euclid Avenue and Kingshighway, St. Louis 10, Missouri

Corner, George Washington, 1940 (8), American Philosophical Society, 104 South Fifth Street, Philadelphia 6, Pennsylvania

Couch, John Nathaniel, 1943 (7), University of North Carolina, Chapel Hill, North Carolina

Courant, Richard, 1955 (1), New York University, 4 Washington Place, New York 3, New York

Cournand, André Frederic, 1958 (9), Cardio-Pulmonary Laboratory (Columbia University Division), Bellevue Hospital, 462 First Avenue, New York 16, New York

Craig, Lyman Creighton, 1950 (14), Rockefeller Institute, New York 21, New York

Cram, Donald James, 1961 (5), Department of Chemistry, University of California, Los Angeles 24, California

Crawford, Bryce, Jr., 1956 (5), Graduate School, University of Minnesota, Minneapolis 14, Minnesota

Crow, James Franklin, 1961 (8), Department of Medical Genetics, University of Wisconsin, Madison 6, Wisconsin

Curme, George Oliver, Jr., 1944 (4), Union Carbide Corporation, 270 Park Avenue, New York 17, New York

Dalldorf, Gilbert, 1955 (10), Sloan-Kettering Institute for Cancer Research, 145 Boston Post Road, Rye, New York

Danforth, Charles Haskell, 1942 (8), Department of Anatomy, Stanford University, Stanford, California

Daniels, Farrington, 1947 (5), Solar Energy Laboratory, University of Wisconsin, Madison 6, Wisconsin

Darken, Lawrence Stamper, 1961 (4), United States Steel Corporation, Research Center, Monroeville, Pennsylvania

Davidson, Norman Ralph, 1960 (5), Gates and Crellin Laboratories of Chemistry, California Institute of Technology, Pasadena 4, California

Davis, Hallowell, 1948 (9), Central Institute for the Deaf, 818 South Kingshighway, St. Louis 10, Missouri

Debye, Peter, (1931) 1947* (5), Baker Laboratory, Cornell University, Ithaca, New York

Delbrück, Max, 1949 (7), Genetisches Institut, Weyertal 115, Köln-Lindenthal, Germany

Demerec, Milislav, 1946 (8), Department of Biology, Brookhaven National Laboratory, Upton, Long Island, New York

Den Hartog, Jacob Pieter, 1953 (4), Department of Mechanical Engineering, Massachusetts Institute of Technology, Cambridge 39, Massachusetts

Dennison, David Mathias, 1953 (3), Randall Laboratory of Physics, University of Michigan, Ann Arbor, Michigan

Deutsch, Martin, 1958 (3), Laboratory for Nuclear Science, Massachusetts Institute of Technology, Cambridge 39, Massachusetts

Dingle, John Holmes, 1958 (10), School of Medicine, Western Reserve University, Cleveland 6, Ohio

---

*Elected a foreign associate in 1931; became a naturalized citizen in 1946 and a member of the Academy in 1947.

Djerassi, Carl, 1961 (5), Department of Chemistry, Stanford University, Stanford, California

Dobzhansky, Theodosius, 1943 (8), Rockefeller Institute, New York 21, New York

Dochez, Alphonse Raymond, 1933 (10), Presbyterian Hospital, 620 West 168th Street, New York 32, New York

Doering, William von Eggers, 1961 (5), Yale University, 1901 A Yale Station, New Haven 11, Connecticut

Doisy, Edward Adelbert, 1938 (14), St. Louis University School of Medicine, 1402 South Grand Boulevard, St. Louis 4, Missouri

Doob, Joseph Leo, 1957 (1), Department of Mathematics, University of Illinois, Urbana, Illinois

Doty, Paul Mead, 1957 (14), Department of Chemistry, Harvard University, 12 Oxford Street, Cambridge 38, Massachusetts

Doudoroff, Michael, 1962 (14), Department of Bacteriology, University of California, Berkeley 4, California

Douglas, Jesse, 1946 (1), 109–33 Seventy-first Road, Forest Hills 75, New York

Dragstedt, Lester Reynold, 1950 (10), Department of Surgery, University of Florida, Gainesville, Florida

Draper, Charles Stark, 1957 (4), Room 33–207, Department of Aeronautics and Astronautics, Massachusetts Institute of Technology, Cambridge 39, Massachusetts

Dryden, Hugh Latimer, 1944 (4), National Aeronautics and Space Administration, 400 Maryland Avenue, S. W., Washington 25, D. C.

Dubos, René Jules, 1941 (10), Rockefeller Institute, New York 21, New York

DuBridge, Lee Alvin, 1943 (3), California Institute of Technology, Pasadena, California

Dulbecco, Renato, 1961 (10), Division of Biology, California Institute of Technology, Pasadena, California

DuMond, Jesse William Monroe, 1953 (3), Department of Physics, California Institute of Technology, Pasadena 4, California

Dunbar, Carl Owen, 1944 (6), Peabody Museum, Yale University, New Haven 11, Connecticut

Dunn, Leslie Clarence, 1943 (8), 635 West 247th Street, New York 71, New York

Dunning, John Ray, 1948 (3), School of Engineering and Applied Science, 510 Mudd Building, Columbia University, New York 27, New York

du Vigneaud, Vincent, 1944 (14), Cornell University Medical College, 1300 York Avenue, New York 21, New York

Eckart, Carl, 1953 (13), University of California, San Diego, La Jolla, California

Edsall, John Tileston, 1951 (14), The Biological Laboratories, Harvard University, 16 Divinity Avenue, Cambridge 38, Massachusetts

Eilenberg, Samuel, 1959 (1), Department of Mathematics, Columbia University, New York 27, New York

Eisenhart, Luther Pfahler, 1922 (1), 25 Alexander Street, Princeton, New Jersey

Elderfield, Robert Cooley, 1949 (5), Department of Chemistry, University of Michigan, Ann Arbor, Michigan

Elsasser, Walter Maurice, 1957 (13), Scripps Institution of Oceanography, University of California, San Diego, La Jolla, California

Elvehjem, Conrad Arnold, 1942 (14), Bascom Hall, University of Wisconsin, Madison 6, Wisconsin

Emerson, Alfred Edwards, 1962 (8), Department of Zoology, University of Chicago, Chicago 37, Illinois

Emmett, Paul Hugh, 1955 (5), Department of Chemistry, Johns Hopkins University, Baltimore 18, Maryland

Enders, John Franklin, 1953 (10), The Children's Hospital Medical Center, 300 Longwood Avenue, Boston 15, Massachusetts

Epstein, Paul Sophus, 1930 (3), 1484 Oakdale Street, Pasadena 4, California

Erlanger, Joseph, 1922 (9), 5127 Waterman Boulevard, St. Louis 8, Missouri

Esau, Katherine, 1957 (7), Department of Botany, University of California, Davis, California

Evans, Griffith Conrad, 1933 (1), Department of Mathematics, University of California, Berkeley 4, California

Evans, Herbert McLean, 1927 (9), Institute of Experimental Biology, University of California, Berkeley 4, California

Ewing, William Maurice, 1948 (13), Lamont Geological Observatory of Columbia University, Torrey Cliff, Palisades, New York

Eyring, Henry, 1945 (5), Graduate School, University of Utah, Salt Lake City, Utah

Feller, William, 1960 (1), Fine Hall, Princeton University, Princeton, New Jersey

Fenn, Wallace Osgood, 1943 (9), School of Medicine and Dentistry, University of Rochester, 260 Crittenden Boulevard, Rochester 20, New York

Ferry, John Douglass, 1959 (5), Department of Chemistry, University of Wisconsin, Madison 6, Wisconsin

Feynman, Richard Phillips, 1954 (3), Norman Bridge Laboratory of Physics, California Institute of Technology, Pasadena, California

Fieser, Louis Frederick, 1940 (5), Harvard University, Cambridge 38, Massachusetts

Fisk, James Brown, 1954 (4), Bell Telephone Laboratories, Incorporated, Murray Hill, New Jersey

Fletcher, Harvey, 1935 (4), College of Physical and Engineering Sciences, Brigham Young University, Provo, Utah

Flory, Paul John, 1953 (5), Department of Chemistry, Stanford University, Stanford, California

Folkers, Karl August, 1948 (5), Fundamental Research, Merck Sharp & Dohme Research Laboratories, Rahway, New Jersey

Foote, Paul Darwin, 1943 (4), 5144 Macomb Street, N. W., Washington 16, D. C.

Forbes, Alexander, 1936 (9), 610 Harland Street, Milton, Massachusetts

Forbush, Scott Ellsworth, 1962 (13), Department of Terrestrial Magnetism, Carnegie Institution of Washington, 5241 Broad Branch Road, N. W., Washington 15, D. C.

Fowler, William Alfred, 1956 (3), W. K. Kellogg Radiation Laboratory, California Institute of Technology, Pasadena, California

Francis, Thomas, Jr., 1948 (10), Department of Epidemiology, School of Public Health, University of Michigan, Ann Arbor, Michigan

Franck, James, 1944 (3), Department of Chemistry, University of Chicago, Chicago 37, Illinois

Fred, Edwin Broun, 1931 (7), University of Wisconsin, Madison 6, Wisconsin

Friedman, Herbert, 1960 (13), United States Naval Research Laboratory, Washington 25, D. C.

Friedmann, Herbert, 1962 (8), Los Angeles County Museum, 900 Exposition Boulevard, Los Angeles 7, California

Friedrichs, Kurt Otto, 1959 (1), Courant Institute of Mathematical Sciences, New York University, 25 Waverly Place, New York 3, New York

Fruton, Joseph Stewart, 1952 (14), Department of Biochemistry, Yale University, 333 Cedar Street, New Haven 11, Connecticut

Fuoss, Raymond Matthew, 1951 (5), 57 Mill Rock Road, New Haven 11, Connecticut

Fuson, Reynold Clayton, 1944 (5), 263 Noyes Laboratory, University of Illinois, Urbana, Illinois

Galambos, Robert, 1960 (12), Yale University, 333 Cedar Street, New Haven Connecticut

Gamow, George, 1953 (3), Department of Physics, University of Colorado, Boulder, Colorado

Garrels, Robert Minard, 1962 (6), Department of Geological Sciences, Harvard University, Cambridge 38, Massachusetts

Gasser, Herbert Spencer, 1934 (9), Rockefeller Institute, New York 21, New York

Gates, Marshall DeMotte, Jr., 1958 (5), Department of Chemistry, University of Rochester, Rochester 20, New York

Gell-Mann, Murray, 1960 (3), Department of Physics, California Institute of Technology, Pasadena, California

Gerard, Ralph Waldo, 1955 (9), Mental Health Research Institute, University of Michigan, Ann Arbor, Michigan

Giauque, William Francis, 1936 (5), Department of Chemistry, University of California, Berkeley 4, California

Gibbs, William Francis, 1949 (4), One Broadway, New York 4, New York

Gilliland, Edwin Richard, 1948 (4), Department of Chemical Engineering, Massachusetts Institute of Technology, Cambridge 39, Massachusetts

Gilluly, James, 1947 (6), United States Geological Survey, Denver Federal Center, Denver 25, Colorado

Gilman, Henry, 1945 (5), Department of Chemistry, Iowa State University, Ames, Iowa

Glaser, Donald Arthur, 1962 (3), Department of Physics, University of California, Berkeley 4, California

Glass, Hiram Bentley, 1959 (8), Department of Biology, Johns Hopkins University, Baltimore 18, Maryland

Goddard, David Rockwell, 1950 (7), Provost's Office, 102 College Hall, University of Pennsylvania, Philadelphia 4, Pennsylvania

Gödel, Kurt, 1955 (1), The Institute for Advanced Study, Princeton, New Jersey

Goebel, Walther Frederick, 1958 (10), Rockefeller Institute, New York 21, New York

Goldberg, Leo, 1958 (2), Harvard College Observatory, Cambridge 38, Massachusetts

Goldhaber, Maurice, 1958 (3), Director's Office, Brookhaven National Laboratory, Upton, Long Island, New York

Goudsmit, Samuel Abraham, 1947 (3), Department of Physics, Brookhaven National Laboratory, Upton, Long Island, New York

Graham, Clarence **H**enry, 1946 (12), Department of Psychology, Columbia University, New York 27, New York

Green, David Ezra, 1962 (14), Institute for Enzyme Research, University of Wisconsin, 1710 University Avenue, Madison 6, Wisconsin

Greenewalt, Crawford Hallock, 1952 (4), E. I. du Pont de Nemours and Company, Incorporated, Wilmington 98, Delaware

Greenstein, Jesse Leonard, 1957 (2), Mount Wilson and Palomar Observatories, California Institute of Technology, Pasadena, California

Gregory, William King, 1927 (6), Woodstock, New York

Griffin, Donald Redfield, 1960 (8), The Biological Laboratories, Harvard University, 16 Divinity Avenue, Cambridge 38, Massachusetts

Griggs, David Tressel, 1952 (13), Institute of Geophysics, University of California, Los Angeles 24, California

Guilford, Joy **P**aul, 1954 (12), P. O. Box 1288, Beverly Hills, California

Gunn, Ross, 1951 (13), 4437 Lowell Street, N. W., Washington 16, D. C.

Gutowsky, Herbert **S**ander, 1960 (5), Department of Chemistry and Chemical Engineering, University of Illinois, Urbana, Illinois

Hallowell, Alfred **I**rving, 1961 (11), Department of Anthropology, The University Museum, 33rd and Spruce Streets, Philadelphia 4, Pennsylvania

Hamburger, Viktor, 1953 (8), Department of Zoology, Washington University, St. Louis 30, Missouri

Hammett, Louis Plack, 1943 (5), R. D. 4, Box 310, Newton, New Jersey

Harlow, Harry F., 1951 (12), Primate Laboratory, 22 North Charter Street, Madison 5, Wisconsin

Harned, Herbert Spencer, 1950 (5), Sterling Chemistry Laboratory, Yale University, 225 Prospect Street, New Haven 11, Connecticut

Hartline, Haldan **K**effer, 1948 (9), Rockefeller Institute, New York 21, New York

Haskins, Caryl Parker, 1956 (8), Carnegie Institution of Washington, 1530 P Street, N. W., Washington 5, D. C.

Hassid, William **Z**ev, 1958 (14), Department of Biochemistry, 337 Biochemistry and Virus Laboratory, University of California, Berkeley 4, California

Hastings, Albert **B**aird, 1939 (9), Scripps Clinic and Research Foundation, 476 Prospect Street, La Jolla, California

Haurwitz, Bernhard, 1960 (13), Department of Astrogeophysics, University of Colorado, Boulder, Colorado

Haury, Emil Walter, 1956 (11), Department of Anthropology, University of Arizona, Tucson, Arizona

Hauser, Charles Roy, 1958 (5), Department of Chemistry, Duke University, Durham, North Carolina

Hedberg, Hollis Dow, 1960 (6), Department of Geology, Princeton University, Princeton, New Jersey

Heidelberger, Michael, 1942 (10), Institute of Microbiology, Rutgers, The State University, New Brunswick, New Jersey

Hendricks, Sterling Brown, 1952 (5), Plant Industry Station, Beltsville, Maryland

Herb, Raymond George, 1955 (3), Department of Physics, University of Wisconsin, Madison 6, Wisconsin

Herget, Paul, 1962 (2), The Cincinnati Observatory, Cincinnati 8, Ohio

Hershey, Alfred Day, 1958 (7), Department of Genetics, Carnegie Institution of Washington, Cold Spring Harbor, Long Island, New York

Herskovits, Melville Jean, 1959 (11), Department of Anthropology, Northwestern University, Evanston, Illinois

Herzfeld, Karl Ferdinand, 1960 (3), Department of Physics, Catholic University of America, Washington 17, D. C.

Hess, Harry Hammond, 1952 (6), Department of Geology, Princeton University, Princeton, New Jersey

Hewett, Donnel Foster, 1937 (6), 345 Middlefield Road, Menlo Park, California

Hildebrand, Joel Henry, 1929 (5), Department of Chemistry, University of California, Berkeley 4, California

Hilgard, Ernest Ropiequet, 1948 (12), Department of Psychology, Stanford University, Stanford, California

Hille, Carl Einar, 1953 (1), Department of Mathematics, Yale University, New Haven 11, Connecticut

Hirschfelder, Joseph Oakland, 1953 (5), Theoretical Chemistry Institute, Chemistry Research Building, University of Wisconsin, Madison 6, Wisconsin

Hisaw, Frederick Lee, 1947 (8), The Biological Laboratories, Harvard University, 16 Divinity Avenue, Cambridge 38, Massachusetts

Hofstadter, Robert, 1958 (3), Department of Physics, Stanford University, Stanford, California

Hollaender, Alexander, 1957 (7), Biology Division, Oak Ridge National Laboratory, P. O. Box Y, Oak Ridge, Tennessee

Holtfreter, Johannes, 1955 (8), Biological Laboratories, University of Rochester, Rochester 20, New York

Hoover, Herbert, 1922 (4), Waldorf Astoria Towers, New York, New York

Horecker, Bernard Leonard, 1961 (14), Department of Microbiology, New York University School of Medicine, 550 First Avenue, New York 16, New York

Hornig, Donald Frederick, 1957 (5), Department of Chemistry, Princeton University, Princeton, New Jersey

Horsfall, Frank Lappin, Jr., 1948 (10), Sloan-Kettering Institute for Cancer Research, 410 East 68th Street, New York 21, New York

Horsfall, James Gordon, 1953 (7), Connecticut Agricultural Experiment Station, Box 1106, New Haven 4, Connecticut

Hotchkiss, Rollin Douglas, 1961 (10), Rockefeller Institute, New York 21, New York

Houston, William Vermillion, 1943 (3), Rice University, Houston 1, Texas

Hubbert, Marion King, 1955 (6), Shell Development Company, P. O. Box 481, Houston 1, Texas

Hubbs, Carl Leavitt, 1952 (8), Scripps Institution of Oceanography, La Jolla, California

Huebner, Robert Joseph, 1960 (10), National Institutes of Health, Bethesda 14, Maryland

Huggins, Charles Brenton, 1949 (10), The Ben May Laboratory for Cancer Research, University of Chicago, 950 East 59th Street, Chicago 37, Illinois

Hull, Albert Wallace, 1929 (3), General Electric Research Laboratory, The Knolls, Schenectady, New York

Hunsaker, Jerome Clark, 1935 (4), Room 33–207, Massachusetts Institute of Technology, Cambridge 39, Massachusetts

Hutchinson, George **Evelyn,** 1950 (8), Osborn Zoological Laboratory, Yale University, New Haven 11, Connecticut

Hyman, Libbie Henrietta, 1961 (8), American Museum of Natural History, Central Park West at 79th Street, New York 24, New York

Inghram, Mark Gordon, 1961 (3), Department of Physics, University of Chicago, Chicago 37, Illinois

Irwin, Malcolm Robert, 1950 (8), Department of Genetics, University of Wisconsin, Madison 6, Wisconsin

Iselin, Columbus **O'Donnell,** 1951 (13), Woods Hole Oceanographic Institution, Woods Hole, Massachusetts

Jacobs, Merkel Henry, 1939 (8), School of Medicine, University of Pennsylvania, Philadelphia 4, Pennsylvania

Jacobs, Walter Abraham, 1932 (5), Rockefeller Institute, New York 21, New York

Jacobson, Nathan, 1954 (1), Department of Mathematics, Yale University, New Haven 11, Connecticut

James, Harold Lloyd, 1962 (6), Department of Geology, University of Minnesota, Minneapolis 14, Minnesota

Jeffries, Zay, 1939 (4), General Electric Company, 1 Plastics Avenue, Pittsfield, Massachusetts

Johnson, John Raven, 1948 (5), Department of Chemistry, Cornell University, Ithaca, New York

Johnson, William Summer, 1952 (5), Department of Chemistry, Stanford University, Stanford, California

Jones, Donald Forsha, 1939 (7), Department of Genetics, Connecticut Agricultural Experiment Station, P. O. Box 1106, New Haven 4, Connecticut

Joy, Alfred Harrison, 1944 (2), Mount Wilson and Palomar Observatories, 813 Santa Barbara Street, Pasadena 4, California

Kalckar, Herman Moritz, 1959 (14), Biochemical Research Department, Massachusetts General Hospital, Boston 14, Massachusetts

Kamen, Martin David, 1962 (14), School of Science and Engineering, University of California, San Diego, La Jolla, California

Kaplan, Joseph, 1957 (13), Department of Physics, University of California, Los Angeles 24, California

Kaufmann, Berwind Petersen, 1952 (7), Department of Genetics, Carnegie Institution of Washington, Cold Spring Harbor, Long Island, New York. After September 1, 1962: Department of Zoology, University of Michigan, Ann Arbor, Michigan

Kellogg, Arthur **Remington,** 1951 (8), 5305 28th Street, N. W., Washington 15, D. C.

Kelly, Mervin J., 1945 (4), 2 Windemere Terrace, Short Hills, New Jersey

Kemble, Edwin Crawford, 1931 (3), Physics Laboratories, Harvard University, Cambridge 38, Massachusetts

Kendall, Edward Calvin, 1950 (14), 3 Queenston Place, Princeton, New Jersey

Kerst, Donald William, 1951 (3), General Atomic, P. O. Box 608, San Diego 12, California

Kety, Seymour Solomon, 1962 (9), Laboratory of Clinical Science, NIMH, National Institutes of Health, Bethesda 14, Maryland

Keyes, Frederick George, 1930 (5), Massachusetts Institute of Technology, Cambridge 39, Massachusetts

Kimball, George Elbert, 1954 (5), Arthur D. Little, Inc., 35 Acorn Park, Cambridge 40, Massachusetts

King, Charles Glen, 1951 (14), The Nutrition Foundation, Inc., 99 Park Avenue, New York 16, New York

Kinzel, Augustus Braun, 1960 (4), Union Carbide Corporation, 270 Park Avenue, New York 17, New York

Kistiakowsky, George Bogdan, 1939 (5), Department of Chemistry, Harvard University, 12 Oxford Street, Cambridge 38, Massachusetts

Kittel, Charles, 1957 (3), Department of Physics, University of California, Berkeley 4, California

Klüver, Heinrich, 1957 (12), Culver Hall, University of Chicago, Chicago 37, Illinois

Knopf, Adolph, 1931 (6), Department of Geology, Stanford University, Stanford, California

Köhler, Wolfgang, 1947 (12), P. O. Box 32, Lebanon, New Hampshire

Kolthoff, Izaak Maurits, 1958 (5), School of Chemistry, University of Minnesota, Minneapolis 14, Minnesota

Kornberg, Arthur, 1957 (14), Department of Biochemistry, School of Medicine, Stanford University, Palo Alto, California

Kramer, Paul Jackson, 1962 (7), Department of Botany, Duke University, Durham, North Carolina

Kraus, Charles August, 1925 (5), 92 Keene Street, Providence 6, Rhode Island

Krauskopf, Konrad Bates, 1959 (6), School of Mineral Sciences, Stanford University, Stanford, California

Kuiper, Gerard Peter, 1950 (2), Lunar and Planetary Laboratory, University of Arizona, Tucson, Arizona

Kusch, Polykarp, 1956 (3), Department of Physics, Columbia University, New York 27, New York

Lamb, Willis Eugene, **Jr.,** 1954 (3), Sloane Physics Laboratory, Yale University, New Haven, Connecticut

Lambert, Walter Davis, 1949 (13), P. O. Box 1025, Canaan, Connecticut

La Mer, Victor Kuhn, 1945 (5), 353 Moore Avenue, Leonia, New Jersey

Land, Edwin Herbert, 1953 (3), Polaroid Corporation, Cambridge 39, Massachusetts

Landis, Eugene Markley, 1954 (9), Department of Physiology, Harvard Medical School, 25 Shattuck Street, Boston 15, Massachusetts

Lardy, Henry Arnold, 1958 (14), Institute for Enzyme Research, University of Wisconsin, 1702 University Avenue, Madison 5, Wisconsin

Lauritsen, Charles Christian, 1941 (3), W. K. Kellogg Radiation Laboratory, California Institute of Technology, Pasadena, California

Lederberg, Joshua, 1957 (14), Genetics Department, School of Medicine, Stanford University, Palo Alto, California

Lefschetz, Solomon, 1925 (1), Fine Hall, Princeton University, Princeton, New Jersey

Lehninger, Albert **L**ester, 1956 (14), School of Medicine, Johns Hopkins University, 725 North Wolfe Street, Baltimore 5, Maryland

Leonard, Nelson Jordan, 1955 (5), Department of Chemistry and Chemical Engineering, University of Illinois, Urbana, Illinois

Lerner, I. Michael, 1959 (8), Department of Genetics, University of California, Berkeley 4, California

Lewis, Warren Harmon, 1936 (8), The Wistar Institute of Anatomy and Biology, Philadelphia 4, Pennsylvania

Lewis, Warren **K**endall, 1938 (4), Massachusetts Institute of Technology, Cambridge 39, Massachusetts

Libby, Willard **F**rank, 1950 (5), Department of Chemistry, University of California, 405 Hilgard Avenue, Los Angeles 24, California

Lin, Chia-**C**hiao, 1962 (1), Department of Mathematics, Massachusetts Institute of Technology, Cambridge 39, Massachusetts

Lind, Samuel **C**olville, 1930 (5), P. O. Box P, Oak Ridge, Tennessee

Lindsley, Donald Benjamin, 1952 (12), Department of Psychology, University of California, Los Angeles 24, California

Link, Karl Paul, 1946 (14), Department of Biochemistry, University of Wisconsin, Madison 6, Wisconsin

Lipmann, Fritz Albert, 1950 (14), Rockefeller Institute, New York 21, New York

Lipscomb, William Nunn, 1961 (5), Department of Chemistry, Harvard University, 12 Oxford Street, Cambridge 38, Massachusetts

Little, Clarence **C**ook, 1945 (10), R. F. D. 1, Ellsworth, Maine

Lloyd, David Pierce **C**aradoc, 1953 (9), Rockefeller Institute, New York 21, New York

Loeb, Robert Frederick, 1946 (9), 950 Park Avenue, New York 28, New York

Long, Cyril **N**orman **H**ugh, 1948 (9), Yale University School of Medicine, 333 Cedar Street, New Haven 11, Connecticut

Long, Esmond Ray, 1946 (10), Pedlar Mills, Virginia

Long, Franklin A., 1962 (5), Department of Chemistry, Cornell University, Ithaca, New York

Longsworth, Lewis Gibson, 1947 (5), Rockefeller Institute, New York 21, New York

Longwell, Chester Ray, 1935 (6), United States Geological Survey, Menlo Park, California

Loomis, Alfred Lee, 1941 (4), The Loomis Institute for Scientific Research, Incorporated, Room 2420, 14 Wall Street, New York 5, New York

Loomis, Francis **W**heeler, 1949 (3), 804 West Illinois Street, Urbana, Illinois

Lorente de Nó, Rafael, 1950 (9), Rockefeller Institute, New York 21, New York

Lothrop, Samuel Kirkland, 1951 (11), Peabody Museum, Harvard University, Cambridge 38, Massachusetts

Lovering, Thomas Seward, 1949 (6), 8001 West 17th Avenue, Lakewood 15, Colorado

Lucas, Howard Johnson, 1957 (5), California Institute of Technology, Pasadena, California

Luria, Salvador Edward, 1960 (7), Department of Biology, Massachusetts Institute of Technology, Cambridge 39, Massachusetts

MacDonald, Gordon James Fraser, 1962 (13), Institute of Geophysics and Planetary Physics, University of California, Los Angeles 24, California

MacInnes, Duncan Arthur, 1937 (5), Rockefeller Institute, New York 21, New York

Mackey, George Whitelaw, 1962 (1), Department of Mathematics, Harvard University, Cambridge 38, Massachusetts

Mac Lane, Saunders, 1949 (1), Eckhart Hall, University of Chicago, Chicago 37, Illinois

MacLeod, Colin Munro, 1955 (10), Department of Medicine, New York University School of Medicine, 550 First Avenue, New York 16, New York

Magoun, Horace Winchell, 1955 (9), Department of Anatomy, University of California Medical Center, Los Angeles 24, California

Mangelsdorf, Paul Christoph, 1945 (7), Botanical Museum, Harvard University, Cambridge 38, Massachusetts

Mann, Frank Charles, 1950 (9), 605 11th Street, S. W., Rochester, Minnesota

Mark, Herman Francis, 1961 (5), Polymer Research Institute, Polytechnic Institute of Brooklyn, Brooklyn 1, New York

Marshak, Robert Eugene, 1958 (3), Department of Physics and Astronomy, University of Rochester, Rochester 20, New York

Marshall, Eli Kennerly, Jr., 1943 (9), Department of Medicine, Johns Hopkins Hospital, Baltimore 5, Maryland

Marvel, Carl Shipp, 1938 (5), Department of Chemistry, University of Arizona, Tucson, Arizona

Maxcy, Kenneth Fuller, 1950 (10), 700 St. George's Road, Baltimore 10, Maryland

Mayall, Nicholas Ulrich, 1949 (2), Kitt Peak National Observatory, 950 North Cherry Avenue, Tucson, Arizona

Mayer, Joseph Edward, 1946 (5), School of Science and Engineering, University of California, San Diego, La Jolla, California

Mayer, Maria Goeppert, 1956 (3), School of Science and Engineering, University of California, San Diego, La Jolla, California

Maynard, Leonard Amby, 1944 (14), Savage Hall, Cornell University, Ithaca, New York

Mayr, Ernst, 1954 (8), Museum of Comparative Zoology at Harvard College, Oxford Street, Cambridge 38, Massachusetts

Mazia, Daniel, 1960 (8), Department of Zoology, University of California, Berkeley 4, California

McClintock, Barbara, 1944 (7), Carnegie Institution of Washington, Cold Spring Harbor, Long Island, New York

McCollum, Elmer Verner, 1920 (14), Gilman Hall, Johns Hopkins University, Baltimore 18, Maryland

McElvain, Samuel Marion, 1949 (5), Department of Chemistry, University of Wisconsin, Madison 6, Wisconsin

McMaster, Philip Duryeé, 1952 (10), Rockefeller Institute, New York 21, New York

McMillan, Edwin Mattison, 1947 (3), Lawrence Radiation Laboratory, University of California, Berkeley 4, California

McShane, Edward James, 1948 (1), Department of Mathematics, University of Virginia, Charlottesville, Virginia

Meek, Walter Joseph, 1947 (9), Department of Physiology, University of Wisconsin, Madison 6, Wisconsin

Meggers, William Frederick, 1954 (3), 2904 Brandywine Street, N. W., Washington 8, D. C.

Mehl, Robert Franklin, 1958 (4), Beethovenstrasse 32, Zurich 2, Switzerland

Menzel, Donald Howard, 1948 (2), Harvard College Observatory, Cambridge 38, Massachusetts

Metz, Charles William, 1948 (8), P. O. Box 714, Woods Hole, Massachusetts

Meyer, Karl Friederich, 1940 (10), George Williams Hooper Foundation, University of California Medical Center, San Francisco 22, California

Miles, Walter Richard, 1933 (12), Box 100, Naval Medical Research Laboratory, U. S. N. Submarine Base, Groton, Connecticut

Miller, Alden Holmes, 1957 (8), Museum of Vertebrate Zoology, University of California, Berkeley 4, California

Miller, Charles Phillip, 1956 (10), Department of Medicine, University of Chicago, Chicago 37, Illinois

Miller, George Armitage, 1962 (12), Center for Cognitive Studies, Harvard University, 61 Kirkland Street, Cambridge 38, Massachusetts

Miller, Neal Elgar, 1958 (12), Department of Psychology, Yale University, 333 Cedar Street, New Haven 11, Connecticut

Minkowski, Rudolph Leo, 1959 (2), Radio Astronomy Laboratory, University of California, Berkeley 4, California

Mirsky, Alfred Ezra, 1954 (8), Rockefeller Institute, New York 21, New York

Montgomery, Deane, 1955 (1), School of Mathematics, The Institute for Advanced Study, Princeton, New Jersey

Moore, Robert Lee, 1931 (1), University of Texas, Austin 12, Texas

Moore, Stanford, 1960 (14), Rockefeller Institute, New York 21, New York

Morgan, William Wilson, 1956 (2), Yerkes Observatory, University of Chicago, Williams Bay, Wisconsin

Morrey, Charles Bradfield, Jr., 1962 (1), Department of Mathematics, University of California, Berkeley 4, California

Morse, Harold **Marston,** 1932 (1), The Institute for Advanced Study, Princeton, New Jersey

Morse, Philip McCord, 1955 (3), Department of Physics, Massachusetts Institute of Technology, Cambridge 39, Massachusetts

Movius, Hallam Leonard, Jr., 1957 (11), Peabody Museum, Harvard University, Cambridge 38, Massachusetts

Muller, Hermann Joseph, 1931 (8), 204 Jordan Hall, Indiana University, Bloomington, Indiana

Mulliken, Robert Sanderson, 1936 (3), Laboratory of Molecular Structure and Spectra, Department of Physics, University of Chicago, Chicago 37, Illinois

Munk, Walter Heinrich, 1956 (13), La Jolla Laboratories, Institute of Geophysics and Planetary Physics, University of California, San Diego, La Jolla, California

Murnaghan, Francis Dominic, 1942 (1), 6202 Sycamore Road, Baltimore 12, Maryland

Murphree, Eger Vaughan, 1950 (4), Esso Research and Engineering Company, P. O. Box 111, Linden, New Jersey

Neurath, Hans, 1961 (14), Department of Biochemistry, University of Washington, Seattle 5, Washington

Newman, Melvin Spencer, 1956 (5), 2239 Onandaga Drive, Columbus 21, Ohio

Nicholas, John Spangler, 1949 (8), Osborn Zoological Laboratory, Yale University, New Haven 11, Connecticut

Nicholson, Seth Barnes, 1937 (2), Mount Wilson and Palomar Observatories, 813 Santa Barbara Street, Pasadena, California

Niemann, Carl George, 1952 (5), Gates and Crellin Laboratories of Chemistry, California Institute of Technology, Pasadena 4, California

Nier, Alfred Otto C., 1950 (3), School of Physics, University of Minnesota, Minneapolis 14, Minnesota

Nolan, Thomas Brennan, 1951 (6), 2219 California Street, N. W., Washington 8, D. C.

Northrop, John Howard, 1934 (14), Department of Bacteriology, University of California, Berkeley 4, California

Noyes, William Albert, Jr., 1943 (5), Department of Chemistry, University of Rochester, Rochester 20, New York

O'Brien, Brian, 1954 (3), Box 117, Pomfret, Connecticut

Ochoa, Severo, 1957 (14), New York University School of Medicine, 550 First Avenue, New York 16, New York

Olson, Harry Ferdinand, 1959 (4), RCA Laboratories, David Sarnoff Research Center, Princeton, New Jersey

Oncley, John Lawrence, 1947 (14), Department of Biological Chemistry, Harvard Medical School, 25 Shattuck Street, Boston 15, Massachusetts. After September 1, 1962: Division of Biophysics, Institute of Science and Technology, University of Michigan, Ann Arbor, Michigan

Onsager, Lars, 1947 (5), Sterling Chemistry Laboratory, Yale University, New Haven, Connecticut

Opie, Eugene Lindsay, 1923 (10), Rockefeller Institute, New York 21, New York

Oppenheimer, J. Robert, 1941 (3), The Institute for Advanced Study, Princeton, New Jersey

Osterhout, Winthrop John Vanleuven, 1919 (7), Rockefeller Institute, New York 21, New York

Painter, Theophilus Shickel, 1938 (8), University of Texas, Austin 12, Texas

Pais, Abraham, 1962 (3), The Institute for Advanced Study, Princeton, New Jersey

Palade, George Emil, 1961 (8), Rockefeller Institute, New York 21, New York

Panofsky, Wolfgang K. H., 1954 (3), Stanford Linear Accelerator Center, Stanford University, Stanford, California

Paul, John Rodman, 1945 (10), Yale University School of Medicine, 333 Cedar Street, New Haven 11, Connecticut

Pauling, Linus, 1933 (5), Gates and Crellin Laboratories of Chemistry, California Institute of Technology, Pasadena, California

Pekeris, Chaim Leib, 1952 (13), Department of Applied Mathematics, The Weizmann Institute of Science, Rehovot, Israel

Petrunkevitch, Alexander, 1954 (8), Osborn Zoological Laboratory, Yale University, New Haven 11, Connecticut

Pfaffmann, Carl, 1959 (12), Walter S. Hunter Laboratory of Psychology, Brown University, Providence 12, Rhode Island

Pickering, William Hayward, 1962 (4), Jet Propulsion Laboratory, 4800 Oak Grove Drive, Pasadena, California

Pierce, John Robinson, 1955 (4), Bell Telephone Laboratories, Incorporated, Murray Hill, New Jersey

Piggot, Charles Snowden, 1946 (13), Holly Grove, Route 2, Box 63, Lexington Park, Maryland

Pitts, Robert Franklin, 1956 (9), Cornell University Medical College, 1300 York Avenue, New York 21, New York

Pitzer, Kenneth Sanborn, 1949 (5), Rice University, Houston 1, Texas

Pound, Robert Vivian, 1961 (3), Lyman Laboratory of Physics, Harvard University, Cambridge 38, Massachusetts

Press, Frank, 1958 (13), Seismological Laboratory, California Institute of Technology, 220 North San Rafael Avenue, Pasadena, California

Puck, Theodore Thomas, 1960 (10), Department of Biophysics, University of Colorado Medical Center, Denver 20, Colorado

Purcell, Edward Mills, 1951 (3), Lyman Laboratory of Physics, Harvard University, Cambridge 38, Massachusetts

Rabi, Isidor Isaac, 1940 (3), Department of Physics, Columbia University, New York 27, New York

Ramsey, Norman Foster, 1952 (3), Lyman Laboratory of Physics, Harvard University, Cambridge 38, Massachusetts

Raper, Kenneth Bryan, 1949 (7), Department of Bacteriology, University of Wisconsin, Madison 6, Wisconsin

Raymond, Arthur Emmons, 1950 (4), 73 Oakmont Drive, Los Angeles 49, California

Redfield, Alfred Clarence, 1958 (9), Maury Lane, Woods Hole, Massachusetts

Reichelderfer, Francis Wilton, 1945 (13), United States Weather Bureau, Department of Commerce, Washington 25, D. C.

Revelle, Roger Randall, 1957 (13), Room 5150, Interior Building, Department of the Interior, Washington 25, D. C.

Rhoades, Marcus Morton, 1946 (7), Department of Botany, Indiana University, Bloomington, Indiana

Rich, Arnold Rice, 1954 (10), Johns Hopkins Hospital, Baltimore 5, Maryland

Richards, Alfred Newton, 1927 (9), 737 Rugby Road, Bryn Mawr, Pennsylvania

Richards, Dickinson W., 1958 (9), Columbia University College of Physicians and Surgeons, 630 West 168th Street, New York 32, New York

Richter, Curt Paul, 1948 (12), Johns Hopkins Hospital, Baltimore 5, Maryland

Riddle, Oscar, 1939 (8), Route 4, Plant City, Florida

Riggs, Lorrin Andrews, 1961 (12), Hunter Laboratory of Psychology, Brown University, Providence 12, Rhode Island

Riker, Albert Joyce, 1951 (7), Department of Plant Pathology, University of Wisconsin, Madison 6, Wisconsin

Rittenberg, David, 1953 (14), Columbia University, College of Physicians and Surgeons, 630 West 168th Street, New York 32, New York

Robbins, William Jacob, 1940 (7), 15 Dellwood Circle, Bronxville, New York

Roberts, John D., 1956 (5), Gates and Crellin Laboratories of Chemistry, California Institute of Technology, Pasadena 4, California

Roberts, Richard Brooke, 1961 (7), Department of Terrestrial Magnetism, Carnegie Institution of Washington, 5241 Broad Branch Road, N. W., Washington 15, D. C.

Robertson, Oswald Hope, 1943 (10), 9150 Los Gatos Highway, Santa Cruz, California

Romer, Alfred Sherwood, 1944 (8), Museum of Comparative Zoology at Harvard College, Oxford Street, Cambridge 38, Massachusetts

Rose, William Cumming, 1936 (14), University of Illinois, Urbana, Illinois

Rossi, Bruno Benedetto, 1950 (3), Room 26–569, Department of Physics, Massachusetts Institute of Technology, Cambridge 39, Massachusetts

Rossini, Frederick Dominic, 1951 (5), University of Notre Dame, Notre Dame, Indiana

Rous, Francis **Peyton,** 1927 (10), Rockefeller Institute, New York 21, New York

Rouse, Irving, 1962 (11), Department of Anthropology, Yale University, Box 2114, Yale Station, New Haven, Connecticut

Rubey, William Walden, 1945 (6), Department of Geology and Institute of Geophysics, University of California, Los Angeles 24, California

Russell, Richard Joel, 1959 (6), Coastal Studies Institute, Louisiana State University, Baton Rouge 3, Louisiana

Sabin, Albert Bruce, 1951 (10), The Children's Hospital Research Foundation, University of Cincinnati College of Medicine, Elland Avenue and Bethesda, Cincinnati 29, Ohio

Savage, John Lucian, 1949 (4), 1651 Dahlia Street, Denver 20, Colorado

Sax, Karl, 1941 (7), Bishop Hollow Road, Media, Pennsylvania

Scatchard, George, 1946 (5), Department of Chemistry, Massachusetts Institute of Technology, Cambridge 39, Massachusetts

Schairer, John Frank, 1953 (6), Geophysical Laboratory, Carnegie Institution of Washington, 2801 Upton Street, N. W., Washington 8, D. C.

Schiff, Leonard Isaac, 1957 (3), Department of Physics, Stanford University, Stanford, California

Schmidt, Carl Frederic, 1949 (9), Laboratory of Pharmacology, School of Medicine, University of Pennsylvania, Philadelphia 4, Pennsylvania

Schmitt, Francis Otto, 1948 (8), Department of Biology, Massachusetts Institute of Technology, Cambridge 39, Massachusetts

Scholander, Per Fredrik, 1961 (8), Scripps Institution of Oceanography, University of California, La Jolla, California

Schwarzschild, Martin, 1956 (2), Princeton University Observatory, 14 Prospect Avenue, Princeton, New Jersey

Schwinger, Julian, 1949 (3), Department of Physics, Harvard University, Cambridge 38, Massachusetts

Seaborg, Glenn Theodore, 1948 (5), United States Atomic Energy Commission, Washington 25, D. C.

Seares, Frederick Hanley, 1919 (2), El Mirasol Hotel, Santa Barbara, California

Segrè, Emilio, 1952 (3), Department of Physics, University of California, Berkeley 4, California

Seitz, Frederick, 1951 (3), Department of Physics, University of Illinois, Urbana, Illinois

Serber, Robert, 1952 (3), Department of Physics, Columbia University, New York 27, New York

Shane, Charles **D**onald, 1961 (2), Lick Observatory, Mount Hamilton, California

Shannon, Claude Elwood, 1956 (1), Research Laboratory of Electronics, Massachusetts Institute of Technology, Cambridge 39, Massachusetts

Shapiro, Harry **L**ionel, 1949 (11), American Museum of Natural History, Central Park West at 79th Street, New York 24, New York

Shapley, Harlow, 1924 (2), Sharon Cross Road, Peterboro, New Hampshire

Shedlovsky, Theodore, 1953 (5), Rockefeller Institute, New York 21, New York

Sheehan, John Clark, 1957 (5), Department of Chemistry, Massachusetts Institute of Technology, Cambridge 39, Massachusetts

Shemin, David, 1958 (14), Columbia University College of Physicians and Surgeons, 630 West 168th Street, New York 32, New York

Sherwood, Thomas Kilgore, 1958 (4), Department of Chemical Engineering, Massachusetts Institute of Technology, Cambridge 39, Massachusetts

Shockley, William, 1951 (4), Shockley Transistor, Unit of Clevite Transistor, Stanford Industrial Park, Palo Alto, California

Shope, Richard Edwin, 1940 (10), Rockefeller Institute, New York 21, New York

Simpson, George **G**aylord, 1941 (6), Museum of Comparative Zoology at Harvard College, Cambridge 38, Massachusetts

Simpson, John Alexander, 1959 (3), The Enrico Fermi Institute for Nuclear Studies, University of Chicago, Chicago 37, Illinois

Sinnott, Edmund Ware, 1936 (7), Osborn Botanical Laboratory, Yale University, New Haven, Connecticut

Skinner, Burrhus **F**rederic, 1950 (12), Memorial Hall, Harvard University, Cambridge 38, Massachusetts

Skoog, Folke Karl, 1956 (7), Department of Botany, Birge Hall, University of Wisconsin, Madison 6, Wisconsin

Slater, John Clarke, 1932 (3), Massachusetts Institute of Technology, Cambridge 39, Massachusetts

Slepian, Joseph, 1941 (4), 1115 Lancaster Street, Pittsburgh 18, Pennsylvania

Slichter, Louis Byrne, 1944 (13), Institute of Geophysics, University of California, Los Angeles 24, California

Slipher, Vesto **M**elvin, 1921 (2), Lowell Observatory, Flagstaff, Arizona

Smadel, Joseph Edwin, 1957 (10), Laboratory of Virology and Rickettsiology, Division of Biologics Standards, National Institutes of Health, Bethesda 14, Maryland

Smith, Cyril Stanley, 1957 (4), Room 14N–317, Massachusetts Institute of Technology, Cambridge 39, Massachusetts

Smith, Emil L., 1962 (14), Laboratory for the Study of Hereditary and Metabolic Disorders, University of Utah College of Medicine, Salt Lake City 12, Utah

Smith, Lee Irvin, 1944 (5), School of Chemistry, University of Minnesota, Minneapolis 14, Minnesota

Smith, Paul Althaus, 1947 (1), Department of Mathematics, Columbia University, New York 27, New York

Smith, Philip Edward, 1939 (8), Department of Anatomy, Stanford University, Stanford, California

Smyth, Charles Phelps, 1955 (5), Department of Chemistry, Princeton University, Princeton, New Jersey

Snell, Esmond Emerson, 1955 (14), Department of Biochemistry, University of California, Berkeley 4, California

Soderberg, Carl Richard, 1947 (4), Massachusetts Institute of Technology, Cambridge 39, Massachusetts

Sonneborn, Tracy Morton, 1946 (8), 220 Jordan Hall, Indiana University, Bloomington, Indiana

Spedding, Frank Harold, 1952 (5), Box 14-A, University Station, Institute for Atomic Research, Iowa State University, Ames, Iowa

Spence, Kenneth Wartinbe, 1955 (12), Department of Psychology, State University of Iowa, Iowa City, Iowa

Spencer, Donald Clayton, 1961 (1), Fine Hall, Princeton University, P. O. Box 708, Princeton, New Jersey

Sperry, Roger Wolcott, 1960 (12), Division of Biology, California Institute of Technology, Pasadena, California

Spitzer, Lyman, Jr., 1952 (2), Princeton University Observatory, 14 Prospect Avenue, Princeton, New Jersey

Sporn, Philip, 1962 (4), American Electric Power Company, Inc., 2 Broadway, New York 8, New York

Stakman, Elvin Charles, 1934 (7), Institute of Agriculture, University of Minnesota, St. Paul 1, Minnesota

Stanley, Wendell Meredith, 1941 (14), Virus Laboratory, University of California, Berkeley 4, California

Stebbins, George Ledyard, 1952 (7), Department of Genetics, University of California, Davis, California

Stebbins, Joel, 1920 (2), 69 University Drive, Menlo Park, California

Steenrod, Norman Earl, 1956 (1), Fine Hall, Princeton University, P. O. Box 708, Princeton, New Jersey

Stein, William Howard, 1960 (14), Rockefeller Institute, New York 21, New York

Stern, Curt, 1948 (8), Department of Zoology, University of California, Berkeley 4 California

Stern, Otto, 1945 (3), 759 Cragmont Avenue, Berkeley 8, California

Stevens, Stanley Smith, 1946 (12), Memorial Hall, Harvard University, Cambridge 38, Massachusetts

Steward, Julian H., 1954 (11), Department of Anthropology, 137 Davenport Hall, University of Illinois, Urbana, Illinois

Stewart, Thomas Dale, 1962 (11), Department of Anthropology, United States National Museum, Smithsonian Institution, Washington 25, D. C.

Stockmayer, Walter Hugo, 1956 (5), Department of Chemistry, Dartmouth College, Hanover, New Hampshire

Stommel, Henry Melson, 1961 (13), Pierce Hall, Harvard University, Cambridge 38, Massachusetts

Stone, Marshall Harvey, 1938 (1), 303 Eckhart Hall, University of Chicago, Chicago 37, Illinois

Stone, Wilson Stuart, 1960 (8), Genetics Foundation, University of Texas, Austin 12, Texas

Stork, Gilbert Josse, 1960 (5), Department of Chemistry, Columbia University, New York 27, New York

Stratton, Julius Adams, 1950 (4), Massachusetts Institute of Technology, Cambridge 39, Massachusetts

Straus, William Louis, Jr., 1962 (8), Department of Anatomy, School of Medicine, Johns Hopkins University, 725 North Wolfe Street, Baltimore 5, Maryland

Street, Jabez Curry, 1953 (3), Jefferson Physical Laboratory, Harvard University, Cambridge 38, Massachusetts

Sturtevant, Alfred Henry, 1930 (8), California Institute of Technology, Pasadena 4, California

Suits, Chauncey Guy, 1946 (4), General Electric Research Laboratory, The Knolls, Schenectady, New York

Szent-Györgyi, Albert, 1956 (14), Institute for Muscle Research, P. O. Box 187, Woods Hole, Massachusetts

Szilard, Leo, 1961 (3), The Enrico Fermi Institute for Nuclear Studies, University of Chicago, Chicago 37, Illinois

Taliaferro, William Hay, 1940 (10), Argonne National Laboratory, 9700 South Cass Avenue, Argonne, Illinois

Tarbell, Dean Stanley, 1959 (5), Department of Chemistry, University of Rochester, Rochester 20, New York

Tatum, Edward Lawrie, 1952 (14), Rockefeller Institute, New York 21, New York

Taube, Henry, 1959 (5), Department of Chemistry, Stanford University, Stanford, California

Teller, Edward, 1948 (3), Lawrence Radiation Laboratory, University of California, Berkeley 4, California

Terman, Frederick Emmons, 1946 (4), Provost's Office, Stanford University, Stanford, California

Thimann, Kenneth Vivian, 1948 (7), The Biological Laboratories, Harvard University, 16 Divinity Avenue, Cambridge 38, Massachusetts

Thomas, Charles Allen, 1948 (4), Monsanto Chemical Company, 800 North Lindbergh Boulevard, St. Louis 66, Missouri

Thomas, Llewellyn Hilleth, 1958 (3), Watson Scientific Computing Laboratory, 612 West 115th Street, New York 25, New York

Thomas, Tracy Yerkes, 1941 (1), Department of Mathematics, University of California, San Diego, La Jolla, California

Tillett, William Smith, 1951 (10), New York University School of Medicine, 550 First Avenue, New York 16, New York

Timoshenko, Stephen Prokop, 1940 (4), 536 West Crescent Drive, Palo Alto, California

Tishler, Max, 1953 (5), Merck & Co., Inc., Rahway, New Jersey

Tousey, Richard, 1960 (2), United States Naval Research Laboratory, Washington 25, D. C.

Townes, Charles Hard, 1956 (3), Provost's Office, Massachusetts Institute of Technology, Cambridge 39, Massachusetts

Tukey, John Wilder, 1961 (1), Fine Hall, Princeton University, P. O. Box 708, Princeton, New Jersey

Turner, Francis John, 1956 (6), Department of Geology, University of California, Berkeley 4, California

Tuve, Merle Antony, 1946 (3), Department of Terrestrial Magnetism, Carnegie Institution of Washington, 5241 Broad Branch Road, N. W., Washington 15, D. C.

Twitty, Victor Chandler, 1950 (8), Department of Biological Sciences, Stanford University, Stanford, California

Uhlenbeck, George Eugene, 1955 (3), Rockefeller Institute, New York 21, New York

Urey, Harold Clayton, 1935 (5), University of California, San Diego, La Jolla, California

Van Allen, James Alfred, 1959 (13), Department of Physics and Astronomy, State University of Iowa, Iowa City, Iowa

Van Niel, Cornelis Bernardus, 1945 (7), Hopkins Marine Station of Stanford University, Pacific Grove, California

Van Slyke, Donald Dexter, 1921 (14), Brookhaven National Laboratory, Upton, Long Island, New York

Van Vleck, John Hasbrouck, 1935 (3), Lyman Laboratory of Physics, Harvard University, Cambridge 38, Massachusetts

Verhoogen, John, 1956 (13), Department of Geology, University of California, Berkeley 4, California

Vestine, Ernest Harry, 1954 (13), Rand Corporation, 1700 Main Street, Santa Monica, California

Vickery, Hubert Bradford, 1943 (14), Connecticut Agricultural Experiment Station, New Haven 4, Connecticut

Villard, Oswald Garrison, Jr., 1958 (13), Radioscience Laboratory, Stanford University, Stanford, California

Visscher, Maurice Bolks, 1956 (9), Department of Physiology, University of Minnesota, Minneapolis 14, Minnesota

von **Békésy, Georg**, 1956 (12), Psycho-Acoustic Laboratory, Memorial Hall, Harvard University, Cambridge 38, Massachusetts

von Kármán, Theodore, 1938 (4), 1501 South Marengo Avenue, Pasadena 5, California

Waksman, Selman Abraham, 1942 (10), Institute of Microbiology, Rutgers, The State University, New Brunswick, New Jersey

Wald, George, 1950 (14), The Biological Laboratories, Harvard University, 16 Divinity Avenue, Cambridge 38, Massachusetts

Walker, John Charles, 1945 (7), 206 Horticulture Building, University of Wisconsin, Madison 6, Wisconsin

Wall, Frederick Theodore, 1961 (5), Department of Chemistry and Chemical Engineering, University of Illinois, Urbana, Illinois

Walsh, Joseph Leonard, 1936 (1), Widener 474, Harvard University, Cambridge 38, Massachusetts

Warner, John Christian, 1956 (5), Carnegie Institute of Technology, Pittsburgh 13, Pennsylvania

Warren, Shields, 1962 (10), Cancer Research Institute, New England Deaconess Hospital, 194 Pilgrim Road, Boston 15, Massachusetts

Watson, Cecil James, 1959 (10), Department of Medicine, University of Minnesota Hospital, Minneapolis 14, Minnesota

Watson, James Dewey, 1962 (14), The Biological Laboratories, Harvard University, 16 Divinity Avenue, Cambridge 38, Massachusetts

Webster, David Locke, 1923 (3), 1830 Cowper Street, Palo Alto, California

Weinberg, Alvin Martin, 1961 (3), Oak Ridge National Laboratory, P. O. Box X, Oak Ridge, Tennessee

Weiss, Paul Alfred, 1947 (8), Rockefeller Institute, New York 21, New York

Weisskopf, Victor Frederick, 1952 (3), CERN, Geneva 23, Switzerland

Went, Frits Warmolt, 1947 (7), Missouri Botanical Garden, 2315 Tower Grove Avenue, St. Louis 10, Missouri

Wentzel, Gregor, 1959 (3), The Enrico Fermi Institute for Nuclear Studies, University of Chicago, Chicago 37, Illinois

Werkman, Chester Hamlin, 1946 (14), Department of Bacteriology, Iowa State University, Ames, Iowa

Westheimer, Frank Henry, 1954 (5), Department of Chemistry, Harvard University, 12 Oxford Street, Cambridge 38, Massachusetts

Wetmore, Alexander, 1945 (8), Smithsonian Institution, Washington 25, D. C.

Wetmore, Ralph Hartley, 1954 (7), The Biological Laboratories, Harvard University, 16 Divinity Avenue, Cambridge 38, Massachusetts. From September 1962 to June 1963: Laboratoire de Physiologie Vegetate, C.N.R.A., Route de St.-Cyr, Versailles (Seine et Oise), France

Wever, Ernest Glen, 1940 (12), 110 Eno Hall, Princeton University, Princeton, New Jersey

Wheeler, John Archibald, 1952 (3), Palmer Physical Laboratory, Princeton University, Princeton, New Jersey

Whipple, Fred Lawrence, 1959 (2), Astrophysical Observatory, Smithsonian Institution, 60 Garden Street, Cambridge 38, Massachusetts

Whipple, George Hoyt, 1929 (10), School of Medicine and Dentistry, University of Rochester, 260 Crittenden Boulevard, Rochester 20, New York

Whitford, Albert Edward, 1954 (2), Lick Observatory, Mount Hamilton, California

Whitney, Hassler, 1945 (1), The Institute for Advanced Study, Princeton, New Jersey

Whyburn, Gordon Thomas, 1951 (1), Department of Mathematics, University of Virginia, Charlottesville, Virginia

Wiesner, Jerome Bert, 1960 (4), The White House, Washington, D. C.

Wiggers, Carl John, 1951 (9), Terrace Park Apartments, 13800 Terrace Road, East Cleveland 12, Ohio

Wigner, Eugene Paul, 1945 (3), Fine Hall, Princeton University, Princeton, New Jersey

Willey, Gordon Randolph, 1960 (11), Peabody Museum, Harvard University, Cambridge 38, Massachusetts

Williams, Carroll Milton, 1960 (8), The Biological Laboratories, Harvard University, 16 Divinity Avenue, Cambridge 38, Massachusetts

Williams, Howel, 1950 (6), Department of Geology, University of California, Berkeley 4, California

Williams, John Harry, 1961 (3), School of Physics, University of Minnesota, Minneapolis 14, Minnesota

Williams, John Warren, 1952 (5), Department of Chemistry, University of Wisconsin, Madison 6, Wisconsin

Williams, Robert R., 1945 (5), 45 Woodland Avenue, Summit, New Jersey

Williams, Robley Cook, 1955 (14), Virus Laboratory, University of California, Berkeley 4, California

Williams, Roger John, 1946 (14), Clayton Foundation Biochemical Institute, University of Texas, Austin 12, Texas

Willier, Benjamin Harrison, 1945 (8), Department of Biology, Johns Hopkins University, Baltimore 18, Maryland

Wilson, David Wright, 1955 (14), Department of Biochemistry, School of Medicine, University of Pennsylvania, Philadelphia 4, Pennsylvania

Wilson, Edgar Bright, Jr., 1947 (5), Department of Chemistry, Harvard University, 12 Oxford Street, Cambridge 38, Massachusetts

Wilson, Edwin Bidwell, 1919 (3), 42 Brington Road, Brookline 46, Massachusetts

Wilson, Olin Chaddock, 1960 (2), Mount Wilson and Palomar Observatories, 813 Santa Barbara Street, Pasadena, California

Wilson, Perry William, 1955 (7), Department of Bacteriology, University of Wisconsin, Madison 6, Wisconsin

Wilson, Robert Erastus, 1947 (4), United States Atomic Energy Commission, Washington 25, D. C.

Wilson, Robert Rathbun, 1957 (3), Laboratory of Nuclear Studies, Cornell University, Ithaca, New York

Winstein, Saul, 1955 (5), Department of Chemistry, University of California, Los Angeles 24, California

Wintersteiner, Oskar, 1950 (14), Squibb Institute for Medical Research, New Brunswick, New Jersey

Wolfrom, Melville Lawrence, 1950 (5), Department of Chemistry, The Ohio State University, 88 West 18th Avenue, Columbus 10, Ohio

Wood, Harland Goff, 1953 (14), Department of Biochemistry, School of Medicine, Western Reserve University, Cleveland 6, Ohio

Wood, William Barry, Jr., 1959 (10), School of Medicine, Johns Hopkins University, 725 North Wolfe Street, Baltimore 5, Maryland

Woodring, Wendell Phillips, 1946 (6), United States National Museum, Washington 25, D. C.

Woodward, Robert Burns, 1953 (5), Department of Chemistry, Harvard University, 12 Oxford Street, Cambridge 38, Massachusetts

Woodworth, Robert Sessions, 1921 (12), 400 West 119th Street, New York 27, New York

Woolley, Dilworth Wayne, 1952 (14), Rockefeller Institute, New York 21, New York

Woolsey, Clinton Nathan, 1960 (9), Laboratory of Neurophysiology, 283 Medical Sciences Building, University of Wisconsin, Madison 6, Wisconsin

Wright, Sewall Green, 1934 (8), Department of Genetics, University of Wisconsin, Madison 6, Wisconsin

Wu, Chien-Shiung, 1958 (3), Department of Physics, Columbia University, New York 27, New York

Wulf, Oliver Reynolds, 1949 (13), United States Weather Bureau, Gates and Crellin Laboratories of Chemistry, California Institute of Technology, Pasadena 4, California

Wyckoff, Ralph Walter Graystone, 1949 (5), Department of Physics, University of Arizona, Tucson 25, Arizona

Yoder, Hatten Schuyler, Jr., 1958 (6), Geophysical Laboratory, Carnegie Institution of Washington, 2801 Upton Street, N. W., Washington 8, D. C.

Yost, Don Merlin Lee, 1944 (5), California Institute of Technology, Pasadena 4, California

Young, William Gould, 1951 (5), Department of Chemistry, University of California, Los Angeles 24, California

Zacharias, Jerrold Reinach, 1957 (3), Department of Physics, Massachusetts Institute of Technology, Cambridge 39, Massachusetts

Zachariasen, Frederik William Houlder, 1949 (3), Division of the Physical Sciences, University of Chicago, Chicago 37, Illinois

Zariski, Oscar, 1944 (1), Department of Mathematics, Harvard University, 2 Divinity Avenue, Cambridge 38, Massachusetts

Zener, Clarence Melvin, 1959 (4), Westinghouse Research Laboratories, Beulah Road, Churchill Borough, Pittsburgh 35, Pennsylvania

Zimm, Bruno Hasbrouck, 1958 (5), School of Science and Engineering, University of California, San Diego, La Jolla, California

Zinn, Walter Henry, 1956 (4), Combustion Engineering, Inc., Nuclear Division, Windsor, Connecticut

Zirkle, Raymond Elliott, 1959 (8), Committee on Biophysics, University of Chicago, 5640 Ellis Avenue, Chicago 37, Illinois

Zworykin, Vladimir Kosma, 1943 (4), RCA Laboratories, David Sarnoff Research Center, Princeton, New Jersey

Zygmund, Antoni, 1960 (1), Department of Mathematics, University of Chicago, Chicago 37, Illinois

Number of Members July 1, 1962: 653.

MEMBERS EMERITI

Albright, Fuller, 1952 (10), 271 Goddard Avenue, Brookline 46, Massachusetts

Bailey, Irving Widmer, 1929 (7), Harvard University Herbarium, 22 Divinity Avenue, Cambridge 38, Massachusetts

Coble, Arthur Byron, 1924 (1), Lykens Hotel, Lykens, Pennsylvania

Cole, Rufus, 1922 (10), Mt. Kisco, New York

Coolidge, William David, 1925 (3), 1480 Lenox Road, Schenectady 8, New York

Hartman, Carl Gottfried, 1937 (8), 219 Norwood Avenue, North Plainfield, New Jersey

Kelley, Walter Pearson, 1943 (6), 108 Hilgard Hall, University of California, Berkeley 4, California

Kidder, Alfred Vincent, 1936 (11), 41 Holden Street, Cambridge 38, Massachusetts

Saunders, Frederick Albert, 1925 (3), South Hadley, Massachusetts

Schultz, Adolph Hans, 1939 (11), Anthropologisches Institut, Künstlergasse 15, Zurich, Switzerland

Struve, Otto, 1937 (2), 853 Station Place, Berkeley 7, California

Tyzzer, Ernest Edward, 1942 (10), 484 Water Street, Wakefield, Massachusetts

Vandiver, Harry Shultz, 1934 (1), Box 7881, University of Texas, Austin 12, Texas

Number of Members Emeriti July 1, 1962: 13.

FOREIGN ASSOCIATES

The number in parentheses following the year of election indicates association within the Sections of the National Academy of Sciences.

Adrian of Cambridge, Edgar Douglas, Baron, 1941 (9), Trinity College, Cambridge, England

Alexandroff, Paul A., 1947 (1), Mathematical Institute of the Academy of Sciences of the U. S. S. R., Bolshaya Kalushskaya 19, Moscow, U. S. S. R.

Amaldi, Edoardo, 1962 (3), University of Rome, Piazzale delle Scienze, 5, Rome, Italy

Ambartsumian, Victor Amazaspovich, 1959 (2), Burakan Astronomical Observatory, Erevan, Armenia, U.S.S.R.

Bailey, Sir Edward, 1944 (6), 76 Hampstead Way, London, N. W. 11, England

Bartlett, Sir Frederic Charles, 1947 (12), 161 Huntingdon Road, Cambridge, England

Best, Charles Herbert, 1950 (9), Banting and Best Department of Medical Research, University of Toronto, Toronto, Canada

Bohr, Niels, 1925 (3), Institute for Theoretical Physics, Blegdamsvej 15, Copenhagen, Denmark

Born, Max, 1955 (3), Marcard Strasse 4, Bad Pyrmont, Germany

Bragg, Sir William **Lawrence,** 1945 (3), The Royal Institution, 21 Albemarle Street, London, W. 1, England

de Broglie, Prince Louis, 1948 (3), 94 Rue Perronet, Neuilly-sur-Seine, France

Brun, Edmond Antoine, 1960 (4), University of Paris, 8–10, place du Commerce, Paris XV, France

Bullard, Sir Edward Crisp, 1959 (13), Madingley Rise, Madingley Road, Cambridge, England

Bullen, Keith Edward, 1961 (13), Department of Applied Mathematics, University of Sydney, Sydney, Australia

Burnet, Sir Macfarlane, 1954 (10), The Walter and Eliza Hall Institute of Medical Research, Melbourne, Australia

Caso, Alfonso, 1943 (11), Avenida Central 234, Tlacopac, Villa Obregón, Mexico 20, D. F.

Chapman, Sydney, 1946 (13), High Altitude Observatory, Boulder, Colorado, U. S. A.

Dale, Sir Henry Hallett, 1940 (9), The Wellcome Trust, 52 Queen Anne Street, London, W. 1, England

Dirac, Paul Adrien Maurice, 1949 (1), Department of Mathematics, St. John's College, Cambridge, England

Ephrussi, Boris, 1961 (7), Developmental Biology Center, Western Reserve University, 2127 Cornell Road, Cleveland 6, Ohio, U.S.A.

Eskola, Pentti Eelis, 1951 (6), Helsinki University, Snellmanink. 5, Helsinki, Finland

Fisher, Sir Ronald Aylmer, 1948 (8), Division of Statistics, C.S.I.R.O., University of Adelaide, Adelaide, South Australia

von Frisch, Karl, 1951 (8), The Zoological Institute, University of Munich, Munich, Germany

Geijer, Per, 1958 (6), Agnevaegen 5, Djursholm I, Sweden

Hadamard, Jacques, 1926 (1), 12 Rue Emile Faguet, Paris XIV, France

Hartmann, Max, 1959 (8), Buchenbühl, Post Weiler im Allgäu, West Germany

Heisenberg, Werner, 1961 (3), Max Planck Institut für Physik und Astrophysik, Aumeisterstrasse 6, Munich 23, Germany

Hill, Archibald Vivian, 1941 (9), 16 Bishopswood Road, Highgate, London, N.6, England

Hinshelwood, Sir Cyril Norman, 1960 (5), Department of Chemistry, Exeter College, Oxford, England

Hodge, William Vallance Douglas, 1959 (1), The Master's Lodge, Pembroke College, Cambridge, England

Hopf, Heinz, 1957 (1), Swiss Federal Institute of Technology, Zurich, Switzerland

Houssay, Bernardo Alberto, 1940 (9), Viamonte 2790, Buenos Aires, Argentina

Jeffreys, Sir Harold, 1945 (13), St. John's College, Cambridge, England

Kapitza, Peter Leonidovich, 1946 (3), S. I. Vavilov Institute of Physical Problems, Academy of Sciences of the U.S.S.R., Moscow, U.S.S.R.

Karrer, Paul, 1945 (5), Spyristeig 30, Zurich 7, Switzerland

Kihara, Hitoshi, 1958 (7), National Institute of Genetics, Misima, Japan

Landau, Lev Davidovich, 1960 (3), S. I. Vavilov Institute of Physical Problems, Academy of Sciences of the U.S.S.R., Moscow, U.S.S.R.

Leloir, Luis F., 1960 (14), Instituto de Investigaciones Bioquimicas, Obligado 2490, Buenos Aires, Argentina

Levi, Giuseppe, 1940 (8), Instituto di Anatomia Umana, Corso Massimo D'Azeglio, 52, Turin, Italy

Lim, Robert K. S., 1942 (9), Medical Sciences Research Laboratory, Miles Laboratories, Inc., Elkhart, Indiana, U. S. A.

Lindblad, Bertil, 1955 (2), Stockholm Observatory, Saltsjöbaden, Sweden

Lwoff, André, 1955 (9), Institut Pasteur, Paris XV, France

Lynen, Feodor, 1962 (14), Max-Planck-Institut für Zellchemie, Karlstrasse 23–25, Munich 2, Germany

Michotte, Albert Edouard (Baron Michotte van den Berck), 1956 (12), University of Louvain, Louvain, Belgium

Mott, Nevill Francis, 1957 (3), University of Cambridge, Cavendish Laboratory, Free School Lane, Cambridge, England

Oort, Jan Hendrik, 1953 (2), Observatory of Leiden, Leiden, The Netherlands

Penfield, Wilder, 1953 (10), Montreal Neurological Institute, 3801 University Street, Montreal 2, Canada

Penney, Sir William George, 1962 (4), United Kingdom Atomic Energy Authority, Charles II Street, London, S. W. 1, England

Piéron, Henri, 1949 (12), Institut de Psychologie, 28, rue Serpente, Paris VI, France

Portevin, Albert M. G. R., 1954 (4), 21, Boulevard de Beauséjour, Paris XVI, France

Prelog, Vladimir, 1961 (5), Laboratorium für organische Chemie, Eidgenossische Technische Hochschule, Zurich, Switzerland

Reichstein, Tadeus, 1952 (5), Organisch-chemische Anstalt, St. Johanns-Ring 19, Basel, Switzerland

Robertson, Rutherford **Ness,** 1962 (7), Department of Botany, University of Adelaide, Adelaide, South Australia

Robinson, Sir Robert, 1934 (5), 170 Piccadilly, London, W. 1, England

Ruzicka, Leopold, 1944 (5), Department of Organic Chemistry, Institute of Technology, Zurich, Switzerland

Southwell, Sir Richard Vynne, 1943 (4), The Old House, Trumpington, Cambridge, England

Steacie, Edgar William Richard, 1957 (5), National Research Council, Ottawa, Canada

Svedberg, The, 1945 (5), Fysikalisk-Kemiska Institutionen, Uppsala University, Uppsala, Sweden

Taylor, Sir Geoffrey Ingram, 1945 (1), Trinity College, Cambridge, England

Theorell, Axel **Hugo,** 1957 (14), Nobel Institute of Medicine, Solnavagen 1, Stockholm 60, Sweden

Tiselius, Arne W. K., 1949 (14), Institute of Biochemistry, Uppsala University, Uppsala, Sweden

Todd, Sir Alexander Robertus, 1955 (5), University of Cambridge, University Chemical Laboratory, Pembroke Street, Cambridge, England

Vallée-Poussin, C. de la, 1929 (1), 42, Avenue du Houx, Boitsfort, Belgium

Vening Meinesz, Felix Andries, 1939 (13), Potgieterlaan 5, Amersfoort, The Netherlands

Watson, D. M. S., 1938 (8), University College, Gower Street, London, W.C. 1, England

Winge, Öjvind, 1949 (14), Department of Physiology, Carlsberg Laboratory, Copenhagen (Valby), Denmark

Yukawa, Hideki, 1949 (3), Yukawa Hall, Kyoto University, Kyoto, Japan

Number of Foreign Associates July 1, 1962: 67.

SECTIONS

(1) *Mathematics*—39 members

Whitney, Hassler, *Chairman* (1964)
Ahlfors, L. V.
Albert, A. A.
Alexander, J. W.
Bochner, S.
Brauer, R. D.
Chern, S. S.
Courant, R.
Doob, J. L.
Douglas, Jesse
Eilenberg, S.
Eisenhart, L. P.
Evans, G. C.
Feller, William
Friedrichs, K. O.
Gödel, Kurt
Hille, Einar
Jacobson, Nathan
Lefschetz, Solomon
Lin, C. C.
Mackey, George W.
Mac Lane, Saunders
McShane, E. J.
Montgomery, Deane
Moore, R. L.
Morrey, C. B., Jr.
Morse, Marston
Murnaghan, F. D.
Shannon, C. E.
Smith, Paul A.
Spencer, D. C.
Steenrod, N. E.
Stone, M. H.
Thomas, T. Y.
Tukey, John W.
Walsh, J. L.
Whyburn, G. T.
Zariski, O.
Zygmund, Antoni

Foreign Associates

Alexandroff, P. A.
Dirac, P. A. M.
Hadamard, Jacques
Hodge, W. V. D.
Hopf, Heinz
Taylor, Sir Geoffrey
Vallée-Poussin, C. de la

(2) *Astronomy*—29 members

Menzel, D. H., *Chairman* (1965)
Abbot, C. G.
Aller, L. H.
Babcock, H. D.
Babcock, H. W.
Bowen, I. S.
Brouwer, Dirk
Chandrasekhar, S.
Clemence, G. M.
Goldberg, Leo
Greenstein, J. L.
Herget, Paul
Joy, A. H.
Kuiper, G. P.
Mayall, N. U.
Minkowski, R. L.
Morgan, W. W.
Nicholson, S. B.
Schwarzschild, M.
Seares, F. H.
Shane, C. D.
Shapley, Harlow
Slipher, V. M.
Spitzer, Lyman, Jr.
Stebbins, Joel
Tousey, Richard
Whipple, F. L.
Whitford, A. E.
Wilson, Olin C.

Foreign Associates

Ambartsumian, V.
Lindblad, Bertil
Oort, Jan Hendrik

(3) *Physics*—94 members

Allison, S. K., *Chairman* (1963)
Alvarez, L. W.
Anderson, C. D.
Anderson, H. L.
Bacher, R. F.
Bainbridge, K. T.
Bardeen, John
Beams, J. W.
Bethe, H. J.
Birge, R. T.
Bleakney, Walker
Bloch, Felix
Bloembergen, N.
Bradbury, N. E.
Brattain, W. H.
Breit, Gregory
Brillouin, Leon
Brode, R. B.
Chamberlain, Owen
Chew, Geoffrey F.
Coblentz, W. W.
Condon, E. U.
Dennison, D. M.
Deutsch, M.
DuBridge, L. A.
DuMond, J. W. M.
Dunning, J. R.
Epstein, P. S.
Feynman, R. P.
Fowler, W. A.
Franck, James
Gamow, George

Gell-Mann, Murray
Glaser, Donald A.
Goldhaber, M.
Goudsmit, S. A.
Herb, R. G.
Herzfeld, K. F.
Hofstadter, R.
Houston, W. V.
Hull, A. W.
Inghram, Mark G.
Kemble, E. C.
Kerst, D. W.
Kittel, C.
Kusch, P.
Lamb, W. E., Jr.
Land, E. H.
Lauritsen, C. C.
Loomis, F. W.
Marshak, R. E.
Mayer, M. G.
McMillan, E. M.
Meggers, W. F.
Morse, P. M.
Mulliken, R. S.
Nier, A. O. C.
O'Brien, Brian
Oppenheimer, J. R.
Pais, A.
Panofsky, W. K. H.
Pound, R. V.
Purcell, E. M.
Rabi, I. I.
Ramsey, N. F.
Rossi, Bruno
Schiff, L. I.
Schwinger, Julian
Segrè, E.
Seitz, Frederick
Serber, R.
Simpson, J. A.
Slater, J. C.
Stern, Otto
Street, J. C.
Szilard, Leo
Teller, Edward
Thomas, L. H.
Townes, C. H.
Tuve, M. A.
Uhlenbeck, G. E.
Van Vleck, J. H.
Webster, D. L.
Weinberg, Alvin M.
Weisskopf, V. F.
Wentzel, Gregor
Wheeler, J. A.
Wigner, E. P.
Williams, John H.
Wilson, Edwin B.
Wilson, Robert R.
Wu, C. S.
Zacharias, J. R.
Zachariasen, W. H

Foreign Associates

Amaldi, Edoardo
Bohr, Niels
Born, Max
Bragg, Sir Lawrence
de Broglie, Prince Louis
Heisenberg, Werner
Kapitza, P. L.
Landau, L. D.
Mott, N. F.
Yukawa, Hideki

(4) *Engineering*—50 members

Sherwood, T. K., *Chairman* (1965)
Astin, A. V.
Bain, E. C.
Benedict, Manson
Bode, H. W.
Briggs, L. J.
Brooks, Harvey
Bush, Vannevar
Chipman, John
Curme, G. O., Jr.
Darken, L. S.
Den Hartog, J. P.
Draper, C. S.
Dryden, H. L.
Fisk, J. B.
Fletcher, Harvey
Foote, P. D.
Gibbs, W. F.
Gilliland, E. R.
Greenewalt, C. H.
Hoover, Herbert
Hunsaker, J. C.
Jeffries, Zay
Kelly, M. J.
Kinzel, A. B.
Lewis, W. K.
Loomis, A. L.
Mehl, R. F.
Murphree, E. V.
Olson, Harry F.
Pickering, W. H.
Pierce, J. R.
Raymond, A. E.
Savage, J. L.
Shockley, W.
Slepian, Joseph
Smith, C. S.
Soderberg, C. R.
Sporn, Philip
Stratton, J. A.
Suits, C. G.
Terman, F. E.
Thomas, C. A.
Timoshenko, Stephen
von Kármán, T.
Wiesner, J. B.
Wilson, Robert E.
Zener, Clarence
Zinn, W. H.
Zworykin, V. K.

Foreign Associates

Brun, Edmond A.
Penney, Sir William
Portevin, Albert M. G. R.
Southwell, Sir Richard V.

(5) *Chemistry*—95 members

Niemann, Carl, *Chairman* (1965)
Adams, Roger
Badger, R. M.
Baker, W. O.
Bartlett, P. D.
Blomquist, A. T.
Boekelheide, V.
Bolton, E. K.
Brewer, Leo
Brode, W. R.
Brown, H. C.
Calvin, Melvin
Conant, J. B.
Cope, A. C.
Cram, Donald J.
Crawford, Bryce, Jr.
Daniels, Farrington
Davidson, N.
Debye, Peter
Djerassi, Carl
Doering, William
Elderfield, R. C.
Emmett, P. H.
Eyring, Henry
Ferry, John D.
Fieser, L. F.
Flory, P. J.
Folkers, Karl
Fuoss, R. M.
Fuson, R. C.
Gates, M.
Giauque, W. F.
Gilman, Henry
Gutowsky, H. S.
Hammett, L. P.
Harned, H. S.
Hauser, C. R.
Hendricks, S. B.
Hildebrand, J. H.
Hirschfelder, J. O.
Hornig, D. F.
Jacobs, W. A.
Johnson, J. R.
Johnson, W. S.
Keyes, F. G.
Kimball, G. E.
Kistiakowsky, G. B.
Kolthoff, I. M.
Kraus, C. A.
La Mer, V. K.
Leonard, N. J.
Libby, W. F.
Lind, S. C.
Lipscomb, W. N.
Long, Franklin A.
Longsworth, L. G.
Lucas, H. J.
MacInnes, D. A.
Mark, H. F.
Marvel, C. S.
Mayer, J. E.
McElvain, S. M.
Newman, M. S.
Noyes, W. A., Jr.
Onsager, Lars
Pauling, Linus
Pitzer, K. S.
Roberts, John D.
Rossini, F. D.
Scatchard, George
Seaborg, G. T.
Shedlovsky, Theodore
Sheehan, J. C.
Smith, L. I.
Smyth, C. P.
Spedding, F. H.
Stockmayer, W. H.
Stork, Gilbert
Tarbell, D. S.
Taube, Henry
Tishler, Max
Urey, H. C.
Wall, Frederick T.
Warner, J. C.
Westheimer, F. H.
Williams, J. W.
Williams, Robert R.
Wilson, E. Bright, Jr.
Winstein, Saul
Wolfrom, M. L.
Woodward, R. B.
Wyckoff, R. W. G.
Yost, D. M.
Young, W. G.
Zimm, B. H.

Foreign Associates

Hinshelwood, Sir C. N.
Karrer, Paul
Prelog, Vladimir
Reichstein, Tadeus
Robinson, Sir Robert
Ruzicka, Leopold
Steacie, E. W. R.
Svedberg, The
Todd, Sir Alexander

(6) *Geology*—35 members

Hess, H. H., *Chairman* (1963)
Abelson, P. H.
Allen, E. T.
Anderson, C. A.
Birch, Francis
Blackwelder, Eliot
Bradley, W. H.
Bramlette, M. N.
Bucher, W. H.
Buddington, A. F.
Buerger M. J.
Chaney, R. W.
Cloos, Ernst
Cloud, Preston E., Jr.
Dunbar, C. O.
Garrels, R. M.
Gilluly, James
Gregory, W. K.
Hedberg, H. D.
Hewett, D. F.
Hubbert, M. King
James, Harold L.
Knopf, Adolph

Krauskopf, K. B.
Longwell, C. R.
Lovering, T. S.
Nolan, T. B.
Rubey, W. W.
Russell, R. J.
Schairer, J. F.
Simpson, G. G.
Turner, F. J.
Williams, Howel
Woodring, W. P.
Yoder, H. S., Jr.

Foreign Associates

Bailey, Sir Edward
Eskola, Pentti
Geijer, Per

(7) *Botany*—48 members

Thimann, K. V., *Chairman* (1965)
Anderson, Edgar
Arnold, William A.
Arnon, Daniel I.
Barker, H. A.
Beadle, G. W.
Benzer, Seymour
Blinks, L. R.
Bonner, David M.
Bonner, James
Borthwick, H. A.
Braun, A. C.
Brink, R. A.
Burkholder, P. R.
Burris, R. H.
Chandler, W. H.
Clausen, Jens
Cleland, R. E.
Couch, J. N.
Delbrück, Max
Esau, Katherine
Fred, E. B.
Goddard, D. R.
Hershey, A. D.
Hollaender, A.
Horsfall, J. G.
Jones, D. F.
Kaufmann, B. P.
Kramer, Paul J.
Luria, S. E.
Mangelsdorf, P. C.
McClintock, Barbara
Osterhout, W. J. V.
Raper, K. B.
Rhoades, M. M.
Riker, A. J.
Robbins, W. J.
Roberts, R. B.
Sax, Karl
Sinnott, E. W.
Skoog, Folke
Stakman, E. C.
Stebbins, G. L.
Van Niel, C. B.
Walker, J. C.
Went, F. W.
Wetmore, R. H.
Wilson, P. W.

Foreign Associates

Ephrussi, Boris
Kihara, H.
Robertson, R. N.

(8) *Zoology and Anatomy*—58 members

Mayr, Ernst, *Chairman* (1964)
Bartelmez, G. W.
Bigelow, H. B.
Bloom, William
Bodenstein, D. H.
Bodian, David
Briggs, Robert
Burns, R. K.
Cleveland, L. R.
Colbert, E. H.
Corner, G. W.
Crow, James F.
Danforth, C. H.
Demerec, Milislav
Dobzhansky, Th.
Dunn, L. C.
Emerson, Alfred E.
Friedmann, Herbert
Glass, Bentley
Griffin, D. R.
Hamburger, Viktor
Haskins, C. P.
Hisaw, F. L.
Holtfreter, J.
Hubbs, C. L.
Hutchinson, G. E.
Hyman, Libbie
Irwin, M. R.
Jacobs, M. H.
Kellogg, Remington
Lerner, I. M.
Lewis, W. H.
Mazia, Daniel
Metz, C. W.
Miller, A. H.
Mirsky, A. E.
Muller, H. J.
Nicholas, J. S.
Painter, T. S.
Palade, G. E.
Petrunkevitch, A.
Riddle, Oscar
Romer, A. S.
Schmitt, F. O.
Scholander, Per F.
Smith, Philip E.
Sonneborn, T. M.
Stern, Curt
Stone, W. S.
Straus, W. L., Jr.

Sturtevant, A. H.
Twitty, V. C.
Weiss, Paul
Wetmore, Alexander
Williams, C. M.
Willier, B. H.
Wright, Sewall
Zirkle, R. E.

Foreign Associates

Fisher, Sir Ronald
von Frisch, Karl
Hartmann, Max
Levi, Giuseppe
Watson, D. M. S.

(9) *Physiology*—35 members

Long, C. N. H., *Chairman* (1963)
Astwood, E. B.
Aub, Joseph C.
Bard, Philip
Brink, Frank, Jr.
Bronk, Detlev W.
Cole, K. S.
Comroe, Julius H., Jr.
Cournand, André
Davis, Hallowell
Erlanger, Joseph
Evans, H. M.
Fenn, W. O.
Forbes, Alexander
Gasser, H. S.
Gerard, R. W.
Hartline, H. K.
Hastings, A. B.
Kety, Seymour S.
Landis, E. M.
Lloyd, D. P. C.
Loeb, R. F.
Lorente de Nó, R.
Magoun, H. W.
Mann, Frank
Marshall, E. K., Jr.
Meek, W. J.
Pitts, R. F.
Redfield, A. C.
Richards, A. N.
Richards, D. W.
Schmidt, C. F.
Visscher, M. B.
Wiggers, C. J.
Woolsey, C. N.

Foreign Associates

Lord Adrian
Best, C. H.
Dale, Sir Henry
Hill, A. V.
Houssay, B. A.
Lim, Robert K. S.
Lwoff, André

(10) *Pathology and Microbiology*—44 members

Shope, R. E., *Chairman* (1963)
Armstrong, Charles
Bailey, P.
Blalock, Alfred
Cannon, P. R.
Castle, W. B.
Coggeshall, L. T.
Coons, Albert H.
Dalldorf, Gilbert
Dingle, J. H.
Dochez, A. R.
Dragstedt, L. R.
Dubos, R. J.
Dulbecco, Renato
Enders, J. F.
Francis, Thomas, Jr.
Goebel, W. F.
Heidelberger, Michael
Horsfall, F. L., Jr.
Hotchkiss, R. D.
Huebner, R. J.
Huggins, C. B.
Little, C. C.
Long, E. R.
MacLeod, C. M.
Maxcy, K. F.
McMaster, P. D.
Meyer, K. F.
Miller, C. P.
Opie, E. L.
Paul, John R.
Puck, T. T.
Rich, A. R.
Robertson, O. H.
Rous, Peyton
Sabin, Albert B.
Smadel, J. E.
Taliaferro, W. H.
Tillett, W. S.
Waksman, S. A.
Warren, Shields
Watson, C. J.
Whipple, G. H.
Wood, W. Barry, Jr.

Foreign Associates

Burnet, Sir Macfarlane
Penfield, Wilder

(11) *Anthropology*—12 members

Haury, Emil W., *Chairman* (1963)
Albright, W. F.
Coon, C. S.
Hallowell, A. I.
Herskovits, M. J.
Lothrop, S. K.
Movius, H. L., Jr.
Rouse, Irving
Shapiro, H. L.
Steward, J. H.
Stewart, T. D.
Willey, G. R.

Foreign Associate

Caso, Alfonso

(12) *Psychology*—24 members

Hilgard, E. R., *Chairman* (1965)
Beach, F. A.
Boring, E. G.
Carmichael, Leonard
Galambos, R.
Graham, C. H.
Guilford, J. P.
Harlow, H. F.
Klüver, Heinrich
Köhler, Wolfgang
Lindsley, D. B.
Miles, W. R.
Miller, George A.
Miller, N. E.
Pfaffmann, Carl
Richter, C. P.
Riggs, Lorrin A.
Skinner, B. F.
Spence, K. W.
Sperry, R. W.
Stevens, S. S.
v. Békésy, Georg
Wever, E. G.
Woodworth, R. S.

Foreign Associates

Bartlett, Sir Frederic
Michotte, Albert E.
Piéron, Henri

(13) *Geophysics*—33 members

Slichter, L. B., *Chairman* (1963)
Adams, L. H.
Benioff, Hugo
Berkner, L. V.
Bjerknes, J.
Booker, H. G.
Brown, Harrison
Byerly, Perry
Byers, H. R.
Eckart, Carl
Elsasser, W. M.
Ewing, Maurice
Forbush, Scott E.
Friedman, H.
Griggs, D. T.
Gunn, Ross
Haurwitz, B.
Iselin, C. O'D.
Kaplan, Joseph
Lambert, W. D.
MacDonald, G. J. F.
Munk, W. H.
Pekeris, C. L.
Piggot, C. S.
Press, Frank
Reichelderfer, F. W.
Revelle, Roger
Stommel, Henry
Van Allen, J. A.
Verhoogen, John
Vestine, E. H.
Villard, O. G., Jr.
Wulf, O. R.

Foreign Associates

Bullard, Sir Edward
Bullen, Keith Edward
Chapman, Sydney
Jeffreys, Sir Harold
Vening Meinesz, F. A.

(14) *Biochemistry*—57 members

Edsall, John T., *Chairman* (1964)
Ball, E. G.
Balls, A. K.
Bloch, K. E.
Buchanan, John M.
Carter, H. E.
Chance, Britton
Clark, W. M.
Clarke, H. T.
Cori, Carl F.
Craig, L. C.
Doisy, E. A.
Doty, Paul
Doudoroff, Michael
du Vigneaud, V.
Elvehjem, C. A.
Fruton, J. S.
Green, David E.
Hassid, W. Z.
Horecker, B. L.
Kalckar, H. M.
Kamen, Martin D.
Kendall, E. C.
King, C. G.
Kornberg, A.
Lardy, Henry
Lederberg, Joshua
Lehninger, A. L.
Link, K. P.
Lipmann, Fritz
Maynard, L. A.
McCollum, E. V.
Moore, Stanford
Neurath, Hans
Northrop, J. H.
Ochoa, Severo
Oncley, J. L.
Rittenberg, David
Rose, W. C.
Shemin, David
Smith, Emil L.
Snell, E. E.
Stanley, W. M.
Stein, W. H.
Szent-Györgyi, A.
Tatum, E. L.
Van Slyke, D. D.
Vickery, H. B.
Wald, George
Watson, J. D.
Werkman, C. H.
Williams, R. C.
Williams, R. J.
Wilson, D. W.
Wintersteiner, O.
Wood, H. G.
Woolley, D. W.

Foreign Associates

Leloir, Luis F.
Lynen, Feodor
Theorell, Hugo
Tiselius, Arne W. K.
Winge, Öjvind

GEOGRAPHICAL LISTING OF ACADEMY MEMBERS

Arizona

Haury, Emil W.
Kuiper, G. P.
Marvel, C. S.
Mayall, N. U.
Slipher, V. M.
Wyckoff, R. W. G.

California

Adams, L. H.
Aller, L. H.
Alvarez, L. W.
Anderson, C. D.
Arnon, D. I.
Babcock, H. D.
Babcock, H. W.
Bacher, R. F.
Badger, R. M.
Balls, A. K.
Barker, H. A.
Beach, F. A.
Benioff, Hugo
Birge, R. T.
Bjerknes, J.
Blackwelder, Eliot
Blinks, L. R.
Bloch, Felix
Bonner, David M.
Bonner, James
Bowen, I. S.
Bramlette, M. N.
Brewer, Leo
Brode, R. B.
Brown, Harrison
Byerly, Perry
Calvin, Melvin
Chamberlain, Owen
Chandler, W. H.
Chaney, R. W.
Chern, Shiing-shen
Chew, G. F.
Clausen, Jens
Comroe, Julius H., Jr.
Cram, Donald J.
Danforth, C. H.
Davidson, N.
Djerassi, Carl
Doudoroff, Michael
DuBridge, L. A.
Dulbecco, Renato
DuMond, J. W. M.
Eckart, Carl
Elsasser, W. M.
Epstein, P. S.
Esau, Katherine
Evans, G. C.
Evans, H. M.
Feynman, R. P.
Flory, Paul J.
Fowler, W. A.
Friedmann, Herbert
Gell-Mann, Murray
Giauque, W. F.
Glaser, D. A.
Greenstein, J. L.
Griggs, D. T.
Guilford, J. P.
Hassid, W. Z.
Hastings, A. Baird
Hewett, D. F.
Hildebrand, J. H.
Hilgard, E. R.
Hofstadter, R.
Hubbs, C. L.
Johnson, W. S.
Joy, A. H.
Kamen, M. D.
Kaplan, Joseph
Kelley, W. P.
Kerst, D. W.
Kittel, C.
Knopf, Adolph
Kornberg, A.
Krauskopf, K. B.
Lauritsen, C. C.
Lederberg, J.
Lerner, I. M.
Libby, W. F.
Lindsley, D. B.
Longwell, C. R.
Lucas, H. J.
MacDonald, G. J. F.
Magoun, H. W.
Mayer, J. E.
Mayer, M. G.
Mazia, Daniel
McMillan, E. M.
Meyer, K. F.
Miller, A. H.
Minkowski, R. L.
Morrey, C. B., Jr.
Munk, W. H.
Nicholson, S. B.
Niemann, Carl
Northrop, J. H.
Panofsky, W. K. H.
Pauling, Linus
Pickering, W. H.
Press, Frank
Raymond, A. E.
Roberts, John D.
Robertson, O. H.
Rubey, W. W.
Schiff, L. I.
Scholander, Per F.
Seares, F. H.
Segrè, Emilio
Shane, C. D.
Shockley, W.
Slichter, L. B.
Smith, P. E.
Snell, E. E.
Sperry, R. W.
Stanley, W. M.
Stebbins, G. L.
Stebbins, Joel
Stern, Curt
Stern, Otto
Struve, Otto
Sturtevant, A. H.
Taube, Henry
Teller, Edward
Terman, F. E.
Thomas, T. Y.
Timoshenko, S. P.
Turner, F. J.
Twitty, V. C.
Urey, H. C.
Van Niel, C. B.
Verhoogen, John
Vestine, E. H.
Villard, O. G., Jr.
von Kármán, T.
Webster, D. L.
Whitford, A. E.
Williams, Howel
Williams, R. C.

Wilson, Olin C.
Winstein, Saul
Wulf, O. R.
Yost, D. M.
Young, W. G.
Zimm, B. H.

Colorado

*Chapman, Sydney
Gamow, George
Gilluly, James
Haurwitz, B.
Lovering, T. S.
Puck, T. T.
Savage, J. L.

Connecticut

Breit, G.
Brouwer, Dirk
Clarke, H. T.
Doering, William
Dunbar, C. O.
Fruton, J. S.
Fuoss, R. M.
Galambos, Robert
Harned, H. S.
Hille, Einar
Horsfall, J. G.
Hutchinson, G. E.
Jacobson, Nathan
Jones, D. F.
Lamb, W. E., Jr.
Lambert, W. D.
Long, C. N. H.
Miles, W. R.
Miller, N. E.
Nicholas, J. S.
O'Brien, Brian
Onsager, Lars
Paul, J. R.
Petrunkevitch, A.
Rouse, Irving
Sinnott, E. W.
Vickery, H. B.
Zinn, W. H.

Delaware

Bolton, E. K.
Greenewalt, C. H.

District of Columbia

Abbot, C. G.
Abelson, P. H.
Anderson, C. A.
Astin, A. V.
Bradley, W. H.
Briggs, L. J.
Brode, W. R.
Carmichael, Leonard
Clemence, G. M.
Coblentz, W. W.
Dryden, H. L.
Foote, P. D.
Forbush, S. E.
Friedman, Herbert
Gunn, Ross
Haskins, C. P.
Herzfeld, K. F.
Kellogg, Remington
Meggers, W. F.
Nolan, T. B.
Reichelderfer, F. W.
Revelle, Roger
Roberts, R. B.
Schairer, J. F.
Seaborg, G. T.
Stewart, T. D.
Tousey, R.
Tuve, M. A.
Wetmore, Alexander
Wiesner, J. B.
Wilson, R. E.
Woodring, W. P.
Yoder, H. S., Jr.

Florida

Dragstedt, L. R.
Riddle, Oscar

Georgia

Cleveland, L. R.

Illinois

Adams, Roger
Albert, A. A.
Allison, S. K.
Anderson, H. L.
Bailey, P.
Bardeen, John
Beadle, G. W.
Bloom, William
Byers, H. R.
Cannon, Paul
Carter, H. E.
Coggeshall, L. T.
Doob, J. L.
Emerson, A. E.
Franck, James
Fuson, R. C.
Gutowsky, H. S.
Herskovits, M. J.
Huggins, Charles
Inghram, M. G.
Klüver, Heinrich
Leonard, N. J.
Loomis, F. W.
Mac Lane, Saunders
Miller, C. P.
Mulliken, R. S.
Rose, W. C.
Seitz, Frederick
Simpson, J. A.
Steward, J. H.
Stone, M. H.
Szilard, Leo
Taliaferro, W. H.
Wall, Frederick T.
Wentzel, Gregor
Zachariasen, W. H.
Zirkle, R. E.
Zygmund, Antoni

Indiana

Benzer, Seymour
Briggs, Robert
Brown, H. C.
Cleland, R. E.
*Lim, R. K. S.
Muller, H. J.
Rhoades, M. M.
Rossini, F. D.
Sonneborn, T. M.

Iowa

Gilman, Henry
Spedding, F. H.
Spence, K. W.
Van Allen, J. A.
Werkman, C. H.

Louisiana

Russell, R. J.

Maine

Little, C. C.

*Foreign Associate

Maryland

Albright, W. F.
Armstrong, Charles
Bard, Philip
Blalock, Alfred
Bodian, David
Borthwick, H. A.
Clark, W. M.
Cloos, Ernst
Cole, K. S.
Emmett, P. H.
Glass, Bentley
Hendricks, S. B.
Huebner, R. J.
Kety, S. S.
Lehninger, A. L.
Marshall, E. K., Jr.
Maxcy, K. F.
McCollum, E. V.
Murnaghan, F. D.
Piggot, C. S.
Rich, A. R.
Richter, C. P.
Smadel, J. E.
Straus, W. L., Jr.
Willier, B. H.
Wood, W. B., Jr.

Massachusetts

Ahlfors, L. V.
Albright, Fuller
Allen, E. T.
Astwood, E. B.
Aub, Joseph C.
Bailey, I. W.
Bainbridge, K. T.
Ball, E. G.
Bartlett, P. D.
Benedict, Manson
Bigelow, H. B.
Birch, Francis
Bloch, K. E.
Bloembergen, N.
Boring, E. G.
Brauer, R.
Brooks, Harvey
Buchanan, J. M.
Buerger, M. J.
Bush, Vannevar
Castle, W. B.
Chipman, John
Coons, A. H.
Cope, A. C.
Den Hartog, J. P.
Deutsch, M.
Doty, Paul
Draper, C. S.
Edsall, J. T.
Enders, J. F.
Fieser, L. F.
Forbes, Alexander
Garrels, R. M.
Gilliland, E. R.
Goldberg, Leo
Griffin, D. R.
Hisaw, F. L.
Hunsaker, J. C.
Iselin, C. O'D.
Jeffries, Zay
Kalckar, H. M.
Kemble, E. C.
Keyes, F. G.
Kidder, A. V.
Kimball, G. E.
Kistiakowsky, G. B.
Land, E. H.
Landis, E. M.
Lewis, W. K.
Lin, C. C.
Lipscomb, W. N.
Lothrop, S. K.
Luria, S. E.
Mackey, G. W.
Mangelsdorf, P. C.
Mayr, Ernst
Menzel, D. H.
Metz, C. W.
Miller, G. A.
Morse, P. M.
Movius, H. L., Jr.
Pound, R. V.
Purcell, E. M.
Ramsey, Norman
Redfield, A. C.
Romer, A. S.
Rossi, B. B.
Saunders, F. A.
Scatchard, George
Schmitt, F. O.
Schwinger, Julian
Shannon, C. E.
Sheehan, J. C.
Sherwood, T. K.
Simpson, G. G.
Skinner, B. F.
Slater, J. C.
Smith, C. S.
Soderberg, C. R.
Stevens, S. S.
Stommel, Henry
Stratton, J. A.
Street, J. C.
Szent-Györgyi, A.
Thimann, K. V.
Townes, C. H.
Tyzzer, E. E.
Van Vleck, J. H.
v. Békésy, Georg
Wald, George
Walsh, J. L.
Warren, Shields
Watson, J. D.
Westheimer, F. H.
Wetmore, R. H.
Whipple, F. L.
Willey, G. R.
Williams, C. M.
Wilson, E. Bright, Jr.
Wilson, Edwin B.
Woodward, R. B.
Zacharias, J. R.
Zariski, Oscar

Michigan

Dennison, D. M.
Elderfield, R. C.
Francis, Thomas, Jr.
Gerard, R. W.
Kaufmann, B. P.
Oncley, J. L.

Minnesota

Cloud, P. E., Jr.
Crawford, Bryce, Jr.
James, H. L.
Kolthoff, I. M.
Mann, F. C.
Nier, A. O. C.
Smith, L. I.
Stakman, E. C.
Visscher, M. B.
Watson, C. J.
Williams, John H.

Missouri

Anderson, Edgar
Cori, C. F.
Davis, Hallowell
Doisy, E. A.
Erlanger, Joseph
Hamburger, Viktor
Thomas, C. A.
Went, F. W.

Montana

Bartelmez, G. W.

New Hampshire

Köhler, Wolfgang
Shapley, Harlow
Stockmayer, W.

New Jersey

Alexander, J. W.
Baker, W. O.
Bleakney, Walker
Bochner, S.
Bode, H. W.
Brattain, W. H.
Buddington, A. F.
Eisenhart, L. P.
Feller, William
Fisk, J. B.
Folkers, Karl
Gödel, Kurt
Hammett, L. P.
Hartman, C. G.
Hedberg, H. D.
Heidelberger, M.
Hess, H. H.
Hornig, D. F.
Kelly, M. J.
Kendall, E. C.
La Mer, V. K.
Lefschetz, Solomon
Montgomery, Deane
Morse, Marston
Murphree, E. V.
Olson, Harry F.
Oppenheimer, J. R.
Pais, Abraham
Pierce, J. R.
Schwarzschild, M.
Smyth, C. P.
Spencer, D. C.
Spitzer, Lyman, Jr.
Steenrod, N. E.
Tishler, Max
Tukey, John W.
Waksman, S. A.
Wever, E. G.
Wheeler, J. A.
Whitney, Hassler
Wigner, E. P.
Williams, R. R.
Wintersteiner, Oskar
Zworykin, V. K.

New Mexico

Bradbury, N. E.

New York

Bethe, H. A.
Blomquist, A. T.
Booker, H. G.
Braun, A. C.
Brillouin, Leon
Brink, Frank, Jr.
Bronk, D. W.
Bucher, W. H.
Burkholder, P. R.
Colbert, E. H.
Cole, Rufus
Conant, J. B.
Coolidge, W. D.
Courant, Richard
Cournand, André
Craig, L. C.
Curme, G. O., Jr.
Dalldorf, Gilbert
Debye, Peter
Demerec, Milislav
Dobzhansky, Th.
Dochez, A. R.
Douglas, Jesse
Dubos, R. J.
Dunn, L. C.
Dunning, J. R.
du Vigneaud, Vincent
Eilenberg, Samuel
Ewing, Maurice
Fenn, W. O.
Friedrichs, K. O.
Gasser, H. S.
Gates, M.
Gibbs, W. F
Goebel, W. F.
Goldhaber, M.
Goudsmit, S. A.
Graham, C. H
Gregory, W. K.
Hartline, H. K.
Hershey, A. D.
Holtfreter, J.
Hoover, Herbert
Horecker, B. L.
Horsfall, F. L., Jr.
Hotchkiss, R. D.
Hull, A. W.
Hyman, Libbie
Jacobs, W. A.
Johnson, J. R.
King, C. G.
Kinzel, A. B.
Kusch, P.
Lipmann, Fritz
Lloyd, D. P. C.
Loeb, R. F.
Long, F. A.
Longsworth, L. G.
Loomis, A. L.
Lorente de Nó, R.
MacInnes, D. A.
MacLeod, C. M.
Mark, H. F.
Marshak, R. E.
Maynard, L. A.
McClintock, Barbara
McMaster, P. D.
Mirsky, A. E.
Moore, Stanford
Noyes, W. A., Jr.
Ochoa, Severo
Opie, E. L.
Osterhout, W. J. V.
Palade, George E.
Pitts, R. F.
Rabi, I. I.
Richards, D. W.
Rittenberg, David
Robbins, W. J.
Rous, Peyton
Serber, Robert
Shapiro, H. L.

Shedlovsky, Theodore
Shemin, David
Shope, R. E.
Smith, P. A.
Sporn, Philip
Stein, W. H.
Stork, Gilbert
Suits, C. G.
Tarbell, D. S.
Tatum, E. L.
Thomas, L. H.
Tillett, W. S.
Uhlenbeck, G. E.
Van Slyke, D. D.
Weiss, Paul
Whipple, G. H.
Wilson, Robert R.
Woodworth, R. S.
Woolley, D. W.
Wu, C. S.

North Carolina

Couch, J. N.
Hauser, C. R.
Kramer, P. J.

Ohio

Condon, E. U.
Dingle, J. H.
*Ephrussi, Boris
Herget, Paul
Newman, M. S.
Sabin, A. B.
Wiggers, C. J.
Wolfrom, M. L.
Wood, H. G.

Oregon

Boekelheide, Virgil

Pennsylvania

Bain, E. C.
Chance, Britton
Coble, A. B.
Coon, C. S.
Corner, G. W.
Darken, L. S.
Goddard, D. R.
Hallowell, A. I.
Jacobs, M. H.
Lewis, W. H.
Richards, A. N.
Sax, Karl
Schmidt, C. F.
Slepian, Joseph
Warner, J. C.
Wilson, D. W.
Zener, Clarence

Rhode Island

Kraus, C. A.
Pfaffmann, Carl
Riggs, L. A.

Tennessee

Arnold, W. A.
Hollaender, A.
Lind, S. C.
Weinberg, A. M.

Texas

Berkner, L. V.
Houston, W. V.
Hubbert, M. K.
Moore, R. L.
Painter, T. S.
Pitzer, K. S.
Stone, W. S.
Vandiver, H. S.
Williams, R. J.

Utah

Eyring, Henry
Fletcher, Harvey
Smith, E. L.

Virginia

Beams, J. W.
Bodenstein, D. H.
Burns, R. K.
Long, E. R.
McShane, E. J.
Whyburn, G. T.

Washington

Neurath, Hans

Wisconsin

Brink, R. A.
Burris, R. H.
Chandrasekhar, S.
Crow, J. F.
Daniels, Farrington
Elvehjem, C. A.
Ferry, John D.
Fred, E. B.
Green, D. E.
Harlow, H. F.
Herb, R. G.
Hirschfelder, J. O.
Irwin, M. R.
Lardy, Henry
Link, K. P.
McElvain, S. M.
Meek, W. J.
Morgan, W. W.
Raper, K. B.
Riker, A. J.
Skoog, Folke
Walker, J. C.
Williams, J. W.
Wilson, P. W.
Woolsey, C. N.
Wright, Sewall

Members Abroad

Germany—

Delbrück, Max

Israel—

Pekeris, C. L.

Switzerland—

Mehl, R. F.
Schultz, A. H.
Weisskopf, V. F.

* Foreign Associate.

National Academy of Sciences

WASHINGTON, D. C.

ELECTIONS

25 April 1961

The Academy on 25 April 1961 elected the following officers, members, and foreign associates:

VICE PRESIDENT

J. A. STRATTON

MEMBERS OF THE COUNCIL

GEORGE B. KISTIAKOWSKY

KENNETH B. RAPER

MEMBERS

DANIEL I. ARNON	Professor of Cell Physiology University of California at Berkeley
WILLIAM OLIVER BAKER	Vice President-Research Bell Telephone Laboratories, Incorporated
SEYMOUR BENZER	Professor of Biophysics Purdue University
HARRY ALFRED BORTHWICK	Chief Plant Physiologist Agricultural Research Service, USDA
ROBERT HARZA BURRIS	Professor of Biochemistry University of Wisconsin
SHIING-SHEN CHERN	Professor of Mathematics University of California at Berkeley
PRESTON ERCELLE CLOUD, JR.	Research Geologist United States Geological Survey
JULIUS HIRAM COMROE, JR.	Director, Cardiovascular Research Institute University of California at San Francisco
DONALD JAMES CRAM	Professor of Chemistry University of California at Los Angeles
JAMES FRANKLIN CROW	Professor of Medical Genetics University of Wisconsin
LAWRENCE STAMPER DARKEN	Associate Director Edgar C. Bain Laboratory for Fundamental Research United States Steel Corporation
CARL DJERASSI	Professor of Chemistry Stanford University
WILLIAM VON EGGERS DOERING	Professor of Organic Chemistry Yale University
RENATO DULBECCO	Professor of Biology California Institute of Technology
ALFRED IRVING HALLOWELL	Professor of Anthropology University of Pennsylvania
BERNARD LEONARD HORECKER	Professor of Microbiology New York University School of Medicine
ROLLIN DOUGLAS HOTCHKISS	Member and Professor Rockefeller Institute
LIBBIE HENRIETTA HYMAN	Research Associate American Museum of Natural History

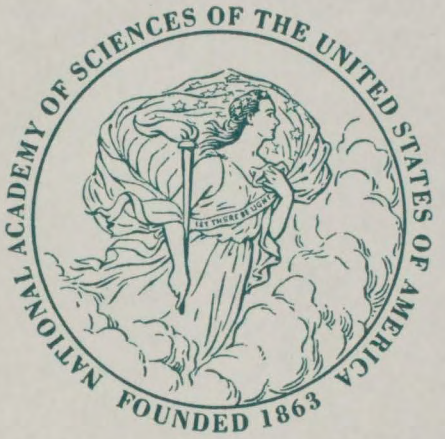
MARK GORDON INGHRAM	Professor of Physics University of Chicago
WILLIAM NUNN LIPSCOMB	Professor of Chemistry Harvard University
HERMAN FRANCIS MARK	Director, Polymer Research Institute Polytechnic Institute of Brooklyn
HANS NEURATH	Professor of Biochemistry University of Washington
GEORGE EMIL PALADE	Member and Professor Rockefeller Institute
ROBERT VIVIAN POUND	Professor of Physics Harvard University
LORRIN ANDREWS RIGGS	Professor of Psychology Brown University
RICHARD BROOKE ROBERTS	Staff Member Department of Terrestrial Magnetism Carnegie Institution of Washington
PER FREDRIK SCHOLANDER	Professor of Physiology Scripps Institution of Oceanography
CHARLES DONALD SHANE	Astronomer Lick Observatory
DONALD CLAYTON SPENCER	Professor of Mathematics Princeton University
HENRY MELSON STOMMEL	Professor of Oceanography Harvard University
LEO SZILARD	Professor of Biophysics University of Chicago
JOHN WILDER TUKEY	Professor of Mathematics Princeton University
FREDERICK THEODORE WALL	Professor of Chemistry University of Illinois
ALVIN MARTIN WEINBERG	Director Oak Ridge National Laboratory
JOHN HARRY WILLIAMS	Professor of Physics University of Minnesota

FOREIGN ASSOCIATES

KEITH EDWARD BULLEN	Professor of Applied Mathematics University of Sydney Sydney, Australia
BORIS EPHRUSSI	Director, Laboratoire de Génétique Physiologique du Centre National de la Recherche Scientifique Gif sur Yvette, France
WERNER HEISENBERG	Director Max Planck Institut für Physik und Astrophysik Munich, Germany
VLADIMIR PRELOG	Professor of Organic Chemistry Swiss Federal Institute Zurich, Switzerland

National Academy of Sciences

of the United States of America



MEMBERSHIP

July 1, 1960

NATIONAL ACADEMY OF SCIENCES

July 1, 1960

OFFICERS

	Term expires
President—Detlev W. Bronk	June 30, 1962
Vice President—Farrington Daniels	June 30, 1961
Home Secretary—Hugh L. Dryden	June 30, 1963
Foreign Secretary—H. P. Robertson	June 30, 1962
Treasurer—L. V. Berkner	June 30, 1964

Executive Officer
S. D. Cornell

Business Manager
G. D. Meid

COUNCIL

Adams, Roger	(1962)	*Houston, W. V.	(1962)
*Berkner, L. V.	(1964)	Hutchinson, G. Evelyn	(1963)
*Bronk, Detlev W.	(1962)	Mac Lane, Saunders	(1961)
*Daniels, Farrington	(1961)	*Robertson, H. P.	(1962)
*Dryden, Hugh L.	(1963)	Williams, Robley C.	(1963)
*Francis, Thomas, Jr.	(1961)		

MEMBERS

The number in parentheses, following year of election, indicates the Section to which the member belongs, as follows:

(1) Mathematics	(8) Zoology and Anatomy
(2) Astronomy	(9) Physiology
(3) Physics	(10) Pathology and Microbiology
(4) Engineering	(11) Anthropology
(5) Chemistry	(12) Psychology
(6) Geology	(13) Geophysics
(7) Botany	(14) Biochemistry

Abbot, Charles Greeley, 1915 (2), Smithsonian Institution, Washington 25, D. C.

Abelson, Philip Hauge, 1959 (6), Geophysical Laboratory, Carnegie Institution of Washington, 2801 Upton Street, N. W., Washington 8, D. C.

Adams, Leason Heberling, 1943 (13), Institute of Geophysics, University of California, Los Angeles 24, California

Adams, Roger, 1929 (5), Department of Chemistry and Chemical Engineering, University of Illinois, Urbana, Illinois

Ahlfors, Lars Valerian, 1953 (1), Department of Mathematics, Harvard University, 2 Divinity Avenue, Cambridge 38, Massachusetts

Albert, Abraham Adrian, 1943 (1), Department of Mathematics, University of Chicago, Chicago 37, Illinois

Albright, William Foxwell, 1955 (11), Oriental Seminary, Johns Hopkins University, Baltimore 18, Maryland

Alexander, James Waddell, 1930 (1), 29 Cleveland Lane, Princeton, New Jersey

* Members of the Executive Committee of the Council of the Academy.

Allen, Eugene Thomas, 1930 (6), 135 Pleasant Street, Arlington 74, Massachusetts

Allison, Samuel King, 1946 (3), The Enrico Fermi Institute for Nuclear Studies, University of Chicago, Chicago 37, Illinois

Alvarez, Luis Walter, 1947 (3), Lawrence Radiation Laboratory, University of California, Berkeley 4, California

Anderson, Carl David, 1938 (3), California Institute of Technology, Pasadena 4, California

Anderson, Charles Alfred, 1957 (6), United States Geological Survey, Department of the Interior, Washington 25, D. C.

Anderson, Edgar, 1954 (7), Missouri Botanical Garden, 2315 Tower Grove Avenue, St. Louis 10, Missouri

Anderson, Herbert Lawrence, 1960 (3), The Enrico Fermi Institute for Nuclear Studies, University of Chicago, Chicago 37, Illinois

Anderson, Rudolph John, 1946 (14), 101 Cottage Street, New Haven 11, Connecticut

Armstrong, Charles, 1944 (10), National Institutes of Health, Bethesda 14, Maryland

Artin, Emil, 1958 (1), Universität Hamburg, Hamburg, Germany

Astin, Allen Varley, 1960 (4), National Bureau of Standards, Washington 25, D. C.

Astwood, Edwin Bennett, 1957 (9), New England Center Hospital, Harrison Avenue and Bennet Street, Boston 11, Massachusetts

Aub, Joseph Charles, 1957 (9), Massachusetts General Hospital, Fruit Street, Boston 14, Massachusetts

Babcock, Harold Delos, 1933 (2), 1820 Atchison Street, Pasadena, California

Babcock, Horace Welcome, 1954 (2), Mount Wilson and Palomar Observatories, 813 Santa Barbara Street, Pasadena 4, California

Bacher, Robert Fox, 1947 (3), California Institute of Technology, Pasadena, California

Badger, Richard McLean, 1952 (5), Gates and Crellin Laboratories of Chemistry, California Institute of Technology, Pasadena 4, California

Bailey, Percival, 1953 (10), Illinois State Psychiatric Institute, 1601 West Taylor Street, Chicago 12, Illinois

Bain, Edgar Collins, 1954 (4), 434 Maple Lane, Edgeworth, Sewickley, Pennsylvania

Bainbridge, Kenneth Tompkins, 1946 (3), Department of Physics, Harvard University, Cambridge 38, Massachusetts

Ball, Eric Glendinning, 1948 (14), Department of Biological Chemistry, Harvard Medical School, 25 Shattuck Street, Boston 15, Massachusetts

Balls, Arnold Kent, 1954 (14), 1988 Thousand Oaks Boulevard, Berkeley 7, California

Bard, Philip, 1944 (9), School of Medicine, Johns Hopkins University, 725 North Wolfe Street, Baltimore 5, Maryland

Bardeen, John, 1954 (3), Department of Physics, University of Illinois, Urbana, Illinois

Barker, Horace Albert, 1953 (7), Department of Biochemistry, 337 Biochemistry and Virus Laboratory, University of California, Berkeley 4, California

Bartelmez, George William 1949 (8), 224 Agnes Avenue, Missoula, Montana

Bartlett, Paul Doughty, 1947 (5), Department of Chemistry, Harvard University, 12 Oxford Street, Cambridge 38, Massachusetts

Beach, Frank Ambrose, 1949 (12), Department of Psychology, University of California, Berkeley 4, California

Beadle, George Wells, 1944 (7), Division of Biology, California Institute of Technology, Pasadena, California

Beams, Jesse Wakefield, 1943 (3), Physics Laboratory, University of Virginia, McCormick Road, Charlottesville, Virginia

Bell, Eric Temple, 1927 (1), 162 Amesti Road, Watsonville, California

Benedict, Manson, 1956 (4), Department of Nuclear Engineering, Massachusetts Institute of Technology, Cambridge 39, Massachusetts

Benioff, Victor Hugo, 1953 (13), Seismological Laboratory, California Institute of Technology, 220 North San Rafael Avenue, Pasadena 2, California

Berkner, Lloyd Viel, 1948 (13), Associated Universities, Incorporated, 10 Columbus Circle, New York 19, New York

Bethe, Hans Albrecht, 1944 (3), Laboratory of Nuclear Studies, Cornell University, Ithaca, New York

Bigelow, Henry Bryant, 1931 (8), Museum of Comparative Zoology at Harvard College, Oxford Street, Cambridge 38, Massachusetts

Birch, Albert Francis, 1950 (6), Dunbar Laboratory, Harvard University, Cambridge 38, Massachusetts

Birge, Raymond Thayer, 1932 (3), University of California, Berkeley 4, California

Bjerknes, Jacob, 1947 (13), Department of Meteorology, University of California, Los Angeles 24, California

Blackwelder, Eliot, 1936 (6), P. O. Box 6506, Stanford, California

Blalock, Alfred, 1945 (10), Johns Hopkins Hospital, Baltimore 5, Maryland

Bleakney, Walker, 1959 (3), P. O. Box 708, Palmer Physical Laboratory, Princeton University, Princeton, New Jersey

Blinks, Lawrence Rogers, 1955 (7), Hopkins Marine Station of Stanford University, Pacific Grove, California

Bloch, Felix, 1948 (3), Department of Physics, Stanford University, Stanford, California

Bloch, Konrad Emil, 1956 (14), Department of Chemistry, Harvard University, 12 Oxford Street, Cambridge 38, Massachusetts

Bloembergen, Nicolaas, 1960 (3), Pierce Hall, Harvard University, Cambridge 38, Massachusetts

Blomquist, Alfred Theodore, 1960 (5), Department of Chemistry, Cornell University, Ithaca, New York

Bloom, William, 1954 (8), University of Chicago, 5640 South Ellis Avenue, Chicago 37, Illinois

Bochner, Salomon, 1950 (1), Department of Mathematics, Princeton University, Box 708, Princeton, New Jersey

Bode, Hendrik Wade, 1957 (4), Bell Telephone Laboratories, Incorporated, Whippany, New Jersey

Bodenstein, Dietrich H. F. A., 1958 (8), Department of Biology, University of Virginia, Charlottesville, Virginia

Bodian, David, 1958 (8), Department of Anatomy, School of Medicine, Johns Hopkins University, 725 North Wolfe Street, Baltimore 5, Maryland

Bolton, Elmer K., 1946 (5), 2310 West 11th Street, Wilmington, Delaware

Bonner, David Mahlon, 1959 (7), Department of Microbiology, Yale University, 310 Cedar Street, New Haven 11, Connecticut

Bonner, James Frederick, 1950 (7), Division of Biology, California Institute of Technology, Pasadena 4, California

Bonner, Tom Wilkerson, 1959 (3), Department of Physics, Rice University, Houston 1, Texas

Booker, Henry George, 1960 (13), School of Electrical Engineering, Cornell University, Ithaca, New York

Boring, Edwin Garrigues, 1932 (12), Memorial Hall, Harvard University, Cambridge 38, Massachusetts

Bowen, Ira Sprague, 1936 (2), Mount Wilson and Palomar Observatories, 813 Santa Barbara Street, Pasadena, California

Bradbury, Norris Edwin, 1951 (3), Los Alamos Scientific Laboratory, P. O. Box 1663, Los Alamos, New Mexico

Bradley, Wilmot Hyde, 1946 (6), United States Geological Survey, Department of the Interior, Washington 25, D. C.

Bramlette, Milton Nunn, 1954 (6), Scripps Institution of Oceanography, La Jolla, California

Brattain, Walter Houser, 1959 (3), Bell Telephone Laboratories, Incorporated, Murray Hill, New Jersey

Brauer, Richard Dagobert, 1955 (1), Department of Mathematics, Harvard University, 2 Divinity Avenue, Cambridge 38, Massachusetts

Braun, Armin Charles, 1960 (7), Rockefeller Institute, New York 21, New York

Breit, Gregory, 1939 (3), Sloane Physics Laboratory, Yale University, P. O. Box 2014, New Haven 11, Connecticut

Brewer, Leo, 1959 (5), Department of Chemistry, University of California, Berkeley 4, California

Bridgman, Percy Williams, 1918 (3), Lyman Laboratory of Physics, Harvard University, Cambridge 38, Massachusetts

Briggs, Lyman James, 1942 (4), National Bureau of Standards, Washington 25, D. C.

Brillouin, Leon, 1953 (3), 88 Central Park West, New York 23, New York

Brink, Frank, Jr., 1959 (9), Rockefeller Institute, New York 21, New York

Brink, Royal Alexander, 1947 (7), Department of Genetics, University of Wisconsin, Madison 6, Wisconsin

Brode, Robert Bigham, 1949 (3), Department of Physics, University of California, Berkeley 4, California

Brode, Wallace Reed, 1954 (5), 3900 Connecticut Avenue, Washington 8, D. C.

Bronk, Detlev Wulf, 1939 (9), Rockefeller Institute, New York 21, New York

Brouwer, Dirk, 1951 (2), Yale University Observatory, Box 2023, Yale Station, New Haven, Connecticut

Brown, Harrison Scott, 1955 (13), Division of Geological Sciences, California Institute of Technology, Pasadena, California

Brown, Herbert Charles, 1957 (5), Department of Chemistry, Purdue University, Lafayette, Indiana

Bucher, Walter Hermann, 1938 (6), Department of Geology, Columbia University, New York 27, New York

Buddington, Arthur Francis, 1943 (6), Department of Geology, Princeton University, Princeton, New Jersey

Buerger, Martin Julian, 1953 (6), Department of Geology and Geophysics, Massachusetts Institute of Technology, Cambridge 39, Massachusetts

Burkholder, Paul Rufus, 1949 (7), Kitchawan Research Laboratory of the Brooklyn Botanic Garden, R.F.D. 1, Ossining, New York

Burns, Robert Kyle, 1955 (8), Department of Embryology, Carnegie Institution of Washington, Wolfe and Madison Streets, Baltimore 5, Maryland

Bush, Vannevar, 1934 (4), Massachusetts Institute of Technology, Cambridge 39, Massachusetts

Byerly, Perry, 1946 (13), Seismographic Station, University of California, Berkeley 4, California

Byers, Horace Robert, 1952 (13), Department of Meteorology, University of Chicago, Chicago 37, Illinois

Calvin, Melvin, 1954 (5), Department of Chemistry, University of California, Berkeley 4, California

Cannon, Paul Roberts, 1946 (10), Department of Pathology, University of Chicago, Chicago 37, Illinois

Carmichael, Leonard, 1943 (12), Smithsonian Institution, Washington 25, D. C.

Carter, Herbert Edmund, 1953 (14), Department of Chemistry, University of Illinois, Urbana, Illinois

Castle, William Bosworth, 1939 (10), Boston City Hospital, Boston 18, Massachusetts

Castle, William Ernest, 1915 (8), 421 Spruce Street, Berkeley 8, California

Chamberlain, Owen, 1960 (3), Department of Physics, University of California, Berkeley 4, California

Chance, Britton, 1954 (14), Eldridge Reeves Johnson Foundation for Medical Physics, University of Pennsylvania, Philadelphia 4, Pennsylvania

Chandler, William Henry, 1943 (7), 341 South Almont Drive, Beverly Hills, California

Chandrasekhar, Subrahmanyan, 1955 (2), Yerkes Observatory, University of Chicago, Williams Bay, Wisconsin

Chaney, Ralph Works, 1947 (6), Department of Paleontology, University of California, Berkeley 4, California

Chipman, John, 1955 (4), Department of Metallurgy, Massachusetts Institute of Technology, Cambridge 39, Massachusetts

Clark, William **Mansfield,** 1928 (14), Department of Chemistry, Johns Hopkins University, Baltimore 18, Maryland

Clarke, Hans Thacher, 1942 (14), Department of Biochemistry, Yale University School of Medicine, 333 Cedar Street, New Haven 11, Connecticut

Clausen, Jens Christian, 1959 (7), Department of Plant Biology, Carnegie Institution of Washington, Stanford, California

Cleland, Ralph Erskine, 1942 (7), Department of Botany, Indiana University, Bloomington, Indiana

Clemence, Gerald Maurice, 1952 (2), United States Naval Observatory, Washington 25, D. C.

Cleveland, Lemuel Roscoe, 1952 (8), Department of Zoology, University of Georgia, Athens, Georgia

Cloos, Ernst, 1950 (6), Department of Geology, Johns Hopkins University, Baltimore 18, Maryland

Coblentz, William Weber, 1930 (3), 2737 Macomb Street, N. W., Washington 8, D. C.

Coggeshall, Lowell Thelwell, 1949 (10), University of Chicago, Chicago 37, Illinois

Colbert, Edwin Harris, 1957 (8), American Museum of Natural History, Central Park West at 79th Street, New York 24, New York

Cole, Kenneth Stewart, 1956 (9), National Institutes of Health, Bethesda 14, Maryland

Cole, Rufus, 1922 (10), Mt. Kisco, New York

Compton, Arthur Holly, 1927 (3), Washington University, St. Louis 30, Missouri

Conant, James Bryant, 1929 (5), 588 Fifth Avenue, New York 36, New York

Condon, Edward Uhler, 1944 (3), Department of Physics, Washington University, St. Louis 30, Missouri

Coon, Carleton Stevens, 1955 (11), The University Museum, University of Pennsylvania, 33rd and Spruce Streets, Philadelphia 4, Pennsylvania

Cope, Arthur Clay, 1947 (5), Department of Chemistry, Massachusetts Institute of Technology, Cambridge 39, Massachusetts

Cori, Carl Ferdinand, 1940 (14), School of Medicine, Washington University, Euclid Avenue and Kingshighway, St. Louis 10, Missouri

Corner, George Washington, 1940 (8), Rockefeller Institute, New York 21, New York

Couch, John Nathaniel, 1943 (7), University of North Carolina, Chapel Hill, North Carolina

Courant, Richard, 1955 (1), AEC Computing Center, New York University, 4 Washington Place, New York 3, New York

Cournand, André Frederic, 1958 (9), Cardio-Pulmonary Laboratory (Columbia University Division), Bellevue Hospital, 462 First Avenue, New York 16, New York

Craig, Lyman Creighton, 1950 (14), Rockefeller Institute, New York 21, New York

Crawford, Bryce, Jr., 1956 (5), Graduate School, University of Minnesota, Minneapolis 14, Minnesota

Curme, George Oliver, Jr., 1944 (4), Union Carbide Corporation, 30 East 42nd Street, New York 17, New York

Dalldorf, Gilbert, 1955 (10), Sloan-Kettering Institute for Cancer Research, 145 Boston Post Road, Rye, New York

Danforth, Charles Haskell, 1942 (8), Department of Anatomy, Stanford University, Stanford, California

Daniels, Farrington, 1947 (5), Department of Chemistry, University of Wisconsin, Madison 6, Wisconsin

Davidson, Norman Ralph, 1960 (5), Gates and Crellin Laboratories of Chemistry, California Institute of Technology, Pasadena 4, California

Davis, Hallowell, 1948 (9), Central Institute for the Deaf, 818 South Kingshighway, St. Louis 10, Missouri

Debye, Peter, (1931) 1947* (5), Baker Laboratory, Cornell University, Ithaca, New York

Delbrück, Max, 1949 (7), Kerckhoff Laboratories of Biology, California Institute of Technology, Pasadena 4, California

Demerec, Milislav, 1946 (8), Department of Biology, Brookhaven National Laboratory, Upton, Long Island, New York

Den Hartog, Jacob Pieter, 1953 (4), Department of Mechanical Engineering, Massachusetts Institute of Technology, Cambridge 39, Massachusetts

Dennison, David Mathias, 1953 (3), Randall Laboratory of Physics, University of Michigan, Ann Arbor, Michigan

Deutsch, Martin, 1958 (3), Laboratory for Nuclear Science, Massachusetts Institute of Technology, Cambridge 39, Massachusetts

Dingle, John Holmes, 1958 (10), School of Medicine, Western Reserve University, Cleveland 6, Ohio

Dobzhansky, Theodosius, 1943 (8), Department of Zoology, Columbia University, New York 27, New York

Dochez, Alphonse Raymond, 1933 (10), Presbyterian Hospital, 620 West 168th Street, New York 32, New York

Dodge, Bernard Ogilvie, 1933 (7), 39 Claremont Avenue, New York 27, New York

Doisy, Edward Adelbert, 1938 (14), St. Louis University School of Medicine, 1402 South Grand Boulevard, St. Louis 4, Missouri

Doob, Joseph Leo, 1957 (1), Department of Mathematics, University of Illinois, Urbana, Illinois

Doty, Paul Mead, 1957 (5), Department of Chemistry, Harvard University, 12 Oxford Street, Cambridge 38, Massachusetts

Douglas, Jesse, 1946 (1), Forest Hills Inn, Forest Hills 75, New York

Dragstedt, Lester Reynold, 1950 (10), Department of Surgery, University of Florida, Gainesville, Florida

Draper, Charles Stark, 1957 (4), Room 33–207, Department of Aeronautics and Astronautics, Massachusetts Institute of Technology, Cambridge 39, Massachusetts

Dryden, Hugh Latimer, 1944 (4), National Aeronautics and Space Administration, 1520 H Street, N. W., Washington 25, D. C.

Dubos, René Jules, 1941 (10), Rockefeller Institute, New York 21, New York

DuBridge, Lee Alvin, 1943 (3), California Institute of Technology, Pasadena, California

DuMond, Jesse William Monroe, 1953 (3), Department of Physics, California Institute of Technology, Pasadena 4, California

Dunbar, Carl Owen, 1944 (6), Peabody Museum, Yale University, New Haven 11, Connecticut

* Elected a foreign associate in 1931; became a naturalized citizen in 1946 and a member of the Academy in 1947.

Dunn, Leslie Clarence, 1943 (8), Department of Zoology, Columbia University, New York 27, New York

Dunning, John Ray, 1948 (3), 301 Engineering Building, Columbia University, New York 27, New York

du Vigneaud, Vincent, 1944 (14), Cornell University Medical College, 1300 York Avenue, New York 21, New York

Eckart, Carl, 1953 (13), University of California, La Jolla, La Jolla, California

Edsall, John Tileston, 1951 (14), The Biological Laboratories, Harvard University, 16 Divinity Avenue, Cambridge 38, Massachusetts

Eilenberg, Samuel, 1959 (1), Department of Mathematics, Columbia University, New York 27, New York

Eisenhart, Luther Pfahler, 1922 (1), 25 Alexander Street, Princeton, New Jersey

Elderfield, Robert Cooley, 1949 (5), Department of Chemistry, University of Michigan, Ann Arbor, Michigan

Elsasser, Walter Maurice, 1957 (3), Department of Physics, University of New Mexico, Albuquerque, New Mexico

Elvehjem, Conrad Arnold, 1942 (14), Bascom Hall, University of Wisconsin, Madison 6, Wisconsin

Emmett, Paul Hugh, 1955 (5), Department of Chemistry, Johns Hopkins University, Baltimore 18, Maryland

Enders, John Franklin, 1953 (10), The Children's Hospital, 300 Longwood Avenue, Boston 15, Massachusetts

Epstein, Paul Sophus, 1930 (3), 1484 Oakdale Street, Pasadena 4, California

Erlanger, Joseph, 1922 (9), 5127 Waterman Boulevard, St. Louis 8, Missouri

Esau, Katherine, 1957 (7), Department of Botany, University of California, Davis, California

Evans, Griffith Conrad, 1933 (1), Department of Mathematics, University of California, Berkeley 4, California

Evans, Herbert McLean, 1927 (9), Institute of Experimental Biology, University of California, Berkeley 4, California

Ewing, William Maurice, 1948 (13), Columbia University, Lamont Geological Observatory, Torrey Cliff, Palisades, New York

Eyring, Henry, 1945 (5), Graduate School, University of Utah, Salt Lake City, Utah

Feller, William, 1960 (1), Fine Hall, Princeton University, Princeton, New Jersey

Fenn, Wallace Osgood, 1943 (9), School of Medicine and Dentistry, University of Rochester, 260 Crittenden Boulevard, Rochester 20, New York

Ferry, John Douglass, 1959 (5), Department of Chemistry, University of Wisconsin, Madison 6, Wisconsin

Feynman, Richard Phillips, 1954 (3), Norman Bridge Laboratory of Physics, California Institute of Technology, Pasadena 4, California

Fieser, Louis Frederick, 1940 (5), Harvard University, Cambridge 38, Massachusetts

Fisk, James Brown, 1954 (4), Bell Telephone Laboratories, Incorporated, Murray Hill, New Jersey

Fletcher, Harvey, 1935 (4), College of Physical and Engineering Sciences, Brigham Young University, Provo, Utah

Flory, Paul John, 1953 (5), Mellon Institute, 4400 Fifth Avenue, Pittsburgh 13, Pennsylvania

Folkers, Karl August, 1948 (5), Fundamental Research, Merck Sharp & Dohme Research Laboratories, Rahway, New Jersey

Foote, Paul Darwin, 1943 (4), 5144 Macomb Street, N. W., Washington 16, D. C.

Forbes, Alexander, 1936 (9), The Biological Laboratories, Harvard University, 16 Divinity Avenue, Cambridge 38, Massachusetts

Fowler, William Alfred, 1956 (3), W. K. Kellogg Radiation Laboratory, California Institute of Technology, Pasadena, California

Francis, Thomas, Jr., 1948 (10), Department of Epidemiology, School of Public Health, University of Michigan, Ann Arbor, Michigan

Franck, James, 1944 (3), Department of Chemistry, University of Chicago, Chicago 37, Illinois

Fred, Edwin Broun, 1931 (7), University of Wisconsin, Madison 6, Wisconsin

Friedman, Herbert, 1960 (13), United States Naval Research Laboratory, Washington 25, D. C.

Friedrichs, Kurt Otto, 1959 (1), Institute of Mathematical Sciences, New York University, 25 Waverly Place, New York 3, New York

Fruton, Joseph Stewart, 1952 (14), Department of Biochemistry, Yale University, 333 Cedar Street, New Haven 11, Connecticut

Fuoss, Raymond Matthew, 1951 (5), 57 Mill Rock Road, New Haven 11, Connecticut

Fuson, Reynold Clayton, 1944 (5), 263 Noyes Laboratory, University of Illinois, Urbana, Illinois

Galambos, Robert, 1960 (12), Department of Neurophysiology, Walter Reed Army Institute of Research, Washington 12, D. C.

Gamow, George, 1953 (3), Department of Physics, University of Colorado, Boulder, Colorado

Gasser, Herbert Spencer, 1934 (9), Rockefeller Institute, New York 21, New York

Gates, Marshall DeMotte, Jr., 1958 (5), Department of Chemistry, University of Rochester, Rochester 20, New York

Gell-Mann, Murray, 1960 (3), Department of Physics, California Institute of Technology, Pasadena, California

Gerard, Ralph Waldo, 1955 (9), Mental Health Research Institute, University of Michigan, Ann Arbor, Michigan

Gesell, Arnold, 1947 (12), Gesell Institute of Child Development, 310 Prospect Street, New Haven 11, Connecticut

Giauque, William Francis, 1936 (5), Department of Chemistry, University of California, Berkeley 4, California

Gibbs, William Francis, 1949 (4), One Broadway, New York 4, New York

Gilliland, Edwin Richard, 1948 (4), Department of Chemical Engineering, Massachusetts Institute of Technology, Cambridge 39, Massachusetts

Gilluly, James, 1947 (6), United States Geological Survey, Denver Federal Center, Denver 25, Colorado

Gilman, Henry, 1945 (5), Department of Chemistry, Iowa State University, Ames, Iowa

Glass, Hiram Bentley, 1959 (8), Department of Biology, Johns Hopkins University, Baltimore 18, Maryland

Goddard, David Rockwell, 1950 (7), Division of Biology, University of Pennsylvania, Philadelphia 4, Pennsylvania

Gödel, Kurt, 1955 (1), The Institute for Advanced Study, Princeton, New Jersey

Goebel, Walther Frederick, 1958 (10), Rockefeller Institute, New York 21, New York

Goldberg, Leo, 1958 (2), Harvard College Observatory, Cambridge 38, Massachusetts

Goldhaber, Maurice, 1958 (3), Department of Physics, Brookhaven National Laboratory, Upton, Long Island, New York

Goudsmit, Samuel Abraham, 1947 (3), Department of Physics, Brookhaven National Laboratory, Upton, Long Island, New York

Graham, Clarence Henry, 1946 (12), Department of Psychology, Columbia University, New York 27, New York

Greenewalt, Crawford Hallock, 1952 (4), E. I. du Pont de Nemours and Company, Incorporated, Wilmington 98, Delaware

Greenstein, Jesse Leonard, 1957 (2), Mount Wilson and Palomar Observatories, 1201 East California Street, Pasadena, California

Gregory, William King, 1927 (6), Woodstock, New York

Griffin, Donald Redfield, 1960 (8), The Biological Laboratories, Harvard University, 16 Divinity Avenue, Cambridge 38, Massachusetts. From October 1, 1960 to July 1, 1961: Department of Zoology, Cambridge University, Cambridge, England

Griggs, David Tressel, 1952 (13), Institute of Geophysics, University of California, Los Angeles 24, California

Guilford, Joy Paul, 1954 (12), P. O. Box 1288, Beverly Hills, California

Gunn, Ross, 1951 (13), 4437 Lowell Street, N. W., Washington 16, D. C.

Gutowsky, Herbert Sander, 1960 (5), Department of Chemistry and Chemical Engineering, University of Illinois, Urbana, Illinois

Hamburger, Viktor, 1953 (8), Department of Zoology, Washington University, St. Louis 5, Missouri

Hammett, Louis Plack, 1943 (5), Department of Chemistry, Columbia University, New York 27, New York

Harlow, Harry F., 1951 (12), Primate Laboratory, 22 North Charter Street, Madison 5, Wisconsin

Harned, Herbert Spencer, 1950 (5), Sterling Chemistry Laboratory, Yale University, 225 Prospect Street, New Haven 11, Connecticut

Hartline, Haldan Keffer, 1948 (9), Rockefeller Institute, New York 21, New York

Haskins, Caryl Parker, 1956 (8), Carnegie Institution of Washington, 1530 P Street, N. W., Washington 5, D. C.

Hassid, William Zev, 1958 (14), 337 Biochemistry and Virus Laboratory, University of California, Berkeley 4, California

Hastings, Albert Baird, 1939 (9), Scripps Clinic and Research Foundation, 476 Prospect Street, La Jolla, California

Haurwitz, Bernhard, 1960 (13), High Altitude Observatory, University of Colorado, Boulder, Colorado

Haury, Emil Walter, 1956 (11), Department of Anthropology, University of Arizona, Tucson, Arizona

Hauser, Charles Roy, 1958 (5), Department of Chemistry, Duke University, Durham, North Carolina

Hedberg, Hollis Dow, 1960 (6), Department of Geology, Princeton University, Princeton, New Jersey

Heidelberger, Michael, 1942 (10), Institute of Microbiology, Rutgers, The State University, New Brunswick, New Jersey

Hendricks, Sterling Brown, 1952 (5), Plant Industry Station, Beltsville, Maryland

Herb, Raymond George, 1955 (3), Department of Physics, University of Wisconsin, Madison 6, Wisconsin

Hershey, Alfred Day, 1958 (7), Department of Genetics, Carnegie Institution of Washington, Cold Spring Harbor, Long Island, New York

Herskovits, Melville Jean, 1959 (11), Department of Anthropology, Northwestern University, Evanston, Illinois

Herzfeld, Karl Ferdinand, 1960 (3), Department of Physics, Catholic University of America, Washington 17, D. C.

Hess, Harry Hammond, 1952 (6), Department of Geology, Princeton University, Princeton, New Jersey

Hewett, Donnel Foster, 1937 (6), 3 Randall Place, Menlo Park, California

Hildebrand, Joel Henry, 1929 (5), Department of Chemistry, University of California, Berkeley 4, California

Hilgard, Ernest Ropiequet, 1948 (12), Department of Psychology, Stanford University, Stanford, California

Hille, Carl **Einar,** 1953 (1), Department of Mathematics, Yale University, New Haven 11, Connecticut

Hirschfelder, Joseph Oakland, 1953 (5), University of Wisconsin, P. O. Box 2127, Madison 5, Wisconsin

Hisaw, Frederick Lee, 1947 (8), The Biological Laboratories, Harvard University, 16 Divinity Avenue, Cambridge 38, Massachusetts

Hofstadter, Robert, 1958 (3), Department of Physics, Stanford University, Stanford, California

Hollaender, Alexander, 1957 (7), Biology Division, Oak Ridge National Laboratory, P. O. Box Y, Oak Ridge, Tennessee

Holtfreter, Johannes, 1955 (8), Biological Laboratories, University of Rochester, Rochester 3, New York

Hoover, Herbert Clark, 1922 (4), Waldorf Astoria Towers, New York, New York

Hornig, Donald Frederick, 1957 (5), Department of Chemistry, Princeton University, Princeton, New Jersey

Horsfall, Frank Lappin, **Jr.,** 1948 (10), Sloan-Kettering Institute for Cancer Research, 410 East 68th Street, New York 21, New York

Horsfall, James Gordon, 1953 (7), Connecticut Agricultural Experiment Station, Box 1106, New Haven 4, Connecticut

Houston, William Vermillion, 1943 (3), Rice University, Houston 1, Texas

Hovland, Carl Iver, 1960 (12), Department of Psychology, Yale University, 333 Cedar Street, New Haven 11, Connecticut

Hubbert, Marion King, 1955 (6), Shell Development Company, P. O. Box 481, Houston 1, Texas

Hubbs, Carl Leavitt, 1952 (8), Scripps Institution of Oceanography, La Jolla, California

Huebner, Robert Joseph, 1960 (10), National Institutes of Health, Bethesda 14, Maryland

Huggins, Charles Brenton, 1949 (10), Department of Surgery, University of Chicago, 950 East 59th Street, Chicago 37, Illinois

Hull, Albert Wallace, 1929 (3), General Electric Research Laboratory, The Knolls, Schenectady, New York

Hunsaker, Jerome Clark, 1935 (4), Room 33-207, Massachusetts Institute of Technology, Cambridge 39, Massachusetts

Hutchinson, George Evelyn, 1950 (8), Osborn Zoological Laboratory, Yale University, New Haven 11, Connecticut

Irwin, Malcolm Robert, 1950 (8), Department of Genetics, University of Wisconsin, Madison 6, Wisconsin

Iselin, Columbus O'Donnell, 1951 (13), Woods Hole Oceanographic Institution, Woods Hole, Massachusetts

Jacobs, Merkel Henry, 1939 (8), School of Medicine, University of Pennsylvania, Philadelphia 4, Pennsylvania

Jacobs, Walter Abraham, 1932 (5), Rockefeller Institute, New York 21, New York

Jacobson, Nathan, 1954 (1), Department of Mathematics, Yale University, New Haven 11, Connecticut

Jeffries, Zay, 1939 (4), General Electric Company, 1 Plastics Avenue, Pittsfield, Massachusetts

Johnson, John Raven, 1948 (5), Department of Chemistry, Cornell University, Ithaca, New York

Johnson, William Summer, 1952 (5), Department of Chemistry and Chemical Engineering, Stanford University, Stanford, California

Jones, Donald Forsha, 1939 (7), Department of Genetics, Connecticut Agricultural Experiment Station, P. O. Box 1106, New Haven 4, Connecticut

Joy, Alfred Harrison, 1944 (2), Mount Wilson and Palomar Observatories, 813 Santa Barbara Street, Pasadena 4, California

Kalckar, Herman Moritz, 1959 (14), McCollum-Pratt Institute, Johns Hopkins University, Baltimore 18, Maryland

Kaplan, Joseph, 1957 (13), Department of Physics, University of California, Los Angeles 24, California

Kaufmann, Berwind Petersen, 1952 (7), Department of Genetics, Carnegie Institution of Washington, Cold Spring Harbor, Long Island, New York

Kelley, Walter Pearson, 1943 (6), 140 Giannini Hall, University of California, Berkeley 4, California

Kellogg, Arthur **Remington,** 1951 (8), 5305 28th Street, N. W., Washington 15, D. C.

Kelly, Mervin J., 1945 (4), 2 Windemere Terrace, Short Hills, New Jersey

Kemble, Edwin Crawford, 1931 (3), Physics Laboratories, Harvard University, Cambridge 38, Massachusetts

Kendall, Edward Calvin, 1950 (14), 3 Queenston Place, Princeton, New Jersey

Kent, Robert Harrington, 1951 (3), 307 South Union Avenue, Havre de Grace, Maryland

Kerst, Donald William, 1951 (3), General Atomic, P. O. Box 608, San Diego 12, California

Keyes, Frederick George, 1930 (5), Massachusetts Institute of Technology, Cambridge 39, Massachusetts

Kidder, Alfred Vincent, 1936 (11), 41 Holden Street, Cambridge 38, Massachusetts

Kimball, George Elbert, 1954 (5), Arthur D. Little, Inc., 35 Acorn Park, Cambridge 40, Massachusetts

King, Charles Glen, 1951 (14), The Nutrition Foundation, Inc., 99 Park Avenue, New York 16, New York

Kinzel, Augustus Braun, 1960 (4), Union Carbide Corporation, 30 East 42nd Street (After September 15, 1960: 270 Park Avenue), New York 17, New York

Kistiakowsky, George Bogdan, 1939 (5), Department of Chemistry, Harvard University, 12 Oxford Street, Cambridge 38, Massachusetts

Kittel, Charles, 1957 (3), Department of Physics, University of California, Berkeley 4, California

Kluckhohn, Clyde Kay Maben, 1952 (11), Peabody Museum, Cambridge 38, Massachusetts

Klüver, Heinrich, 1957 (12), Culver Hall, University of Chicago, Chicago 37, Illinois

Knopf, Adolph, 1931 (6), Department of Geology, Stanford University, Stanford, California

Köhler, Wolfgang, 1947 (12), P. O. Box 32, Lebanon, New Hampshire

Kolthoff, Izaak Maurits, 1958 (5), School of Chemistry, University of Minnesota, Minneapolis 14, Minnesota

Kornberg, Arthur, 1957 (14), Department of Biochemistry, Stanford University Medical School, Stanford, California

Kraus, Charles August, 1925 (5), 92 Keene Street, Providence 6, Rhode Island

Krauskopf, Konrad Bates, 1959 (6), School of Mineral Sciences, Stanford University, Stanford, California

Kroeber, Alfred L., 1928 (11), Department of Anthropology, University of California, Berkeley 4, California

Kuiper, Gerard Peter, 1950 (2), University of Arizona, Tucson, Arizona

Kusch, Polykarp, 1956 (3), Department of Physics, Columbia University, New York 27, New York

Lamb, Willis Eugene, Jr., 1954 (3), Clarendon Laboratory, Parks Road, Oxford, England

Lambert, Walter Davis, 1949 (13), P. O. Box 687, Canaan, Connecticut

La Mer, Victor Kuhn, 1945 (5), Department of Chemistry, Columbia University, New York 27, New York

Land, Edwin Herbert, 1953 (3), Polaroid Corporation, Cambridge 39, Massachusetts

Landis, Eugene Markley, 1954 (9), Department of Physiology, Harvard Medical School, 25 Shattuck Street, Boston 15, Massachusetts

Lardy, Henry Arnold, 1958 (14), Institute for Enzyme Research, University of Wisconsin, 1702 University Avenue, Madison 5, Wisconsin

Larsen, Esper S., Jr., 1944 (6), Apt. 502 H, 3930 Connecticut Avenue, N. W., Washington 8, D. C.

Lauritsen, Charles Christian, 1941 (3), W. K. Kellogg Radiation Laboratory, California Institute of Technology, Pasadena 4, California

Lederberg, Joshua, 1957 (7), Genetics Department, School of Medicine, Stanford University, Palo Alto, California

Lefschetz, Solomon, 1925 (1), Fine Hall, Princeton University, Princeton, New Jersey

Lehninger, Albert Lester, 1956 (14), School of Medicine, Johns Hopkins University, 725 North Wolfe Street, Baltimore 5, Maryland

Leonard, Nelson Jordan, 1955 (5), Department of Chemistry and Chemical Engineering, University of Illinois, Urbana, Illinois

Lerner, I. Michael, 1959 (8), Department of Genetics, University of California, Berkeley 4, California

Lewis, Warren Harmon, 1936 (8), The Wistar Institute of Anatomy and Biology, Philadelphia 4, Pennsylvania

Lewis, Warren **Kendall,** 1938 (4), Massachusetts Institute of Technology, Cambridge 39, Massachusetts

Libby, Willard **Frank,** 1950 (5), 1016 Chantilly Road, Los Angeles 24, California

Lind, Samuel **Colville,** 1930 (5), P. O. Box P, Oak Ridge, Tennessee

Lindsley, Donald Benjamin, 1952 (12), Department of Psychology, University of California, Los Angeles 24, California

Link, Karl Paul, 1946 (14), Department of Biochemistry, University of Wisconsin, Madison 6, Wisconsin

Lipmann, Fritz Albert, 1950 (14), Rockefeller Institute, New York 21, New York

Little, Clarence **Cook,** 1945 (10), R. F. D. 1, Ellsworth, Maine

Lloyd, David Pierce **Caradoc,** 1953 (9), Rockefeller Institute, New York 21, New York

Loeb, Robert Frederick, 1946 (9), 950 Park Avenue, New York 28, New York

Long, Cyril **Norman Hugh,** 1948 (9), Yale University School of Medicine, 333 Cedar Street, New Haven 11, Connecticut

Long, Esmond Ray, 1946 (10), Pedlar Mills, Virginia

Longsworth, Lewis Gibson, 1947 (5), Rockefeller Institute, New York 21, New York

Longwell, Chester Ray, 1935 (6), United States Geological Survey, Menlo Park, California

Loomis, Alfred Lee, 1941 (4), The Loomis Institute for Scientific Research, Incorporated, Room 2420, 14 Wall Street, New York 5, New York

Loomis, Francis **Wheeler,** 1949 (3), 804 West Illinois Street, Urbana, Illinois

Lorente de Nó, Rafael, 1950 (9), Rockefeller Institute, New York 21, New York

Lothrop, Samuel **Kirkland,** 1951 (11), Peabody Museum, Harvard University, Cambridge 38, Massachusetts

Lovering, Thomas Seward, 1949 (6), 8001 West 17th Avenue, Lakewood 15, Colorado

Lucas, Howard Johnson, 1957 (5), California Institute of Technology, Pasadena, California

Luria, Salvador Edward, 1960 (7), Department of Biology, Massachusetts Institute of Technology, Cambridge 39, Massachusetts

MacInnes, Duncan Arthur, 1937 (5), Rockefeller Institute, New York 21, New York

Mac Lane, Saunders, 1949 (1), Eckhart Hall, University of Chicago, Chicago 37, Illinois

MacLeod, Colin Munro, 1955 (10), Department of Medicine, New York University School of Medicine, 550 First Avenue, New York 16, New York

Magoun, Horace Winchell, 1955 (9), Department of Anatomy, University of California Medical Center, Los Angeles 24, California

Mangelsdorf, Paul Christoph, 1945 (7), Botanical Museum, Harvard University, Cambridge 38, Massachusetts

Mann, Frank Charles, 1950 (9), 605 11th Street, S. W., Rochester, Minnesota

Marshak, Robert Eugene, 1958 (3), Department of Physics and Astronomy, University of Rochester, Rochester 20, New York

Marshall, Eli Kennerly, Jr., 1943 (9), Department of Medicine, Johns Hopkins Hospital, Baltimore 5, Maryland

Marvel, Carl Shipp, 1938 (5), Department of Chemistry, University of Illinois, Urbana, Illinois

Maxcy, Kenneth Fuller, 1950 (10), 700 St. George's Road, Baltimore 10, Maryland

Mayall, Nicholas Ulrich, 1949 (2), Lick Observatory, Mount Hamilton, California After October 1, 1960: Kitt Peak National Observatory, Tucson, Arizona

Mayer, Joseph Edward, 1946 (5), School of Science and Engineering, University of California, La Jolla, California

Mayer, Maria Goeppert, 1956 (3), School of Science and Engineering, University of California, La Jolla, California

Maynard, Leonard Amby, 1944 (14), Savage Hall, Cornell University, Ithaca, New York

Mayr, Ernst, 1954 (8), Museum of Comparative Zoology at Harvard College, Oxford Street, Cambridge 38, Massachusetts

Mazia, Daniel, 1960 (8), Department of Zoology, University of California, Berkeley 4, California

McClintock, Barbara, 1944 (7), Carnegie Institution of Washington, Cold Spring Harbor, Long Island, New York

McCollum, Elmer Verner, 1920 (14), Gilman Hall, Johns Hopkins University, Baltimore 18, Maryland

McElvain, Samuel Marion, 1949 (5), Department of Chemistry, University of Wisconsin, Madison 6, Wisconsin

McMaster, Philip Duryeé, 1952 (10), Rockefeller Institute, New York 21, New York

McMath, Robert Raynolds, 1958 (2), McMath-Hulbert Observatory, University of Michigan, 895 West Lake Angelus Road, Pontiac 4, Michigan

McMillan, Edwin Mattison, 1947 (3), Lawrence Radiation Laboratory, University of California, Berkeley 4, California

McShane, Edward James, 1948 (1), Department of Mathematics, University of Virginia, Charlottesville, Virginia

Meek, Walter Joseph, 1947 (9), Department of Physiology, University of Wisconsin, Madison 6, Wisconsin

Mees, Charles Edward Kenneth, 1950 (5), 4401 Kahala Avenue, Honolulu 15, Hawaii

Meggers, William Frederick, 1954 (3), 2904 Brandywine Street, N. W., Washington 8, D. C.

Mehl, Robert Franklin, 1958 (4), Beethovenstrasse 32, Zurich 2, Switzerland

Menzel, Donald Howard, 1948 (2), Harvard College Observatory, Cambridge 38, Massachusetts

Merrill, Paul Willard, 1929 (2), 813 Santa Barbara Street, Pasadena 4, California

Metz, Charles William, 1948 (8), P. O. Box 714, Woods Hole, Massachusetts

Meyer, Karl Friederich, 1940 (10), George Williams Hooper Foundation, University of California Medical Center, San Francisco 22, California

Miles, Walter Richard, 1933 (12), Box 100, Naval Medical Research Laboratory, U. S. N. Submarine Base, New London, Connecticut

Miller, Alden Holmes, 1957 (8), Museum of Vertebrate Zoology, University of California, Berkeley 4, California

Miller, Charles Phillip, 1956 (10), Department of Medicine, University of Chicago, Chicago 37, Illinois

Miller, Neal Elgar, 1958 (12), Department of Psychology, Yale University, 333 Cedar Street, New Haven 11, Connecticut

Minkowski, Rudolph Leo, 1959 (2), Mount Wilson and Palomar Observatories, 813 Santa Barbara Street, Pasadena, California

Mirsky, Alfred Ezra, 1954 (8), Rockefeller Institute, New York 21, New York

Montgomery, Deane, 1955 (1), School of Mathematics, The Institute for Advanced Study, Princeton, New Jersey

Moore, Robert Lee, 1931 (1), University of Texas, Austin 12, Texas

Moore, Stanford, 1960 (14), Rockefeller Institute, New York 21, New York

Morgan, William Wilson, 1956 (2), Yerkes Observatory, University of Chicago, Williams Bay, Wisconsin

Morse, Harold Marston, 1932 (1), The Institute for Advanced Study, Princeton, New Jersey

Morse, Philip McCord, 1955 (3), Department of Physics, Massachusetts Institute of Technology, Cambridge 39, Massachusetts

Movius, Hallam Leonard, Jr., 1957 (11), Peabody Museum, Harvard University, Cambridge 38, Massachusetts

Muller, Hermann Joseph, 1931 (8), Zoology Department, Indiana University, Bloomington, Indiana

Mulliken, Robert Sanderson, 1936 (3), Laboratory of Molecular Structure and Spectra, Department of Physics, University of Chicago, Chicago 37, Illinois

Munk, Walter Heinrich, 1956 (13), University of California, La Jolla, La Jolla, California

Murnaghan, Francis Dominic, 1942 (1), 6202 Sycamore Road, Baltimore 12, Maryland

Murphree, Eger Vaughan, 1950 (4), Esso Research and Engineering Company, P. O. Box 111, Linden, New Jersey

Newman, Melvin Spencer, 1956 (5), Department of Chemistry, The Ohio State University, Columbus 10, Ohio

Nicholas, John Spangler, 1949 (8), Osborn Zoological Laboratory, Yale University, New Haven 11, Connecticut

Nicholson, Seth Barnes, 1937 (2), Mount Wilson and Palomar Observatories, 813 Santa Barbara Street, Pasadena, California

Niemann, Carl George, 1952 (5), Gates and Crellin Laboratories of Chemistry, California Institute of Technology, Pasadena 4, California

Nier, Alfred Otto C., 1950 (3), School of Physics, University of Minnesota, Minneapolis 14, Minnesota

Nolan, Thomas Brennan, 1951 (6), 2219 California Street, N. W., Washington 8, D. C.

Northrop, John Howard, 1934 (14), Department of Bacteriology, University of California, Berkeley 4, California

Noyes, William Albert, Jr., 1943 (5), Department of Chemistry, University of Rochester, Rochester 20, New York

O'Brien, Brian, 1954 (3), Box 117, Pomfret, Connecticut

Ochoa, Severo, 1957 (14), New York University School of Medicine, 550 First Avenue, New York 16, New York

Olson, Harry Ferdinand, 1959 (4), RCA Laboratories, David Sarnoff Research Center, Princeton, New Jersey

Oncley, John Lawrence, 1947 (14), Department of Biological Chemistry, Harvard Medical School, 25 Shattuck Street, Boston 15, Massachusetts

Onsager, Lars, 1947 (5), Sterling Chemistry Laboratory, Yale University, New Haven, Connecticut

Opie, Eugene Lindsay, 1923 (10), Rockefeller Institute, New York 21, New York

Oppenheimer, J. Robert, 1941 (3), The Institute for Advanced Study, Princeton, New Jersey

Osterhout, Winthrop John Vanleuven, 1919 (7), Rockefeller Institute, New York 21, New York

Painter, Theophilus Shickel, 1938 (8), University of Texas, Austin 12, Texas

Panofsky, Wolfgang K. H., 1954 (3), High-Energy Physics Laboratory, Stanford University, Stanford, California

Patterson, John Thomas, 1941 (8), Department of Zoology, University of Texas, Austin 12, Texas

Paul, John Rodman, 1945 (10), Yale University School of Medicine, 333 Cedar Street, New Haven 11, Connecticut

Pauling, Linus, 1933 (5), Gates and Crellin Laboratories of Chemistry, California Institute of Technology, Pasadena 4, California

Pekeris, Chaim Leib, 1952 (13), Department of Applied Mathematics, The Weizmann Institute of Science, Rehovot, Israel

Petrunkevitch, Alexander, 1954 (8), Osborn Zoological Laboratory, Yale University, New Haven 11, Connecticut

Pfaffmann, Carl, 1959 (12), Walter S. Hunter Laboratory of Psychology, Brown University, Providence 12, Rhode Island

Pierce, John Robinson, 1955 (4), Bell Telephone Laboratories, Incorporated, Murray Hill, New Jersey

Piggot, Charles Snowden, 1946 (13), Holly Grove, Lexington Park, Maryland

Pitts, Robert Franklin, 1956 (9), Cornell University Medical College, 1300 York Avenue, New York 21, New York

Pitzer, Kenneth Sanborn, 1949 (5), Department of Chemistry, University of California, Berkeley 4, California

Press, Frank, 1958 (13), Seismological Laboratory, California Institute of Technology, 220 North San Rafael Avenue, Pasadena, California

Puck, Theodore Thomas, 1960 (10), Department of Biophysics, University of Colorado Medical Center, Denver 20, Colorado

Purcell, Edward Mills, 1951 (3), Lyman Laboratory of Physics, Harvard University, Cambridge 38, Massachusetts

Rabi, Isidor Isaac, 1940 (3), Department of Physics, Columbia University, New York 27, New York

Ramsey, Norman Foster, 1952 (3), Lyman Laboratory of Physics, Harvard University, Cambridge 38, Massachusetts

Raper, Kenneth Bryan, 1949 (7), Department of Bacteriology, University of Wisconsin, Madison 6, Wisconsin

Raymond, Arthur Emmons, 1950 (4), 73 Oakmont Drive, Los Angeles 49, California

Redfield, Alfred Clarence, 1958 (9), Maury Lane, Woods Hole, Massachusetts

Reichelderfer, Francis Wilton, 1945 (13), United States Weather Bureau, Department of Commerce, Washington 25, D. C.

Revelle, Roger Randall, 1957 (13), University of California, La Jolla, La Jolla, California

Rhoades, Marcus Morton, 1946 (7), Department of Botany, Indiana University, Bloomington, Indiana

Rich, Arnold Rice, 1954 (10), Johns Hopkins Hospital, Baltimore 5, Maryland

Richards, Alfred Newton, 1927 (9), 737 Rugby Road, Bryn Mawr, Pennsylvania

Richards, Dickinson W., 1958 (9), Columbia University College of Physicians and Surgeons, 630 West 168th Street, New York 32, New York

Richter, Curt Paul, 1948 (12), Johns Hopkins Hospital, Baltimore 5, Maryland

Riddle, Oscar, 1939 (8), Route 4, Plant City, Florida

Riker, Albert Joyce, 1951 (7), Department of Plant Pathology, University of Wisconsin, Madison 6, Wisconsin

Rittenberg, David, 1953 (14), College of Physicians and Surgeons, 630 West 168th Street, New York 32, New York

Rivers, Thomas Milton, 1934 (10), Rockefeller Institute, New York 21, New York

Robbins, William Jacob, 1940 (7), 15 Dellwood Circle, Bronxville, New York

Roberts, John D., 1956 (5), Gates and Crellin Laboratories of Chemistry, California Institute of Technology, Pasadena 4, California

Robertson, Howard Percy, 1951 (3), California Institute of Technology, Pasadena, California

Robertson, Oswald Hope, 1943 (10), 9150 Los Gatos Highway, Santa Cruz, California

Romer, Alfred Sherwood, 1944 (8), Museum of Comparative Zoology at Harvard College, Oxford Street, Cambridge 38, Massachusetts

Rose, William Cumming, 1936 (14), University of Illinois, Urbana, Illinois

Ross, Frank Elmore, 1930 (2), 1100 Mt. Lowe Drive, Altadena, California

Rossi, Bruno Benedetto, 1950 (3), Room 26-569, Department of Physics, Massachusetts Institute of Technology, Cambridge 39, Massachusetts

Rossini, Frederick Dominic, 1951 (5), University of Notre Dame, Notre Dame, Indiana

Rous, Francis **Peyton,** 1927 (10), Rockefeller Institute, New York 21, New York

Rubey, William Walden, 1945 (6), United States Geological Survey, Department of the Interior, Washington 25, D. C.

Russell, Richard Joel, 1959 (6), Coastal Studies Institute, Louisiana State University, Baton Rouge 3, Louisiana

Sabin, Albert Bruce, 1951 (10), The Children's Hospital Research Foundation, University of Cincinnati College of Medicine, Elland Avenue and Bethesda, Cincinnati 29, Ohio

Savage, John **Lucian,** 1949 (4), 1651 Dahlia Street, Denver 20, Colorado

Sax, Karl, 1941 (7), Department of Botany, Josiah Willard Gibbs Research Laboratory, Yale University, New Haven, Connecticut. From September 1, 1960 to January 1, 1961: Department of Genetics, North Carolina State College, Raleigh, North Carolina

Scatchard, George, 1946 (5), Department of Chemistry, Massachusetts Institute of Technology, Cambridge 39, Massachusetts

Schairer, John **Frank,** 1953 (6), Geophysical Laboratory, Carnegie Institution of Washington, 2801 Upton Street, N. W., Washington 8, D. C.

Schiff, Leonard **Isaac,** 1957 (3), Department of Physics, Stanford University, Stanford, California

Schlesinger, Hermann Irving, 1948 (5), Department of Chemistry, University of Chicago, Chicago 37, Illinois

Schmidt, Carl Frederic, 1949 (9), Laboratory of Pharmacology, School of Medicine, University of Pennsylvania, Philadelphia 4, Pennsylvania

Schmitt, Francis Otto, 1948 (8), Department of Biology, Massachusetts Institute of Technology, Cambridge 39, Massachusetts

Schrader, Franz, 1951 (8), Department of Zoology, Duke University, Durham, North Carolina

Schwarzschild, Martin, 1956 (2), Princeton University Observatory, 14 Prospect Avenue, Princeton, New Jersey

Schwinger, Julian, 1949 (3), Department of Physics, Harvard University, Cambridge 38, Massachusetts

Seaborg, Glenn Theodore, 1948 (5), Lawrence Radiation Laboratory, University of California, Berkeley 4, California

Seares, Frederick **Hanley,** 1919 (2), El Encanto Hotel, Santa Barbara, California

Segrè, Emilio, 1952 (3), Department of Physics, University of California, Berkeley 4, California

Seitz, Frederick, 1951 (3), Department of Physics, University of Illinois, Urbana, Illinois

Serber, Robert, 1952 (3), Department of Physics, Columbia University, New York 27, New York

Shaffer, Philip Anderson, 1928 (14), School of Medicine, Washington University, Euclid Avenue and Kingshighway, St. Louis 10, Missouri

Shannon, Claude Elwood, 1956 (1), Research Laboratory of Electronics, Massachusetts Institute of Technology, Cambridge 39, Massachusetts

Shapiro, Harry **Lionel,** 1949 (11), American Museum of Natural History, Central Park West at 79th Street, New York 24, New York

Shapley, Harlow, 1924 (2), Sharon Cross Road, Peterboro, New Hampshire

Shedlovsky, Theodore, 1953 (5), Rockefeller Institute, New York 21, New York

Sheehan, John Clark, 1957 (5), Department of Chemistry, Massachusetts Institute of Technology, Cambridge 39, Massachusetts

Shemin, David, 1958 (14), Columbia University College of Physicians and Surgeons, 630 West 168th Street, New York 32, New York

Sherwood, Thomas Kilgore, 1958 (4), Department of Chemical Engineering, Massachusetts Institute of Technology, Cambridge 39, Massachusetts

Shockley, William, 1951 (4), Shockley Transistor Unit of Clevite Transistor, Stanford Industrial Park, Palto Alto, California

Shope, Richard Edwin, 1940 (10), Rockefeller Institute, New York 21, New York

Simpson, George Gaylord, 1941 (6), Museum of Comparative Zoology at Harvard College, Cambridge 38, Massachusetts

Simpson, John Alexander, 1959 (3), The Enrico Fermi Institute for Nuclear Studies, University of Chicago, Chicago 37, Illinois

Sinnott, Edmund Ware, 1936 (7), Osborn Botanical Laboratory, Yale University, New Haven, Connecticut

Skinner, Burrhus Frederic, 1950 (12), Memorial Hall, Harvard University, Cambridge 38, Massachusetts

Skoog, Folke Karl, 1956 (7), Department of Botany, Birge Hall, University of Wisconsin, Madison 6, Wisconsin

Slater, John Clarke, 1932 (3), Massachusetts Institute of Technology, Cambridge 39, Massachusetts

Slepian, Joseph, 1941 (4), 1115 Lancaster Street, Pittsburgh 18, Pennsylvania

Slichter, Louis Byrne, 1944 (13), Institute of Geophysics, University of California, Los Angeles 24, California

Slipher, Vesto Melvin, 1921 (2), Lowell Observatory, Flagstaff, Arizona

Smadel, Joseph Edwin, 1957 (10), National Institutes of Health, Bethesda 14, Maryland

Smith, Cyril Stanley, 1957 (4), Institute for the Study of Metals, University of Chicago, Chicago 37, Illinois

Smith, Homer William, 1945 (9), New York University School of Medicine, 550 First Avenue, New York 16, New York

Smith, Lee Irvin, 1944 (5), School of Chemistry, University of Minnesota, Minneapolis 14, Minnesota

Smith, Paul Althaus, 1947 (1), Department of Mathematics, Columbia University, New York 27, New York

Smith, Philip Edward, 1939 (8), Department of Anatomy, Stanford University, Stanford, California

Smyth, Charles Phelps, 1955 (5), Department of Chemistry, Princeton University, Princeton, New Jersey

Snell, Esmond Emerson, 1955 (14), Department of Biochemistry, University of California, Berkeley 4, California

Soderberg, Carl Richard, 1947 (4), Massachusetts Institute of Technology, Cambridge 39, Massachusetts

Sonneborn, Tracy Morton, 1946 (8), 220 Jordan Hall, Indiana University, Bloomington, Indiana

Spedding, Frank Harold, 1952 (5), Box 14-A, Station A, Institute for Atomic Research, Iowa State University, Ames, Iowa

Spence, Kenneth Wartinbe, 1955 (12), Department of Psychology, State University of Iowa, Iowa City, Iowa

Sperry, Roger Wolcott, 1960 (12), Division of Biology, California Institute of Technology, Pasadena, California

Spier, Leslie, 1946 (11), P. O. Box 880, Santa Cruz, California

Spitzer, Lyman, Jr., 1952 (2), Princeton University Observatory, 14 Prospect Avenue, Princeton, New Jersey

Stakman, Elvin Charles, 1934 (7), Institute of Agriculture, University of Minnesota, St. Paul 1, Minnesota

Stanley, Wendell Meredith, 1941 (14), Virus Laboratory, University of California, Berkeley 4, California

Stebbins, George Ledyard, 1952 (7), Department of Genetics, University of California, Davis, California

Stebbins, Joel, 1920 (2), 69 University Drive, Menlo Park, California

Steenrod, Norman Earl, 1956 (1), Box 708, Fine Hall, Princeton University, Princeton, New Jersey

Stein, William Howard, 1960 (14), Rockefeller Institute, New York 21, New York

Stern, Curt, 1948 (8), Department of Zoology, University of California, Berkeley 4, California

Stern, Otto, 1945 (3), 759 Cragmont Avenue, Berkeley 8, California

Stevens, Stanley Smith, 1946 (12), Memorial Hall, Harvard University, Cambridge 38, Massachusetts

Steward, Julian H., 1954 (11), Department of Sociology and Anthropology, 137 Davenport Hall, University of Illinois, Urbana, Illinois

Stockmayer, Walter Hugo, 1956 (5), Department of Chemistry, Massachusetts Institute of Technology, Cambridge 39, Massachusetts

Stone, Marshall Harvey, 1938 (1), 303 Eckhart Hall, University of Chicago, Chicago 37, Illinois

Stone, Wilson Stuart, 1960 (8), Genetics Foundation, University of Texas, Austin 12, Texas

Stork, Gilbert Josse, 1960 (5), Department of Chemistry, Columbia University, New York 27, New York

Stratton, Julius Adams, 1950 (4), Massachusetts Institute of Technology, Cambridge 39, Massachusetts

Street, Jabez Curry, 1953 (3), Jefferson Physical Laboratory, Harvard University, Cambridge 38, Massachusetts

Struve, Otto, 1937 (2), National Radio Astronomy Observatory, Green Bank, West Virginia

Sturtevant, Alfred Henry, 1930 (8), California Institute of Technology, Pasadena 4, California

Suits, Chauncey Guy, 1946 (4), General Electric Research Laboratory, The Knolls, Schenectady, New York

Szent-Györgyi, Albert, 1956 (14), Institute for Muscle Research, P. O. Box 187, Woods Hole, Massachusetts

Taliaferro, William Hay, 1940 (10), Argonne National Laboratory, 9700 South Cass Avenue, Argonne, Illinois

Tarbell, Dean Stanley, 1959 (5), Department of Chemistry, University of Rochester, Rochester 20, New York

Tatum, Edward Lawrie, 1952 (14), Rockefeller Institute, New York 21, New York

Taube, Henry, 1959 (5), Department of Chemistry, University of Chicago, Chicago 37, Illinois

Teller, Edward, 1948 (3), Lawrence Radiation Laboratory, University of California, P. O. Box 808, Livermore, California

Terman, Frederick Emmons, 1946 (4), Provost's Office, Stanford University, Stanford, California

Thimann, Kenneth Vivian, 1948 (7), The Biological Laboratories, Harvard University, 16 Divinity Avenue, Cambridge 38, Massachusetts

Thomas, Charles Allen, 1948 (4), Monsanto Chemical Company, 800 North Lindbergh Boulevard, St. Louis 66, Missouri

Thomas, Llewellyn Hilleth, 1958 (3), Watson Scientific Computing Laboratory, 612 West 116th Street, New York 27, New York

Thomas, Tracy Yerkes, 1941 (1), Graduate Institute for Mathematics and Mechanics, Indiana University, Bloomington, Indiana

Thompson, Thomas Gordon, 1951 (13), Department of Oceanography, University of Washington, Seattle 5, Washington

Tillett, William Smith, 1951 (10), New York University School of Medicine, 550 First Avenue, New York 16, New York

Timoshenko, Stephen Prokop, 1940 (4), 536 West Crescent, Palo Alto, California

Tishler, Max, 1953 (5), Merck & Co., Inc., Rahway, New Jersey

Tousey, Richard, 1960 (2), United States Naval Research Laboratory, Washington 25, D. C.

Townes, Charles Hard, 1956 (3), Department of Physics, Columbia University, New York 27, New York

Turner, Francis John, 1956 (6), Department of Geology, University of California, Berkeley 4, California

Tuve, Merle Antony, 1946 (3), Department of Terrestrial Magnetism, Carnegie Institution of Washington, 5241 Broad Branch Road, N. W., Washington 15, D. C.

Twitty, Victor Chandler, 1950 (8), Department of Biological Sciences, Stanford University, Stanford, California

Uhlenbeck, George Eugene, 1955 (3), Department of Physics, University of Michigan, Ann Arbor, Michigan

Urey, Harold Clayton, 1935 (5), University of California, La Jolla, California

Van Allen, James Alfred, 1959 (13), Department of Physics and Astronomy, State University of Iowa, Iowa City, Iowa

Van Niel, Cornelis Bernardus, 1945 (7), Hopkins Marine Station of Stanford University, Pacific Grove, California

Van Slyke, Donald Dexter, 1921 (14), Brookhaven National Laboratory, Upton, Long Island, New York

Van Vleck, John Hasbrouck, 1935 (3), Lyman Laboratory of Physics, Harvard University, Cambridge 38, Massachusetts

Veblen, Oswald, 1919 (1), The Institute for Advanced Study, Princeton, New Jersey

Verhoogen, John, 1956 (13), Department of Geology, University of California, Berkeley 4, California

Vestine, Ernest Harry, 1954 (13), Rand Corporation, 1700 Main Street, Santa Monica, California

Vickery, Hubert Bradford, 1943 (14), Connecticut Agricultural Experiment Station, New Haven 4, Connecticut

Villard, Oswald Garrison, Jr., 1958 (13), Radioscience Laboratory, Stanford University, Stanford, California

Visscher, Maurice Bolks, 1956 (9), Department of Physiology, University of Minnesota, Minneapolis 14, Minnesota

von **Békésy, Georg,** 1956 (12), Psycho-Acoustic Laboratory, Memorial Hall, Harvard University, Cambridge 38, Massachusetts

von Kármán, Theodore, 1938 (4), 1501 South Marengo Avenue, Pasadena 5, California

Waksman, Selman Abraham, 1942 (10), Institute of Microbiology, Rutgers, The State University, New Brunswick, New Jersey

Wald, George, 1950 (14), The Biological Laboratories, Harvard University, 16 Divinity Avenue, Cambridge 38, Massachusetts

Walker, John Charles, 1945 (7), 206 Horticulture Building, University of Wisconsin, Madison 6, Wisconsin

Walsh, Joseph Leonard, 1936 (1), Widener 474, Harvard University, Cambridge 38, Massachusetts

Warner, John Christian, 1956 (5), Carnegie Institute of Technology, Pittsburgh 13, Pennsylvania

Watson, Cecil James, 1959 (10), Department of Medicine, University of Minnesota Hospital, Minneapolis 14, Minnesota

Webster, David Locke, 1923 (3), 1830 Cowper Street, Palo Alto, California

Weiss, Paul Alfred, 1947 (8), Rockefeller Institute, New York 21, New York

Weisskopf, Victor Frederick, 1952 (3), Department of Physics, Massachusetts Institute of Technology, Cambridge 39, Massachusetts

Went, Frits Warmolt, 1947 (7), Missouri Botanical Garden, 2315 Tower Grove Avenue, St. Louis 10, Missouri

Wentzel, Gregor, 1959 (3), The Enrico Fermi Institute for Nuclear Studies, University of Chicago, Chicago 37, Illinois

Werkman, Chester Hamlin, 1946 (14), Department of Bacteriology, Iowa State University, Ames, Iowa

Westheimer, Frank Henry, 1954 (5), Department of Chemistry, Harvard University, 12 Oxford Street, Cambridge 38, Massachusetts

Wetmore, Alexander, 1945 (8), Smithsonian Institution, Washington 25, D. C.

Wetmore, Ralph Hartley, 1954 (7), The Biological Laboratories, Harvard University, 16 Divinity Avenue, Cambridge 38, Massachusetts

Wever, Ernest Glen, 1940 (12), 110 Eno Hall, Princeton University, Princeton, New Jersey

Wheeler, John Archibald, 1952 (3), Palmer Physical Laboratory, Princeton University, Princeton, New Jersey

Whipple, Fred Lawrence, 1959 (2), Astrophysical Observatory, Smithsonian Institution, 60 Garden Street, Cambridge 38, Massachusetts

Whipple, George Hoyt, 1929 (10), School of Medicine and Dentistry, University of Rochester, 260 Crittenden Boulevard, Rochester 20, New York

Whitford, Albert Edward, 1954 (2), Lick Observatory, Mt. Hamilton, California

Whitney, Hassler, 1945 (1), The Institute for Advanced Study, Princeton, New Jersey

Whyburn, Gordon Thomas, 1951 (1), Department of Mathematics, University of Virginia, Charlottesville, Virginia

Wiesner, Jerome Bert, 1960 (4), Research Laboratory of Electronics, Massachusetts Institute of Technology, Cambridge 39, Massachusetts

Wiggers, Carl John, 1951 (9), 1360 Cleveland Heights Boulevard, Cleveland Heights 21, Ohio

Wigner, Eugene Paul, 1945 (3), 8 Ober Road, Princeton, New Jersey

Willey, Gordon Randolph, 1960 (11), Peabody Museum, Harvard University, Cambridge 38, Massachusetts

Williams, Carroll Milton, 1960 (8), The Biological Laboratories, Harvard University, 16 Divinity Avenue, Cambridge 38, Massachusetts

Williams, Howel, 1950 (6), Department of Geology, University of California, Berkeley 4, Calfornia

Williams, John Warren, 1952 (5), Department of Chemistry, University of Wisconsin, Madison 6, Wisconsin

Williams, Robert R., 1945 (5), 297 Summit Avenue, Summit, New Jersey

Williams, Robley Cook, 1955 (14), Virus Laboratory, University of California, Berkeley 4, California

Williams, Roger John, 1946 (5), Clayton Foundation Biochemical Institute, University of Texas, Austin 12, Texas

Willier, Benjamin Harrison, 1945 (8), Department of Biology, Johns Hopkins University, Baltimore 18, Maryland

Wilson, David Wright, 1955 (14), Department of Biochemistry, School of Medicine, University of Pennsylvania, Philadelphia 4, Pennsylvania

Wilson, Edgar Bright, Jr., 1947 (5), Department of Chemistry, Harvard University, 12 Oxford Street, Cambridge 38, Massachusetts

Wilson, Edwin Bidwell, 1919 (3), 42 Brington Road, Brookline 46, Massachusetts

Wilson, Olin Chaddock, 1960 (2), Mount Wilson and Palomar Observatories, 813 Santa Barbara Street, Pasadena, California

Wilson, Perry William, 1955 (7), Department of Bacteriology, University of Wisconsin, Madison 6, Wisconsin

Wilson, Robert Erastus, 1947 (4), U. S. Atomic Energy Commission, Washington 25, D. C.

Wilson, Robert Rathbun, 1957 (3), Laboratory of Nuclear Studies, Cornell University, Ithaca, New York

Winstein, Saul, 1955 (5), Department of Chemistry, University of California, Los Angeles 24, California

Wintersteiner, Oskar, 1950 (14), Squibb Institute for Medical Research, New Brunswick, New Jersey

Wolfrom, Melville Lawrence, 1950 (5), Department of Chemistry, The Ohio State University, 121 West 19th Avenue, Columbus 10, Ohio

Wood, Harland Goff, 1953 (14), Department of Biochemistry, School of Medicine, Western Reserve University, Cleveland 6, Ohio

Wood, William Barry, Jr., 1959 (10), School of Medicine, Johns Hopkins University, 725 North Wolfe Street, Baltimore 5, Maryland

Woodring, Wendell Phillips, 1946 (6), United States Geological Survey, Washington 25, D. C.

Woodward, Robert Burns, 1953 (5), Department of Chemistry, Harvard University, 12 Oxford Street, Cambridge 38, Massachusetts

Woodworth, Robert Sessions, 1921 (12), 400 West 119th Street, New York 27, New York

Woolley, Dilworth Wayne, 1952 (14), Rockefeller Institute, New York 21, New York

Woolsey, Clinton Nathan, 1960 (9), Laboratory of Neurophysiology, 219 Medical Sciences Building, University of Wisconsin, Madison 6, Wisconsin

Wright, Sewall Green, 1934 (8), Department of Genetics, University of Wisconsin, Madison 6, Wisconsin

Wu, Chien-Shiung, 1958 (3), Department of Physics, Columbia University, New York 27, New York

Wulf, Oliver Reynolds, 1949 (13), United States Weather Bureau, Gates and Crellin Laboratories of Chemistry, California Institute of Technology, Pasadena 4, California

Wyckoff, Ralph Walter Graystone, 1949 (5), Departments of Bacteriology and Physics, University of Arizona, Tucson 25, Arizona

Yoder, Hatten Schuyler, Jr., 1958 (6), Geophysical Laboratory, Carnegie Institution of Washington, 2801 Upton Street, N. W., Washington 8, D. C.

Yost, Don Merlin Lee, 1944 (5), California Institute of Technology, Pasadena 4, California

Young, William Gould, 1951 (5), Department of Chemistry, University of California, Los Angeles 24, California

Zacharias, Jerrold Reinach, 1957 (3), Department of Physics, Massachusetts Institute of Technology, Cambridge 39, Massachusetts

Zachariasen, Frederik **William Houlder,** 1949 (3), Division of the Physical Sciences, University of Chicago, Chicago 37, Illinois

Zariski, Oscar, 1944 (1), Department of Mathematics, Harvard University, 2 Divinity Avenue, Cambridge 38, Massachusetts

Zener, Clarence Melvin, 1959 (4), Westinghouse Research Laboratories, Beulah Road, Churchill Borough, Pittsburgh 35, Pennsylvania

Zimm, Bruno Hasbrouck, 1958 (5), School of Science and Engineering, University of California, La Jolla, California

Zinn, Walter Henry, 1956 (4), Combustion Engineering, Inc., Nuclear Division, Windsor, Connecticut

Zirkle, Raymond Elliott, 1959 (8), Committee on Biophysics, University of Chicago, 5640 Ellis Avenue, Chicago 37, Illinois

Zworykin, Vladimir Kosma, 1943 (4), RCA Laboratories, David Sarnoff Research Center, Princeton, New Jersey

Zygmund, Antoni, 1960 (1), Department of Mathematics, University of Chicago, Chicago 37, Illinois

Number of Members July 1, 1960: 615.

MEMBERS EMERITI

Albright, Fuller, 1952 (10), 271 Goddard Avenue, Brookline 46, Massachusetts

Bailey, Irving Widmer, 1929 (7), Harvard University Herbarium, 22 Divinity Avenue, Cambridge 38, Massachusetts

Coble, Arthur Byron, 1924 (1), Lykens Hotel, Lykens, Pennsylvania

Coolidge, William David, 1925 (3), 1480 Lenox Road, Schenectady 8, New York

Goodpasture, Ernest William, 1937 (10), 3407 Hopkins Lane, Nashville 12, Tennessee

Hartman, Carl Gottfried, 1937 (8), 219 Norwood Avenue, North Plainfield, New Jersey

Mason, Max, 1923 (3), 1035 Harvard Avenue, Claremont, California

Saunders, Frederick Albert, 1925 (3), South Hadley, Massachusetts

Schultz, Adolph Hans, 1939 (11), Anthropologisches Institut, Sempersteig 3, Zurich, Switzerland

Tyzzer, Ernest Edward, 1942 (10), 175 Water Street, Wakefield, Massachusetts

Vandiver, Harry Shultz, 1934 (1), Box 7881, University of Texas, Austin 12, Texas

Number of Members Emeriti July 1, 1960: 11.

FOREIGN ASSOCIATES

The number in parentheses following the year of election indicates association within the sections of the National Academy of Sciences.

Adrian of **Cambridge,** Edgar Douglas, Baron, 1941 (9), Trinity College, Cambridge, England

Alexandroff, Paul A., 1947 (1), Mathematical Institute of the Academy of Sciences of the U.S.S.R., Bolshaya Kalushskaya 19, Moscow, U.S.S.R.

Ambartsumian, Victor Amazaspovich, 1959 (2), Burakan Astronomical Observatory, Erevan, Armenia, U.S.S.R.

Bailey, Sir Edward, 1944 (6), 76 Hampstead Way, London, N. W. 11, England

Bartlett, Sir Frederic Charles, 1947 (12), 161 Huntingdon Road, Cambridge, England

Best, Charles Herbert, 1950 (9), Banting and Best Department of Medical Research, University of Toronto, Toronto, Canada

Bohr, Niels, 1925 (3), Institute for Theoretical Physics, Blegdamsvej 15, Copenhagen, Denmark

Bordet, Jules, 1935 (10), Pasteur Institute, Rue du Remorqueur, 28, Brussels, Belgium

Born, Max, 1955 (3), Marcard Strasse 4, Bad Pyrmont, Germany

Bragg, Sir William Lawrence, 1945 (3), The Royal Institution, 21 Albemarle Street, London, W. 1, England

de Broglie, Prince Louis, 1948 (3), 94 Rue Perronet, Neuilly-sur-Seine, France

Brun, Edmond Antoine, 1960 (4), University of Paris, 8–10, place du Commerce, Paris XV, France

Bullard, Sir Edward Crisp, 1959 (13), Madingley Rise, Madingley Road, Cambridge, England

Burnet, Sir Macfarlane, 1954 (10), The Walter and Eliza Hall Institute of Medical Research, Melbourne, Australia

Caso, Alfonso, 1943 (11), Avenida Central 234, Tlacopac, Villa Obregón, Mexico 20, D. F.

Chapman, Sydney, 1946 (13), High Altitude Observatory, Boulder, Colorado, U. S. A.

Dale, Sir Henry Hallett, 1940 (9), The Wellcome Trust, 52 Queen Anne Street, London, W. 1, England

Dirac, Paul Adrien Maurice, 1949 (1), Department of Mathematics, St. John's College, Cambridge, England

Eskola, Pentti Eelis, 1951 (6), Helsinki University, Snellmanink. 5, Helsinki, Finland

Fisher, Sir Ronald Aylmer, 1948 (8), Division of Statistics, C.S.I.R.O., University of Adelaide, Adelaide, South Australia

von Frisch, Karl, 1951 (8), The Zoological Institute, University of Munich, Munich, Germany

Geijer, Per, 1958 (6), Agnevaegen 5, Djursholm I, Sweden

Gregory, Frederick Gugenheim, 1956 (7), Imperial College of Science and Technology, London, S.W. 7, England

Hadamard, Jacques, 1926 (1), 12 Rue Emile Faguet, Paris XIV, France

Hartmann, Max, 1959 (8), Max Planck Institute for Biology, Tübingen, Germany

Hill, Archibald Vivian, 1941 (9), 16 Bishopswood Road, Highgate, London, N.6, England

Hinshelwood, Sir Cyril Norman, 1960 (5), Department of Chemistry, Exeter College, Oxford, England

Hodge, William Vallance Douglas, 1959 (1), The Master's Lodge, Pembroke College, Cambridge, England

Hopf, Heinz, 1957 (1), Swiss Federal Institute of Technology, Zurich, Switzerland

Houssay, Bernardo Alberto, 1940 (9), Viamonte 2790, Buenos Aires, Argentina

Jeffreys, Sir Harold, 1945 (13), St. John's College, Cambridge, England

Jones, Sir Harold Spencer, 1943 (2), 40 Hesper Mews, London, S.W. 5, England

Kapitza, Peter Leonidovich, 1946 (3), S. I. Vavilov Institute of Physical Problems, Academy of Sciences of the U.S.S.R., Moscow, U.S.S.R.

Karrer, Paul, 1945 (5), University of Zurich, Zurich, Switzerland

Kihara, Hitoshi, 1958 (7), National Institute of Genetics, Misima, Japan

Krishnan, Sir Kariamanikkam Srinivasa, 1956 (3), National Physical Laboratory of India, Hillside Road, New Delhi 12, India

Landau, Lev Davidovich, 1960 (3), S. I. Vavilov Institute of Physical Problems, Academy of Sciences of the U.S.S.R., Moscow, U.S.S.R.

Leloir, Luis F., 1960 (14), Department of Biochemistry, University of Buenos Aires, Buenos Aires, Argentina

Levi, Giuseppe, 1940 (8), Instituto di Anatomia Umana, Corso Massimo D'Azeglio, 52, Turin, Italy

Lim, Robert K. S., 1942 (9), Medical Sciences Research Laboratory, Miles Laboratories, Inc., Elkhart, Indiana, U. S. A.

Lindblad, Bertil, 1955 (2), Stockholm Observatory, Saltsjöbaden, Sweden

Lwoff, André, 1955 (9), Institut Pasteur, Paris XV, France

Michotte, Albert Edouard (Baron Michotte van den Berck), 1956 (12), University of Louvain, Louvain, Belgium

Mott, Nevill **F**rancis, 1957 (3), University of Cambridge, Cavendish Laboratory, Free School Lane, Cambridge, England

Oort, Jan Hendrik, 1953 (2), Observatory of Leiden, Leiden, The Netherlands

Penfield, Wilder, 1953 (10), Montreal Neurological Institute, 3801 University Street, Montreal 2, Canada

Pérès, Joseph Jean Camille, 1956 (1), University of Paris, Paris V, France

Piéron, Henri, 1949 (12), Institute of Psychology, University of Paris, Paris, France

Portevin, Albert M. G. R., 1954 (4), 21, Boulevard de Beauséjour, Paris XVI, France

Reichstein, Tadeus, 1952 (5), Organisch-chemische Anstalt, St. Johanns-Ring 19, Basel, Switzerland

Renner, Otto, 1954 (7), The Botanical Institute, University of Munich, Munich, Germany

Robinson, Sir Robert, 1934 (5), 170 Piccadilly, London, W. 1, England

Ruzicka, Leopold, 1944 (5), Department of Organic Chemistry, Institute of Technology, Zurich, Switzerland

Southwell, Sir Richard Vynne, 1943 (4), The Old House, Trumpington, Cambridge, England

Steacie, Edgar William Richard, 1957 (5), National Research Council, Ottawa, Canada

Svedberg, The, 1945 (5), Fysikalisk-Kemiska Institutionen, Uppsala University, Uppsala, Sweden

Taylor, Sir Geoffrey Ingram, 1945 (1), Trinity College, Cambridge, England

Theorell, Axel **Hugo,** 1957 (14), Nobel Institute of Medicine, Solnavagen 1, Stockholm 60, Sweden

Tiselius, Arne W. K., 1949 (14), Institute of Biochemistry, Uppsala University, Uppsala, Sweden

Todd, Sir Alexander Robertus, 1955 (5), University of Cambridge, University Chemical Laboratory, Pembroke Street, Cambridge, England

Vallée-Poussin, C. de la, 1929 (1), 42, Avenue du Houx, Boitsfort, Belgium

Vening Meinesz, Felix **A**ndries, 1939 (13), Potgieterlaan 5, Amersfoort, The Netherlands

Watson, D. M. S., 1938 (8), University College, Gower Street, London, W.C. 1, England

Winge, Öjvind, 1949 (14), Department of Physiology, Carlsberg Laboratory, Copenhagen (Valby), Denmark

Yukawa, Hideki, 1949 (3), Yukawa Hall, Kyoto University, Kyoto, Japan

Number of Foreign Associates July 1, 1960: 65.

SECTIONS

(1) *Mathematics*—36 members

Albert, A. A., *Chairman* (1961)
Ahlfors, L. V.
Alexander, J. W.
Artin, E.
Bell, E. T.
Bochner, S.
Brauer, R. D.
Courant, R.
Doob, J. L.
Douglas, Jesse
Eilenberg, S.
Eisenhart, L. P.
Evans, G. C.
Feller, William
Friedrichs, K. O.
Gödel, Kurt
Hille, Einar
Jacobson, Nathan
Lefschetz, Solomon
Mac Lane, Saunders
McShane, E. J.
Montgomery, Deane
Moore, R. L.
Morse, Marston
Murnaghan, F. D.
Shannon, C. E.
Smith, Paul A.
Steenrod, N. E.
Stone, M. H.
Thomas, T. Y.
Veblen, Oswald
Walsh, J. L.
Whitney, Hassler
Whyburn, G. T.
Zariski, O.
Zygmund, Antoni

Foreign Associates

Alexandroff, P. A.
Dirac, P. A. M.
Hadamard, Jacques
Hodge, W. V. D.
Hopf, Heinz
Pérès, Joseph
Taylor, Sir Geoffrey
Vallée-Poussin, C. de la

(2) *Astronomy*—30 members

Mayall, N. U., *Chairman* (1962)
Abbot, C. G.
Babcock, H. D.
Babcock, H. W.
Bowen, I. S.
Brouwer, Dirk
Chandrasekhar, S.
Clemence, G. M.
Goldberg, Leo
Greenstein, J. L.
Joy, A. H.
Kuiper, G. P.
McMath, R. R.
Menzel, D. H.
Merrill, P. W.
Minkowski, R. L.
Morgan, W. W.
Nicholson, S. B.
Ross, F. E.
Schwarzschild, M.
Seares, F. H.
Shapley, Harlow
Slipher, V. M.
Spitzer, Lyman, Jr.
Stebbins, Joel
Struve, Otto
Tousey, Richard
Whipple, F. L.
Whitford, A. E.
Wilson, Olin C.

Foreign Associates

Ambartsumian, V.
Jones. Sir H. Spencer
Lindblad, Bertil
Oort, Jan Hendrik

(3) *Physics*—92 members

Allison, S. K., *Chairman* (1963)
Alvarez, L. W.
Anderson, C. D.
Anderson, H. L.
Bacher, R. F.
Bainbridge, K. T.
Bardeen, John
Beams, J. W.
Bethe, H. J.
Birge, R. T.
Bleakney, Walker
Bloch, Felix
Bloembergen, N.
Bonner, T. W.

Bradbury, N. E.
Brattain, W. H.
Breit, Gregory
Bridgman, P. W.
Brillouin, Leon
Brode, R. B.
Chamberlain, Owen
Coblentz, W. W.
Compton, A. H.
Condon, E. U.
Dennison, D. M.
Deutsch, M.
DuBridge, L. A.
DuMond, J. W. M.
Dunning, J. R.
Elsasser, W. M.
Epstein, P. S.
Feynman, R. P.
Fowler, W. A.
Franck, James
Gamow, George
Gell-Mann, Murray
Goldhaber, M.
Goudsmit, S. A.
Herb, R. G.
Herzfeld, K. F.
Hofstadter, R.
Houston, W. V.
Hull, A. W.
Kemble, E. C.
Kent, R. H.
Kerst, D. W.
Kittel, C.
Kusch, P.
Lamb, W. E., Jr. (abroad)
Land, E. H.
Lauritsen, C. C.
Loomis, F. W.
Marshak, R. E.
Mayer, M. G.
McMillan, E. M.
Meggers, W. F.
Morse, P. M.
Mulliken, R. S.
Nier, A. O. C.
O'Brien, Brian
Oppenheimer, J. R.
Panofsky, W. K. H.
Purcell, E. M.
Rabi, I. I.
Ramsey, N. F.
Robertson, H. P.
Rossi, Bruno
Schiff, L. I.
Schwinger, Julian
Segrè, E.
Seitz, Frederick
Serber, R.
Simpson, J. A.
Slater, J. C.
Stern, Otto
Street, J. C.
Teller, Edward
Thomas, L. H.
Townes, C. H.
Tuve, M. A.
Uhlenbeck, G. E.
Van Vleck, J. H.
Webster, D. L.
Weisskopf, V. F.
Wentzel, Gregor
Wheeler, J. A.
Wigner, E. P.
Wilson, Edwin B.
Wilson, Robert R.
Wu, C. S.
Zacharias, J. R.
Zachariasen, W. H.

Foreign Associates

Bohr, Niels
Born, Max
Bragg, Sir Lawrence
de Broglie, Prince Louis
Kapitza, P. L.
Krishnan, Sir K.
Landau, L. D.
Mott, N. F.
Yukawa, Hideki

(4) *Engineering*—46 members

Fisk, J. B., *Chairman* (1962)
Astin, A. V.
Bain, E. C.
Benedict, Manson
Bode, H. W.
Briggs, L. J.
Bush, Vannevar
Chipman, John
Curme, G. O., Jr.
Den Hartog, J. P.
Draper, C. S.
Dryden, H. L.
Fletcher, Harvey
Foote, P. D.
Gibbs, W. F.
Gilliland, E. R.
Greenewalt, C. H.
Hoover, Herbert
Hunsaker, J. C.
Jeffries, Zay
Kelly, M. J.
Kinzel, A. B.
Lewis, W. K.
Loomis, A. L.
Mehl, R. F.
Murphree, E. V.
Olson, Harry F.
Pierce, J. R.
Raymond, A. E.
Savage, J. L.
Sherwood, T. K.
Shockley, W.
Slepian, Joseph
Smith, C. S.
Soderberg, C. R.
Stratton, J. A.
Suits, C. G.
Terman, F. E.
Thomas, C. A.
Timoshenko, Stephen
von Kármán, T.
Wiesner, J. B.
Wilson, Robert E.
Zener, Clarence
Zinn, W. H.
Zworykin, V. K.

Foreign Associates

Brun, Edmond A. Portevin, Albert M. G. R Southwell, Sir Richard V.

(5) *Chemistry*—90 members

Pitzer, K. S., *Chairman* (1962)
Adams, Roger
Badger, R. M.
Bartlett, P. D.
Blomquist, A. T.
Bolton, E. K.
Brewer, Leo
Brode, W. R.
Brown, H. C.
Calvin, Melvin
Conant, J. B.
Cope, A. C.
Crawford, Bryce, Jr.
Daniels, Farrington
Davidson, N.
Debye, Peter
Doty, Paul
Elderfield, R. C.
Emmett, P. H.
Eyring, Henry
Ferry, John D.
Fieser, L. F.
Flory, P. J.
Folkers, Karl
Fuoss, R. M.
Fuson, R. C.
Gates, M.
Giauque, W. F.
Gilman, Henry
Gutowsky, H. S.
Hammett, L. P.
Harned, H. S.
Hauser, C. R.
Hendricks, S. B.
Hildebrand, J. H.
Hirschfelder, J. O.
Hornig, D. F.
Jacobs, W. A.
Johnson, J. R.
Johnson, W. S.
Keyes, F. G.
Kimball, G. E.
Kistiakowsky, G. B.
Kolthoff, I. M.
Kraus, C. A.
La Mer, V. K.
Leonard, N. J.
Libby, W. F.
Lind, S. C.
Longsworth, L. G.
Lucas, H. J.
MacInnes, D. A.
Marvel, C. S.
Mayer, J. E.
McElvain, S. M.
Mees, C. E. K.
Newman, M. S.
Niemann, C. G.
Noyes, W. A., Jr.
Onsager, Lars
Pauling, Linus
Roberts, John D.
Rossini, F. D.
Scatchard, George
Schlesinger, H. I.
Seaborg, G. T.
Shedlovsky, Theodore
Sheehan, J. C.
Smith, L. I.
Smyth, C. P.
Spedding, F. H.
Stockmayer, W. H.
Stork, Gilbert
Tarbell, D. S.
Taube, Henry
Tishler, Max
Urey, H. C.
Warner, J. C.
Westheimer, F. H.
Williams, J. W.
Williams, Robert R.
Williams, Roger J.
Wilson, E. Bright, Jr.
Winstein, Saul
Wolfrom, M. L.
Woodward, R. B.
Wyckoff, R. W. G.
Yost, D. M.
Young, W. G.
Zimm, B. H.

Foreign Associates

Hinshelwood, Sir C.N.
Karrer, Paul
Reichstein, Tadeus
Robinson, Sir Robert
Ruzicka, Leopold
Steacie, E. W. R.
Svedberg, The
Todd, Sir Alexander

(6) *Geology*—34 members

Hess, H. H., *Chairman* (1963)
Abelson, P. H.
Allen, E. T.
Anderson, C. A.
Birch, Francis
Blackwelder, Eliot
Bradley, W. H.
Bramlette, M. N.

Bucher, W. H.
Buddington, A. F.
Buerger, M. J.
Chaney, R. W.
Cloos, Ernst
Dunbar, C. O.
Gilluly, James
Gregory, W. K.
Hedberg, H. D.
Hewett, D. F.
Hubbert, M. King
Kelley, W. P.
Knopf, Adolph
Krauskopf, K. B.
Larsen, E. S., Jr.
Longwell, C. R.
Lovering, T. S.
Nolan, T. B.
Rubey, W. W.
Russell, R. J.
Schairer, J. F.
Simpson, G. G.
Turner, F. J.
Williams, Howel
Woodring, W. P.
Yoder, H. S., Jr.

Foreign Associates

Bailey, Sir Edward
Eskola, Pentti
Geijer, Per

(7) *Botany*—43 members

Riker, A. J., *Chairman* (1962)
Anderson, Edgar
Barker, H. A.
Beadle, G. W.
Blinks, L. R.
Bonner, David M.
Bonner, James
Braun, A. C.
Brink, R. A.
Burkholder, P. R.
Chandler, W. H.
Clausen, Jens
Cleland, R. E.
Couch, J. N.
Delbrück, Max
Dodge, B. O.
Esau, Katherine
Fred, E. B.
Goddard, D. R.
Hershey, A. D.
Hollaender, A.
Horsfall, J. G.
Jones, D. F.
Kaufmann, B. P.
Lederberg, J.
Luria, S. E.
Mangelsdorf, P. C.
McClintock, Barbara
Osterhout, W. J. V.
Raper, K. B.
Rhoades, M. M.
Robbins, W. J.
Sax, Karl
Sinnott, E. W.
Skoog, Folke
Stakman, E. C.
Stebbins, G. L.
Thimann, K. V.
Van Niel, C. B.
Walker, J. C.
Went, F. W.
Wetmore, R. H.
Wilson, P. W.

Foreign Associates

Gregory, F. G.
Kihara, H.
Renner, Otto

(8) *Zoology and Anatomy*—53 members

Demerec, Milislav, *Chairman* (1961)
Bartelmez, G. W.
Bigelow, H. B.
Bloom, William
Bodenstein, D. H.
Bodian, David
Burns, R. K.
Castle, W. E.
Cleveland, L. R.
Colbert, E. H.
Corner, G. W.
Danforth, C. H.
Dobzhansky, Th.
Dunn, L. C.
Glass, Bentley
Griffin, D. R. (abroad)
Hamburger, Viktor
Haskins, C. P.
Hisaw, F. L.
Holtfreter, J.
Hubbs, C. L.
Hutchinson, G. E.
Irwin, M. R.
Jacobs, M. H.
Kellogg, Remington
Lerner, I. M.
Lewis, W. H.
Mayr, Ernst
Mazia, Daniel
Metz, C. W.
Miller, A. H.
Mirsky, A. E.
Muller, H. J.
Nicholas, J. S.
Painter, T. S.
Patterson, J. T.
Petrunkevitch, A.
Riddle, Oscar

Romer, A. S.
Schmitt, F. O.
Schrader, Franz
Smith, Philip E.
Sonneborn, T. M.
Stern, Curt
Stone, W. S.
Sturtevant, A. H.
Twitty, V. C.
Weiss, Paul
Wetmore, Alexander
Williams, C. M.
Willier, B. H.
Wright, Sewall
Zirkle, R. E.

Foreign Associates

Fisher, Sir Ronald
von Frisch, Karl
Hartmann, Max
Levi, Giuseppe
Watson, D. M. S.

(9) *Physiology*—34 members

Long, C. N. H., *Chairman* (1963)
Astwood, E. B.
Aub, Joseph C.
Bard, Philip
Brink, Frank, Jr.
Bronk, Detlev W.
Cole, K. S.
Cournand, André
Davis, Hallowell
Erlanger, Joseph
Evans, H. M.
Fenn, W. O.
Forbes, Alexander
Gasser, H. S.
Gerard, R. W.
Hartline, H. K.
Hastings, A. B.
Landis, E. M.
Lloyd, D. P. C.
Loeb, R. F.
Lorente de Nó, R.
Magoun, H. W.
Mann, Frank
Marshall, E. K., Jr.
Meek, W. J.
Pitts, R. F.
Redfield, A. C.
Richards, A. N.
Richards, D. W.
Schmidt, C. F.
Smith, Homer W.
Visscher, M. B.
Wiggers, C. J.
Woolsey, C. N.

Foreign Associates

Lord Adrian
Best, C. H.
Dale, Sir Henry
Hill, A. V.
Houssay, B. A.
Lim, Robert K. S.
Lwoff, André

(10) *Pathology and Microbiology*—42 members

Shope, R. E., *Chairman* (1963)
Armstrong, Charles
Bailey, P.
Blalock, Alfred
Cannon, P. R.
Castle, W. B.
Coggeshall, L. T.
Cole, Rufus
Dalldorf, Gilbert
Dingle, J. H.
Dochez, A. R.
Dragstedt, L. R.
Dubos, R. J.
Enders, J. F.
Francis, Thomas, Jr.
Goebel, W. F.
Heidelberger, Michael
Horsfall, F. L., Jr.
Huebner, R. J.
Huggins, C. B.
Little, C. C.
Long, E. R.
MacLeod, C. M.
Maxcy, K. F.
McMaster, P. D.
Meyer, K. F.
Miller, C. P.
Opie, E. L.
Paul, John R.
Puck, T. T.
Rich, A. R.
Rivers, T. M.
Robertson, O. H.
Rous, Peyton
Sabin, Albert B.
Smadel, J. E.
Taliaferro, W. H.
Tillett, W. S.
Waksman, S. A.
Watson, C. J.
Whipple, G. H.
Wood, W. Barry, Jr.

Foreign Associates

Bordet, Jules
Burnet, Sir Macfarlane
Penfield, Wilder

(11) *Anthropology*—13 members

Haury, Emil W. *Chairman* (1963)
Albright, W. F.
Coon, C. S.
Herskovits, M. J.
Kidder, A. V.
Kluckhohn, Clyde
Kroeber, A. L.
Lothrop, S. K.
Movius, H. L., Jr.
Shapiro, H. L.
Spier, Leslie
Steward, J. H.
Willey, G. R.

Foreign Associate

Caso, Alfonso

(12) *Psychology*—24 members

Lindsley, D. B., *Chairman* (1962)
Beach, F. A.
Boring, E. G.
Carmichael, Leonard
Galambos, R.
Gesell, Arnold
Graham, C. H.
Guilford, J. P.
Harlow, H. F.
Hilgard, E. R.
Hovland, C. I.
Klüver, Heinrich
Köhler, Wolfgang
Miles, W. R.
Miller, N. E.
Pfaffmann, Carl
Richter, C. P.
Skinner, B. F.
Spence, K. W.
Sperry, R. W.
Stevens, S. S.
v. Békésy, Georg
Wever, E. G.
Woodworth, R. S.

Foreign Associates

Bartlett, Sir Frederic
Michotte, Albert E.
Piéron, Henri

(13) *Geophysics*—30 members

Slichter, L. B., *Chairman* (1963)
Adams, L. H.
Benioff, Hugo
Berkner, L. V.
Bjerknes, J.
Booker, H. G.
Brown, Harrison
Byerly, Perry
Byers, H. R.
Eckart, Carl
Ewing, Maurice
Friedman, H.
Griggs, D. T.
Gunn, Ross
Haurwitz, B.
Iselin, C. O'D.
Kaplan, Joseph
Lambert, W. D.
Munk, W. H.
Pekeris, C. L.
Piggot, C. S.
Press, Frank
Reichelderfer, F. W.
Revelle, Roger
Thompson, T. G.
Van Allen, J. A.
Verhoogen, John
Vestine, E. H.
Villard, O. G., Jr.
Wulf, O. R.

Foreign Associates

Bullard, Sir Edward
Chapman, Sydney
Jeffreys, Sir Harold
Vening Meinesz, F. A.

(14) *Biochemistry*—48 members

du Vigneaud, V., *Chairman* (1961)
Anderson, R. J.
Ball, E. G.
Balls, A. K.
Bloch, K. E.
Carter, H. E.
Chance, Britton
Clark, W. M.

Clarke, H. T.
Cori, Carl F.
Craig, L. C.
Doisy, E. A.
Edsall, J. T.
Elvehjem, C. A.
Fruton, J. S.
Hassid, W. Z.
Kalckar, H. M.
Kendall, E. C.
King, C. G.
Kornberg, A.
Lardy, Henry
Lehninger, A. L.
Link, K. P.
Lipmann, Fritz
Maynard, L. A.
McCollum, E. V.
Moore, Stanford
Northrop, J. H.
Ochoa, Severo
Oncley, J. L.
Rittenberg, David
Rose, W. C.
Shaffer, P. A.
Shemin, David
Snell, E. E.
Stanley, W. M.
Stein, W. H.
Szent-Györgyi, A.
Tatum, E. L.
Van Slyke, D. D.
Vickery, H. B.
Wald, George
Werkman, C. H.
Williams, R. C.
Wilson, D. W.
Wintersteiner, O.
Wood, H. G.
Woolley, D. W.

Foreign Associates

Leloir, Luis F.
Theorell, Hugo
Tiselius, Arne W. K.
Winge, Öjvind

GEOGRAPHICAL LISTING of ACADEMY MEMBERS

Arizona

Haury, Emil W.
Kuiper, G. P.
Slipher, V. M.
Wyckoff, R. W. G.

California

Adams, L. H.
Alvarez, L. W.
Anderson, C. D.
Babcock, H. D.
Babcock, H. W.
Bacher, R. F.
Badger, R. M.
Balls, A. K.
Barker, H. A.
Beach, F. A.
Beadle, G. W.
Bell, E. T.
Benioff, Hugo
Birge, R. T.
Bjerknes, J.
Blackwelder, Eliot
Blinks, L. R.
Bloch, Felix
Bonner, James
Bowen, I. S.
Bramlette, M. N.
Brewer, Leo
Brode, R. B.
Brown, Harrison
Byerly, Perry
Calvin, Melvin
Castle, W. E.
Chamberlain, Owen
Chandler, W. H.
Chaney, R. W.
Clausen, Jens
Danforth, C. H.
Davidson, N.
Delbrück, Max
DuBridge, L. A.
DuMond, J. W. M.
Eckart, Carl
Epstein, P. S.
Esau, Katherine
Evans, G. C.
Evans, H. M.
Feynman, R. P.
Fowler, W. A.
Gell-Mann, Murray
Giauque, W. F.
Greenstein, J. L.
Griggs, D. T.
Guilford, J. P.
Hassid, W. Z.
Hastings, A. Baird
Hewett, D. F.
Hildebrand, J. H.
Hilgard, E. R.
Hofstadter, R.
Hubbs, C. L.
Johnson, W. S.
Joy, A. H.
Kaplan, Joseph
Kelley, W. P.
Kerst, D. W.
Kittel, C.
Knopf, Adolph
Kornberg, A.
Krauskopf, K. B.
Kroeber, A. L.
Lauritsen, C. C.
Lederberg, J.
Lerner, I. M.
Libby, W. F.
Lindsley, D. B.
Longwell, C. R.
Lucas, H. J.
Magoun, H. W.
Mason, Max
Mayall, N. U.
Mayer, J. E.
Mayer, M. G.
Mazia, Daniel
McMillan, E. M.
Merrill, P. W.
Meyer, K. F.
Miller, A. H.
Minkowski, R. L.
Munk, W. H.
Nicholson, S. B.
Niemann, Carl
Northrop, J. H.
Panofsky, W. K. H.
Pauling, Linus
Pitzer, K. S.
Press, Frank
Raymond, A. E.
Revelle, Roger
Roberts, John D.
Robertson, H. P.
Robertson, O. H.
Ross, F. E.
Schiff, L. I.
Seaborg, G. T.
Seares, F. H.
Segrè, Emilio
Shockley, W.
Slichter, L. B.
Smith, P. E.
Snell, E. E.
Sperry, R. W.
Spier, Leslie
Stanley, W. M.
Stebbins, G. L.
Stebbins, Joel
Stern, Curt
Stern, Otto
Sturtevant, A. H.
Teller, Edward
Terman, F. E.
Timoshenko, S. P.
Turner, F. J.
Twitty, V. C.
Urey, H. C.
Van Niel, C. B.
Verhoogen, John
Vestine, E. H.
Villard, O. G., Jr.
von Kármán, T.
Webster, D. L.
Whitford, A. E.
Williams, Howel
Williams, R. C.
Wilson, Olin C.
Winstein, Saul
Wulf, O. R.
Yost, D. M.
Young, W. G.
Zimm, B. H.

Colorado

*Chapman, Sydney
Gamow, George
Gilluly, James

* Foreign Associate

Haurwitz, B.
Lovering, T. S.
Puck, T. T.
Savage, J. L.

Connecticut

Anderson, R. J.
Bonner, David M.
Breit, G.
Brouwer, Dirk
Clarke, H. T.
Dunbar, C. O.
Fruton, J. S.
Fuoss, R. M.
Gesell, Arnold
Harned, H. S.
Hille, Einar
Horsfall, J. G.
Hovland, C. I.
Hutchinson, G. E.
Jacobson, Nathan
Jones, D. F.
Lambert, W. D.
Long, C. N. H.
Miles, W. R.
Miller, N. E.
Nicholas, J. S.
O'Brien, Brian
Onsager, Lars
Paul, J. R.
Petrunkevitch, A.
Sax, Karl
Sinnott, E. W.
Vickery, H. B.
Zinn, W. H.

Delaware

Bolton, E. K.
Greenewalt, C. H.

District of Columbia

Abbot, C. G.
Abelson, P. H.
Anderson, C. A.
Astin, A. V.
Bradley, W. H.
Briggs, L. J.
Brode, W. R.
Carmichael, Leonard
Clemence, G. M.
Coblentz, W. W.
Dryden, H. L.
Foote, P. D.
Friedman, H.
Galambos, R.
Gunn, Ross
Haskins, C. P.
Herzfeld, K. F.
Kellogg, Remington
Larsen, E. S., Jr.
Meggers, W. F.
Nolan, T. B.
Reichelderfer, F. W.
Rubey, W. W.
Schairer, J. F.
Tousey, R.
Tuve, M. A.
Wetmore, Alexander
Wilson, R. E.
Woodring, W. P.
Yoder, H. S., Jr.

Florida

Dragstedt, L. R.
Riddle, Oscar

Georgia

Cleveland, L. R.

Illinois

Adams, Roger
Albert, A. A.
Allison, S. K.
Anderson, H. L.
Bailey, P.
Bardeen, John
Bloom, William
Byers, H. R.
Cannon, Paul
Carter, H. E.
Coggeshall, L. T.
Doob, J. L.
Franck, James
Fuson, R. C.
Gutowsky, H. S.
Herskovits, M. J.
Huggins, Charles
Klüver, Heinrich
Leonard, N. J.
Loomis, F. W.
Mac Lane, Saunders
Marvel, C. S.
Miller, C. P.
Mulliken, R. S.
Rose, W. C.
Schlesinger, H. I.
Seitz, Frederick
Simpson, J. A.
Smith, C. S.
Steward, J. H.
Stone, M. H.
Taliaferro, W. H.
Taube, Henry
Wentzel, Gregor
Zachariasen, W. H.
Zirkle, R. E.
Zygmund, Antoni

Indiana

Brown, H. C.
Cleland, R. E.
*Lim, R. K. S.
Muller, H. J.
Rhoades, M. M.
Rossini, F. D.
Sonneborn, T. M.
Thomas, T. Y.

Iowa

Gilman, Henry
Spedding, F. H.
Spence, K. W.
Van Allen, J. A.
Werkman, C. H.

Louisiana

Russell, R. J.

Maine

Little, C. C.

Maryland

Albright, W. F.
Armstrong, Charles
Bard, Philip
Blalock, Alfred
Bodian, David
Burns, R. K.
Clark, W. M.
Cloos, Ernst
Cole, K. S.

* Foreign Associate

Emmett, P. H.
Glass, Bentley
Hendricks, S. B.
Huebner, R. J.
Kalckar, H. M.
Kent, R. H.
Lehninger, A. L.
Marshall, E. K., Jr.
Maxcy, K. F.
McCollum, E. V.
Murnaghan, F. D.
Piggot, C. S.
Rich, A. R.
Richter, C. P.
Smadel, J. E.
Willier, B. H.
Wood, W. B., Jr.

Massachusetts

Ahlfors, L. V.
Albright, Fuller
Allen, E. T.
Astwood, E. B.
Aub, Joseph C.
Bailey, I. W.
Bainbridge, K. T.
Ball, E. G.
Bartlett, P. D.
Benedict, Manson
Bigelow, H. B.
Birch, Francis
Bloch, K. E.
Bloembergen, N.
Boring, E. G.
Brauer, R.
Bridgman, P. W.
Buerger, M. J.
Bush, Vannevar
Castle, W. B.
Chipman, John
Cope, A. C.
Den Hartog, J. P.
Deutsch, M.
Doty, Paul
Draper, C. S.
Edsall, J. T.
Enders, J. F.
Fieser, L. F.
Forbes, Alexander
Gilliland, E. R.
Goldberg, Leo
Griffin, D. R.
Hisaw, F. L.
Hunsaker, J. C.
Iselin, C. O'D.
Jeffries, Zay
Kemble, E. C.
Keyes, F. G.
Kidder, A. V.
Kimball, G. E.
Kistiakowsky, G. B.
Kluckhohn, Clyde
Land, E. H.
Landis, E. M.
Lewis, W. K.
Lothrop, S. K.
Luria, S. E.
Mangelsdorf, P. C.
Mayr, Ernst
Menzel, D. H.
Metz, C. W.
Morse, P. M.
Movius, H. L., Jr.
Oncley, J. L.
Purcell, E. M.
Ramsey, Norman
Redfield, A. C.
Romer, A. S.
Rossi, B. B.
Saunders, F. A.
Scatchard, George
Schmitt, F. O.
Schwinger, Julian
Shannon, C. E.
Sheehan, J. C.
Sherwood, T. K.
Simpson, G. G.
Skinner, B. F.
Slater, J. C.
Soderberg, C. R.
Stevens, S. S.
Stockmayer, W.
Stratton, J. A.
Street, J. C.
Szent-Györgyi, A.
Thimann, K. V.
Tyzzer, E. E.
Van Vleck, J. H.
v. Békésy, Georg
Wald, George
Walsh, J. L.
Weisskopf, V. F.
Westheimer, F. H.
Wetmore, R. H.
Whipple, F. L.
Wiesner, J. B.
Willey, G. R.
Williams, C. M.
Wilson, E. Bright, Jr.
Wilson, Edwin B.
Woodward, R. B.
Zacharias, J. R.
Zariski, Oscar

Michigan

Dennison, D. M.
Elderfield, R. C.
Francis, Thomas, Jr.
Gerard, R. W.
McMath, R. R.
Uhlenbeck, G. E.

Minnesota

Crawford, Bryce, Jr.
Kolthoff, I. M.
Mann, F. C.
Nier, A. O. C.
Smith, L. I.
Stakman, E. C.
Visscher, M. B.
Watson, C. J.

Missouri

Anderson, Edgar
Compton, A. H.
Condon, E. U.
Cori, C. F.
Davis, Hallowell
Doisy, E. A.
Erlanger, Joseph
Hamburger, Viktor
Shaffer, P. A.
Thomas, C. A.
Went, F. W.

Montana

Bartelmez, G. W.

New Hampshire

Köhler, Wolfgang
Shapley, Harlow

New Jersey

Alexander, J. W.
Bleakney, Walker
Bochner, S.
Bode, H. W.
Brattain, W. H.
Buddington, A. F.
Eisenhart, L. P.
Feller, William
Fisk, J. B.
Folkers, Karl
Gödel, Kurt
Hartman, C. G.
Hedberg, H. D.
Heidelberger, M.
Hess, H. H.
Hornig, D. F.
Kelly, M. J.
Kendall, E. C.
Lefschetz, Solomon
Montgomery, Deane
Morse, Marston
Murphree, E. V.
Olson, Harry F.
Oppenheimer, J. R.
Pierce, J. R.
Schwarzschild, M.
Smyth, C. P.
Spitzer, Lyman, Jr.
Steenrod, N. E.
Tishler, Max
Veblen, Oswald
Waksman, S. A.
Wever, E. G.
Wheeler, J. A.
Whitney, Hassler
Wigner, E. P.
Williams, R. R.
Wintersteiner, Oskar
Zworykin, V. K.

New Mexico

Bradbury, N. E.
Elsasser, W. M.

New York

Berkner, L. V.
Bethe, H. A.
Blomquist, A. T.
Booker, H. G.
Braun, A. C.
Brillouin, Leon
Brink, Frank, Jr.
Bronk, D. W.
Bucher, W. H.
Burkholder, P. R.
Colbert, E. H.
Cole, Rufus
Conant, J. B.
Coolidge, W. D.
Corner, G. W.
Courant, Richard
Cournand, André
Craig, L. C.
Curme, G. O., Jr.
Dalldorf, Gilbert
Debye, Peter
Demerec, Milislav
Dobzhansky, Th.
Dochez, A. R.
Dodge, B. O.
Douglas, Jesse
Dubos, R. J.
Dunn, L. C.
Dunning, J. R.
du Vigneaud, Vincent
Eilenberg, Samuel
Ewing, Maurice
Fenn, W. O.
Friedrichs, K. O.
Gasser, H. S.
Gates, M.
Gibbs, W. F.
Goebel, W. F.
Goldhaber, M.
Goudsmit, S. A.
Graham, C. H.
Gregory, W. K.
Hammett, L. P.
Hartline, H. K.
Hershey, A. D.
Holtfreter, J.
Hoover, Herbert
Horsfall, F. L., Jr.
Hull, A. W.
Jacobs, W. A.
Johnson, J. R.
Kaufmann, B. P.
King, C. G.
Kinzel, A. B.
Kusch, P.
La Mer, V. K.
Lipmann, Fritz
Lloyd, D. P. C.
Loeb, R. F.
Longsworth, L. G.
Loomis, A. L.
Lorente de Nó, R.
MacInnes, D. A.
MacLeod, C. M.
Marshak, R. E.
Maynard, L. A.
McClintock, Barbara
McMaster, P. D.
Mirsky, A. E.
Moore, Stanford
Noyes, W. A., Jr.
Ochoa, Severo
Opie, E. L.
Osterhout, W. J. V.
Pitts, R. F.
Rabi, I. I.
Richards, D. W.
Rittenberg, David
Rivers, T. M.
Robbins, W. J.
Rous, Peyton
Serber, Robert
Shapiro, H. L.
Shedlovsky, Theodore
Shemin, David
Shope, R. E.
Smith, H. W.
Smith, P. A.
Stein, W. H.
Stork, Gilbert
Suits, C. G.
Tarbell, D. S.
Tatum, E. L.
Thomas, L. H.
Tillett, W. S.
Townes, C. H.
Van Slyke, D. D.
Weiss, Paul
Whipple, G. H.
Wilson, Robert R.
Woodworth, R. S.
Woolley, D. W.
Wu, C. S.

North Carolina

Couch, J. N.
Hauser, C. R.
Schrader, Franz

Ohio

Dingle, J. H.
Newman, M. S.
Sabin, A. B.
Wiggers, C. J.
Wolfrom, M. L.
Wood, H. G.

Pennsylvania

Bain, E. C.
Chance, Britton
Coble, A. B.
Coon, C. S.
Flory, P. J.
Goddard, D. R.
Jacobs, M. H.
Lewis, W. H.
Richards, A. N.
Schmidt, C. F.
Slepian, Joseph
Warner, J. C.
Wilson, D. W.
Zener, Clarence

Rhode Island

Kraus, C. A.
Pfaffmann, Carl

Tennessee

Goodpasture, E. W.
Hollaender, A.
Lind, S. C.

Texas

Bonner, T. W.
Houston, W. V.
Hubbert, M. K.
Moore, R. L.
Painter, T. S.
Patterson, J. T.
Stone, W. S.
Vandiver, H. S.
Williams, R. J.

Utah

Eyring, Henry
Fletcher, Harvey

Virginia

Beams, J. W.
Bodenstein, D. H.
Long, E. R.
McShane, E. J.
Whyburn, G. T.

Washington

Thompson, T. G.

West Virginia

Struve, Otto

Wisconsin

Brink, R. A.
Chandrasekhar, S.
Daniels, Farrington
Elvehjem, C. A.
Ferry, John D.
Fred, E. B.
Harlow, H. F.
Herb, R. G.
Hirschfelder, J. O.
Irwin, M. R.
Lardy, Henry
Link, K. P.
McElvain, S. M.
Meek, W. J.
Morgan, W. W.
Raper, K. B.
Riker, A. J.
Skoog, Folke
Walker, J. C.
Williams, J. W.
Wilson, P. W.
Woolsey, C. N.
Wright, Sewall

Hawaii

Mees, C. E. K.

Members Abroad

England—

Lamb, W. E., Jr.

Germany—

Artin, E.

Israel—

Pekeris, C. L.

Switzerland—

Mehl, R. F.
Schultz, A. H.

Volume 46 March 1960 Number 3

p. 281 Fölle: Szilard: papers

Proceedings of the National Academy of Sciences

of the United States of America

NATIONAL ACADEMY OF SCIENCES
2101 CONSTITUTION AVENUE
WASHINGTON 25, D. C.

March 17, 1960

Dear Dr. Szilard:

I am glad to transmit, with the compliments of the Academy, a copy of the March issue of the Proceedings.

It was a great pleasure to hear from you and work with you again. I hope that the printing of these splendid papers is as you wished it to be.

With every good wish,
I remain

Yours sincerely,

Josephine A. Williams

The Proceedings of the National Academy of Sciences

Subscription price is $12.50 for 1 year, $24.00 for 2 years, and $34.50 for 3 years; the price of a single issue is $1.50. Make all remittances payable to the National Academy of Sciences in U.S. currency or its equivalent.

Editorial correspondence should be addressed to the PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES, 2101 Constitution Avenue, Washington 25, D. C.

Business correspondence should be addressed to the Printing and Publishing Office, National Academy of Sciences, 2101 Constitution Ave., Washington 25, D. C.

Subscribers are requested to notify the Printing and Publishing Office of the Academy and their local postmaster immediately of change of address. Notices to the Academy should provide both the old and the new address.

Microfilms of complete volumes of this journal are available to regular subscribers only and may be obtained at the end of the volume year from University Microfilms, 313 N. First Street, Ann Arbor, Michigan.

Second-class postage paid at Easton, Pennsylvania. This publication is authorized to be mailed at the special rates of postage prescribed by Section 132.122.

PRINTED IN THE U. S. A.

THE PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES
is published monthly by
THE NATIONAL ACADEMY OF SCIENCES

Proceedings of the
NATIONAL ACADEMY OF SCIENCES

Volume 46 · Number 3 · March 15, 1960

*CENTIMETER WAVELENGTH RADIO ASTRONOMY INCLUDING OBSERVATIONS USING THE MASER**

By J. A. Giordmaine

COLUMBIA UNIVERSITY

During the past fifteen years, radio astronomy observations have been largely confined to radiation at wavelengths longer than about 20 cm. The purpose of this talk is to give a brief outline of the work to date at shorter wavelengths, in particular wavelengths less than 10 cm, and to describe some of the new techniques being used in this work. Since the extensive field of solar radio astronomy has already been reviewed by Dr. Maxwell,* this talk will be concerned only with sources other than the sun.

The radio astronomer who works at cm wavelengths faces a number of difficulties not found at longer wavelengths. He is first of all limited to observing continuum radiation since none of the spectral lines in this region has so far been detected. Secondly, the flux density and hence, for a given antenna, the antenna temperature available from the discrete nonthermal sources are approximately proportional to λ. A third difficulty is inadequate receiver sensitivity. At wavelengths of 1 m and longer receivers have been available with internal noise temperatures lower than a few hundred degrees Kelvin, which is less than the background noise at the galactic pole. At meter wavelengths, improved receiver sensitivity is not of great importance. In the cm region, however, where the background temperature is only a few degrees Kelvin, the crystal noise in superheterodyne receivers has led to receiver noise temperatures of 1000°K or more. At wavelengths shorter than 3 cm crystal noise temperatures as well as atmospheric absorption rise rapidly. Indeed apart from the sun, the moon, and Venus, no discrete sources have been detected at wavelengths between 3 cm and the optical infrared region.

The necessity of large high-precision antennas has also restricted progress at centimeter wavelengths. For example, with the use of standard superheterodyne techniques and a five second averaging time, a parabolic reflector 10 ft in diameter or its equivalent is required merely to *detect* Cassiopeia A at 3 cm wavelength. Clearly, much larger antennas, constructed with surface tolerances of the order of $^1/_4$ inch, are required for research at these wavelengths. Prior to 1958 the only large antenna suitable for observations of discrete sources at cm wavelengths was the 50-ft reflector[1] at the U. S. Naval Research Laboratory.

In spite of the experimental difficulties a number of significant observations have been made, many of them yielding information accessible only at cm wave length.

SUMMARY OF CENTIMETER WAVELENGTH OBSERVATIONS

Spectra of the Discrete Sources.—The initial effort at observing galactic noise at cm wavelength was probably that of Reber in 1938.[2] Although failing to detect 9 cm radiation with relatively insensitive equipment, he was able to conclude that the spectrum of the radiation is far from that of a black body. Working at 10 cm in 1951, Piddington and Minnett[3] with the use of a "beam swinging" technique found an excess flux density of $7 \times 10^{-21}\ w\ m^{-2}\ (c/s)^{-1}$ associated with the region near the galactic center.

Discrete sources were first detected at wavelengths shorter than 21 cm by Haddock, Mayer, and Sloanaker[4] in the initial application of NRL 50-ft antenna. They reported flux densities at 9.4 cm of Cassiopeia A, M 1, Cygnus A, the galactic center region, Centaurus A, M 87, and IC 443.[5] The flux densities together with those measured at longer wavelengths were found to be in rough accord with a λ^x law,[6] with the exception of a possible departure near 70 cm.[7] The spectra of the strongest of these sources were further extended to 3 cm by Haddock and McCullough in 1955.[8]

Subsequent studies of the strong discrete sources at 10 cm and 3 cm have been made by Razin and Pletchkov,[9] Kaydanovsky and Kardashev,[10] Jennison,[11] Broten and Medd,[12] and others.

The region in Sagittarius near the galactic center has recently been mapped by Drake[13] with a resolution of about 6′. Observing simultaneously at 68 cm, 21 cm, and 3.75 cm with the 85-ft antenna of the National Radio Astronomy Observatory, he has resolved four distinct centers of emission in the galactic plane arranged more or less symmetrically within 100 parsecs of the center. Professor Oort* has already commented on the correlation between this result and recent hydrogen line studies of the same region.

Ionized Hydrogen Regions.—The bright gaseous emission nebulae were identified as a new class of discrete radio source by Haddock, Mayer, and Sloanaker in 1954.[14] They reported detection at 9.4 cm of the Orion Nebula, as well as M 17, M 8, M 20, and an extended region of hydrogen emission nebulae near the galactic center. The cm wavelength emission intensity from these sources is found to be proportional to the intensity of their $H\alpha$ emission corrected for optical extinction, in accord with the interpretation of the radio emission as thermal radiation arising from free-free transitions in H II.[15] Further evidence for the thermal model is the radio spectrum of the Orion Nebula. The intensity is frequency independent at wavelengths shorter than about 20 cm and proportional to λ^{-2} at longer wavelengths at which the nebula is optically thick.

Thermal emission from planetary nebulae also appears to be a source of detectable radiation. In 1958 Drake and Ewen reported detection of 3.75 cm radiation associated with NGC 7293 and NGC 6853, the Helix and Dumbbell nebulae respectively.[16] Although this observation has not yet been corroborated at nearby wavelengths, it appears that cm wavelength observations will become a useful and independent tool in the study of the planetaries, for many of which the optical estimates of electron density are not of high precision.

Polarization of Discrete Sources.—Polarization of radio radiation from a discrete source was first detected by Mayer, McCullough, and Sloanaker at 3.15 cm.[17] They measured 7 per cent plane polarization for the Crab Nebula at a position angle

of 149° for the electric vector. A later measurement at 9.6 cm showed 3 per cent polarization at 142°.[18] The close agreement of these results with others at nearby wavelengths[19] and with the average optical position angle provides strong support for the synchrotron mechanism of emission from this source and indicates that Faraday rotation along the path between the Crab Nebula and the earth is small at cm wavelengths. Polarization of this source is not observed at longer wavelengths presumably because of the obscuring effect of enhanced Faraday rotation. Other strong sources studied at 10.2 cm show less than one per cent plane polarization.[19] Since Faraday rotation varies as λ^2, the cm region is uniquely suited for unambiguous polarization measurements of the discrete sources.

The Moon.—Measurements of continuum radiation at cm wavelengths from the moon and planets have yielded information on surface temperatures and on the characteristics of the surface material. The first such measurement was made by Dicke and Beringer[20] at 1.25 cm in 1945. They found the average disk temperature of the full moon to be 270°K. Piddington and Minnett[21] made an extensive series of observations at the same wavelength of the phase variation of the disk temperature. They reported the disk temperature of the new moon to be 145°K and the constant component of temperature to be 234°K. The latter is presumably the temperature of a well-insulated layer far below the surface. In contrast to infrared measurements in the 8–12 μ region, the microwave thermal radiation shows a phase lag of about 45° behind the lunar phase angle. The measurements were interpreted as indicating a dust layer of the order of a few mm in thickness and an effective depth of origin of the radiation of about 40 cm. Subsequent observations of thermal radiation from the moon as a function of lunar phase angle and during lunar eclipses have been made at 10 cm,[22] 3.2 cm,[23] and 8.6 mm.[24] Troitzky and Khaikin,[25] from an analysis of the 3.2 cm and optical data, calculate a constant component of radio temperature of 170°K and considerably less penetration than suggested in Ref. (21). The 8.6 mm measurements together with infrared data appear to suggest a dust layer one inch or more in thickness.[24] Additional and more precise observations seem necessary before a detailed and consistent model of the lunar surface is available. The radio measurements have recently been extended to 4.3 mm by Coates.[26] In this work scans of the lunar surface with 7′ resolution showed distinct features with various brightness characteristics.

The Planets.—Planetary radiation at radio wavelengths was detected in 1955 by Burke and Franklin,[26a] who identified Jupiter as the source of burstlike radiation in a narrow band around 15 m wavelength. Radiation resembling thermal emission was discovered by Mayer, McCullough, and Sloanaker[27, 28] in observations of Venus, Jupiter, and Mars at 3 cm wavelength. The results of these and subsequent measurements at cm wavelength are listed in Table 1. The temperature T is the apparent black body temperature of the disk. The notation $C + n$ refers to an observation made n days after inferior conjunction of Venus.

The cm wavelength observations of the planets have led to the discovery of at least two unexpected phenomena whose interpretation is still not clear.

(1) Venus has an apparent temperature of about 600°K, over twice the apparent infrared temperature of the region above the cloud surface and much higher than expected near the cloud surface on the basis of solar heating and a CO_2 atmosphere. The apparent temperature appears to be roughly wavelength independent, at least

TABLE 1

CENTIMETER AND DECIMETER WAVELENGTH OBSERVATIONS OF THE PLANETS

Planet	λ cm	T, °K	Comments	Ref.
Venus	3.15	620 ± 110	C − 48 to C − 30, 1956	(27)
	3.15	560 ± 73	C − 30 to C + 1, 1956	(27)
	3.4	518 ± 47	C + 15 to C + 36, 1958	(28a)
	3.37	575 ± 58	C + 80, 1958, (with maser)	(29)
	9.4	580 ± 160	C + 3 to C + 5, 1956	(27)
	0.86	410 ± 160	C + 1, 1958	(30)
Jupiter	3.15	145 ± 26	.....	(28)
	3.2 ± 0.2	177 ± 22	(With maser)	(45)
	3.75	210 ±	.....	(16)
	10.3	640 ± 85	.....	(31)
	21.0	2,500 ± 450	.....	(32)
	21.1	3,000 ± 1,300	Estimated from data in Ref. (34)	...
	21.4	3,500 ± 1,700	.....	(35)
	31	5,500 ± 1,500	.....	(33)
	68	70,000 ± 30,000	.....	(35)
Mars	3.15	218 ± 76	Opposition, 1956	(28)
	3.14	211 ± 28	Opposition, 1958, (with maser)	(45)
Saturn	3.75	...	Flux density 4×10^{-26} $w\ m^{-2}\ (cps)^{-1}$	(16)

between 0.86 and 10 cm, a behavior consistent with the interpretation that this is a real temperature, presumably that of a layer many kilometers below the cloud surface. The presence of such a high temperature would imply either a greenhouse mechanism of surprisingly high efficiency in the region of the cloud layer or the presence of an internal heat source.

(2) Jupiter is a source of high intensity radiation at centimeter and decimeter wavelengths. The radiation appears to be variable, with a suggestion in some observations of correlation with the rotation of the planet.[31] At least at decimeter wavelengths the radiation is probably not primarily of thermal or atmospheric origin. A tentative explanation proposed by Drake and Field[35] is that the nonthermal component is cyclotron or synchrotron radiation. The former envisages a belt of electrons surrounding the planet and trapped in magnetic fields between 150 and 1,000 oersteds. Much smaller magnetic fields can account for the observed radiation if the particles are relativistic. However, the required flux of relativistic particles seems higher than can be accounted for in cosmic rays and solar corpuscular emission.

Radar Astronomy.—Studies of radar return from the moon, first detected in 1946,[37] have yielded several different kinds of information. The measurement of the reflection coefficients as a function of wavelength gives information on the electrical characteristics of the lunar surface. From an analysis of the available data at wavelengths from 10 cm to 2.5 m, Senior and Siegel[38] have calculated the effective permittivity and conductivity of the surface to be 8.2×10^{-12} *farads/m* and 4.3×10^{-4} *mho/m* respectively. The details of echo fading of short pulses are capable, in principle, of providing information on the topography of the lunar surface. Echo fading at meter wavelengths, on the other hand, is in part due to the Faraday effect in the earth's ionosphere, and analysis of this effect has yielded a measure of the total electron content of the ionosphere.[39]

Precise range measurements at 10 cm wavelength using 2 μs pulses have recently led to a new estimate of the earth-moon distance with a precision of ±3 km.[40] In addition, the data provide indirect measurements of the mean equatorial radius of the earth and the mean horizontal parallax of the moon. The values ob-

tained show small but definite deviations from the accepted values as well as unexplained monthly and diurnal variations.

The only planet detected to date by radar is Venus. Its detection at 68-cm wavelength, reported by a group at Lincoln Laboratory,[41] required an 84-ft antenna, a receiver noise temperature of 170°K, and the use of automatic data processing equipment for statistical analysis of the result. Because of the marginal nature of the detection, little conclusive information could be obtained on the reflection characteristics of the planet or on the precise range.

NEW TECHNIQUES IN CENTIMETER WAVELENGTH RECEIVERS

Since future observations at cm wavelengths will probably rely heavily on recently-developed high sensitivity amplifiers as well as on antennas of increased area, it seems worthwhile to review briefly some of the new amplification techniques. The main part of this section will be devoted to a discussion of masers.

Two distinct approaches have been used to obtain greater sensitivity than is provided by the conventional superheterodyne receiver. The first consists of using a bandwidth much larger than the usual 5 or 10 mc. By an increase in bandwidth from 10 to 1,000 mc with the use of a traveling wave tube amplifier, Drake and Ewen[16] have obtained an order of magnitude decrease in output fluctuation level. With an integration time of 100 sec, they report an output noise level corresponding to 0.01°K in antenna temperature, even with a receiver noise temperature of about 4,000°K. The upper limit of receiver bandwith is determined by man-made interference and to a lesser extent by the desired spectral resolution.

The second approach is to decrease the receiver noise temperature by the addition of a low noise preamplifier such as a parametric device or a maser. With the use of a maser radiometer on the U. S. Naval Research Laboratory 50-ft antenna, Alsop, Giordmaine, Mayer, and Townes[42] have obtained a receiver noise temperature of 85°K, including the contributions of radiation from the ground and from the atmosphere. With an averaging time of 5 sec the output fluctuation level was 0.04°K. The maser preamplifier was developed at the Columbia Radiation Laboratory. Another solid-state maser amplifier with a system noise temperature of 170°K[41] was used in the radar detection of Venus and others have been or are being installed on antennas at Harvard College Observatory and the University of Michigan Observatory.

The NRL maser radiometer has already been described elsewhere in detail,[42] and the following is an outline of its characteristics. It consists of a superheterodyne receiver preceded by a three-level[43] ruby maser preamplifier, both mounted adjacent to the focus of the 50-ft antenna. The maser medium is a single crystal of ruby[44] maintained at liquid helium temperature in a multiply-resonant microwave cavity, in a magnetic field of about 3,500 oersteds. Under these conditions four energy levels separated by about 1 cm^{-1} are accessible to the Cr^{+3} paramagnetic impurity atoms. The equilibrium population distribution of the levels is disturbed by continuous saturation of the first (ground) level and the third level by power at 1.3 cm wavelength. In this situation the population of the third level can be made higher than that of the second, and amplification by stimulated emission is possible at the difference frequency, in this case, 3 cm wavelength. The microwave cavity is of such dimension as to be resonant at both the "pump-

ing" frequency and the amplification frequency when completely filled with ruby. The product of (voltage gain) × (bandwidth) is about 50 mc in this device. This quantity remains constant as the gain of the amplifier is changed by varying the strength of the coupling between the input waveguide and the cavity.

The inherent noise in such a radiometer is quite low. Almost all of the 85°K noise arises from thermal radiation from ancillary components and from the ground. The contribution to the noise from spontaneous emission, which determines the ultimate sensitivity of an ideal maser amplifier, is only about 3°K.

Liquid helium is necessary in this and other masers suitable for radio astronomy at present, in order to provide a large population difference for the amplifying transition and consequently a useful gain-bandwidth product. A ruby maser has been operated at dry ice temperature, but only at great expense of gain and bandwidth.[46] In principle, however, liquid helium temperature is not essential to attain low noise temperature, and in future we may expect masers for radio astronomy that can be used with more convenient coolants.

The signal from the feed horn at the antenna focus is introduced to the reflection-type maser cavity through a ferrite circulator, which also transmits the amplified signal to the superheterodyne receiver and isolates the maser cavity from noise originating in the mixer crystals. The maser input is switched at 30 cps between the feed horn and a "reference" horn of broad beamwidth pointing at the sky. An adjustable attenuator in the reference branch allows the two signals to be balanced to within a few tenths of a degree, so that the receiver acts as a null system. With the antenna stationary, the rms gain variation is of the order of 0.01 db per minute.

The addition of the maser preamplifier provided an improvement in sensitivity of about 12 compared with the superheterodyne receiver alone, accepting both image bands. The noise temperature of 85°K can probably be reduced an order of magnitude by improvements in component and maser design and by precautions to reduce antenna spillover. A 5.4 cm traveling wave maser with horn antenna has been operated by de Grasse, Hogg, Ohm, and Scovil[44a] with a total noise temperature of 18°K including contributions from spillover. With more efficient design antenna temperature sensitivities of the order of 10^{-3}°K should soon be feasible at cm wavelengths. The upper limit of useful receiver sensitivity imposed by receiver gain fluctuations, fluctuations in atmospheric absorption and background radiation, and source confusion in the case of all but the largest antennas probably occurs close to this sensitivity.

OBSERVATIONS USING THE MASER

The following is a summary of some of the results obtained by Alsop, Giordmaine, Mayer, and Townes with the use of the maser radiometer on the NRL 50-ft antenna.[45, 47]

Venus.—The increased sensitivity of the maser permitted a measurement of the apparent temperature of Venus 80 days after the conjunction of 1958 (Table 1). At that time the antenna temperature due to Venus was 0.45°K. In the 80 days following conjunction the fraction of the visible disk illuminated by the sun increases from less than 1 per cent to about 55 per cent. During this period there appears to be no conclusive change in the apparent disk temperature. There is, however, a suggestion of a slightly lower night temperature after conjunction than

before. Such an effect, if corroborated, would be consistent with retrograde rotation of Venus. Retrograde rotation has also been suggested, although inconclusively, by spectroscopic observations. The approximate equality of the day and night temperatures, as measured by both infrared and microwave techniques, indicates that the rotation period is appreciably different from the period of revolution, and in principle can be used to set a lower limit to the rotation period.

Jupiter.—Observations of Jupiter were made on 18 days in the period April, 1958 to February, 1959 in the wavelength range 3.0 to 3.4 cm. From a total of 153 flux measurements the average apparent temperature of the visible disk was found to be 177 ± 22°K. The observations are summarized in Figure 1. Each point represents an average of 9 measurements of peak antenna temperature on a particular day. The relative mean error is the average statistical error of each point. The absolute mean error includes possible systematic errors common to all the points, for example the uncertainty in antenna calibration. In this work individual drift curves, representing a peak antenna temperature of about 0.4°K, were analyzed with a template and the peak temperatures combined to form the daily averages.

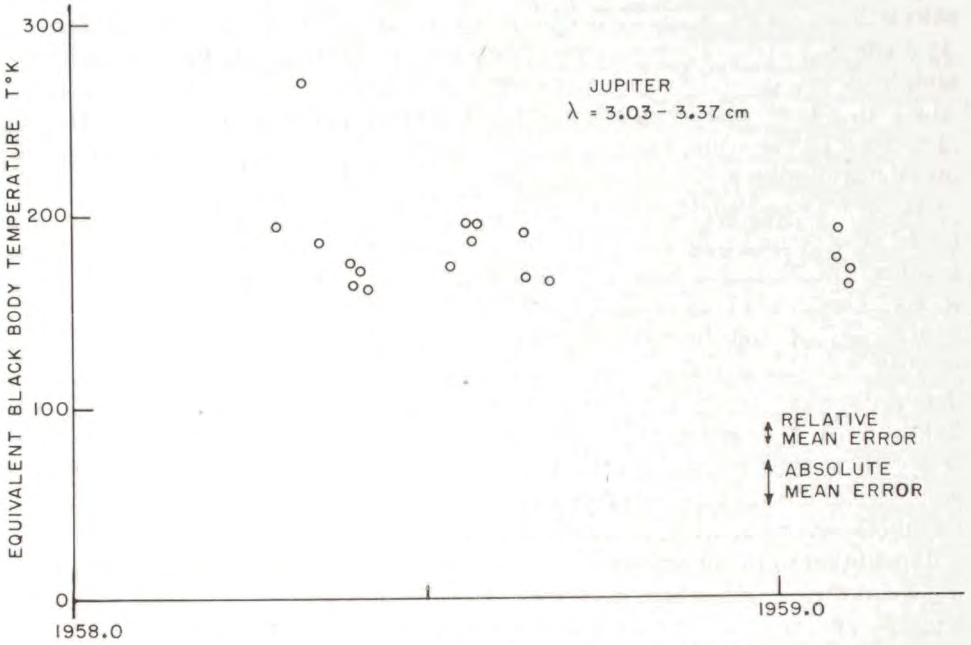


FIG. 1.—Observations of Jupiter at 3 cm wavelength.[45]

Between 3.2 and 3.4 cm wavelength there is a decrease in apparent temperature with increasing frequency of 12 ± 11°K/kmc. The average temperature during this period appears to be significantly higher than the average temperature measured in 1957 (Table 1). The beginning of our observation period, April 16, 1958, immediately preceded an outbreak of activity in the south equatorial belt, between April 18 and April 26.[48] The anomalously high temperature recorded April 30 to May 1, about 270°K, refers to the hemisphere of Jupiter containing the head

of the outburst. One can conclude that there are detectable fluctuations in the 3 cm radiation temperature of the planet, with the suggestion that changes in the apparent temperature may be correlated with changes in the appearance of the planet.

No correlation was observed between the apparent temperature and the rotation of the planet nor between apparent temperature and solar activity as measured by the 10 cm solar flux intensity. There was no detectable linear polarization.

The magnitude of the 3 cm radiation can be interpreted[36, 45] entirely in terms of thermal radiation from NH_3 known from spectroscopic measurements to be present in the atmosphere. NH_3 radiates in the cm region through the pressure-broadened inversion line at 1.28 cm wavelength. Let us assume that H_2, He, and CH_4 are present in the atmosphere above the cloud surface in relative abundances corresponding to the mixtures "(a)" and "(b)" proposed by Kuiper.[49] We assume further that the region above the cloud surface has an adiabatic temperature gradient and is saturated with NH_3. These assumptions, together with the measured NH_3 and CH_4 abundances, fix the temperature, pressure, and composition distribution above the cloud surface. The apparent temperature as a function of wavelength can then be calculated from the NH_3 absorption coefficient, whose calculation as a function of height above the cloud surface is straightforward. At 3 cm the expected temperatures are about 160 and 183°K for mixtures "(a)" and "(b)", respectively, in adequate agreement with the observed value (Table 1). The higher temperature for mixture "(b)" arises from lower atmospheric pressure at a given temperature, reduced pressure broadening, and thus deeper penetration into the atmosphere.

At longer wavelengths the temperatures predicted on the basis of reasonable models of thermal radiation from the atmosphere fall short of the observed temperatures which rise as high as 70,000°K at 68 cm. Possible nonthermal mechanisms have already been discussed.

Mars.—Radiation from Mars was measured at 3.14 cm close to the opposition of 1958. Separate drift scans at an antenna temperature of 0.08°K were readily detected and averaged in this work. The apparent black body temperature was 211 ± 28°K. This temperature is about 50°K less than the apparent infrared temperature and presumably is the temperature of a cooler subsurface layer. Analysis of similar data at this and other wavelengths will provide a new source of information on the average surface characteristics of Mars.

In addition to the observations of the planets, a number of sources were detected at 3 cm wavelength which had previously been detected only at longer wavelengths. Among these were the following, for which flux densities were measured: Virgo A, IC443, IAU 16N04A, and the H II regions M8, M20, and NGC 6357.

A thorough search was made for several planetary nebulae, including NGC 6853, NGC 7009, and NGC 7293. Preliminary analysis of the data indicates that an upper limit of about 0.1°K can be set for the antenna temperatures associated with these objects.

DIRECTIONS OF FUTURE CENTIMETER WAVELENGTH RESEARCH

In conclusion, I would like to list briefly some of the predictable areas in which cm wavelength research is likely to proceed in the next few years. Much of this

work will require the combination of low noise amplifiers and the largest antennas.

(1) Extension of the spectra of the brighter sources to the mm region, and the spectra of many of the weaker sources to 10 and 3 cm; systematic surveys at 10 and 3 cm.

(2) Precise position measurements, facilitating efforts toward optical identification.

(3) Search for spectral lines, including the hyperfine transition in He^3 II at 3.46 cm and the fine structure transition in metastable H I at 3.03 cm.[50]

(4) High resolution studies of size and brightness distribution of extended sources.

(5) Sensitive polarization measurements on the discrete sources, including the planets.

(6) Study of ionized hydrogen regions including the planetary nebulae.

(7) Study of problems connected with the planets: for example, the nature of the cloud layer and surface of Venus, the rotation period of Venus, the radiation mechanism on Jupiter, and the structure of planetary atmospheres as accessible for example through the radiation profile of the Jovian NH_3 inversion line and the absorption profile of the terrestrial lines of O_2 in the mm region.

* One of four papers presented in a symposium on radio astronomy at the Autumn Meeting of the National Academy of Sciences at Indiana University, November 17, 1959. Other papers from the symposium, by J. H. Oort, and R. Minkowski, appear on pages 1–19 (vol. 46). The remaining paper, by Alan Maxwell, will be published upon receipt.

[1] Hagen, J. P., *J. Geophys. Res.*, **59**, 183 (1954).

[2] Reber, G., *Proc. Inst. Radio Engrs.*, **46**, 15 (1958).

[3] Piddington, J. H., and H. C. Minnett, *Aust. J. Sci. Research* A, **4**, 459 (1951).

[4] Haddock, F. T., C. H. Mayer, and R. M. Sloanaker, *J. Geophys. Res.*, **59**, 155 (1954).

[5] Haddock, F. T., C. H. Mayer, and R. M. Sloanaker, *Nature*, **174**, 176 (1954).

[6] Whitfield, G. R., *M.N.R.A.S.*, **117**, 680 (1957); *Paris Symposium on Radio Astronomy* (Stanford University Press, 1959), p. 297.

[7] Hagen, J. P., *Radio Astronomy* (*IAU Symposium No. 4*) (Cambridge, England, 1957), p. 142.

[8] Haddock, F. T., and T. P. McCullough, *Astron. J.*, **60**, 161 (1955).

[9] Razin, V. A., and V. M. Pletchkov, *Radio Astronomy* (*IAU Symposium No. 4*) (Cambridge, England, 1957), p. 155.

[10] Kaydanovsky, N. L., and N. S. Kardashev, *Pub. of the Fifth Cosmogonical Conference* (Moscow, 1956), p. 346.

[11] Jennison, R. C., *Paris Symposium on Radio Astronomy* (Stanford University Press, 1959), p. 309.

[12] Broten, N. W., and W. J. Medd, *Astron. J.* (to be published).

[13] Drake, F. D., *Astron. J.* (to be published).

[14] Haddock, F. T., C. H. Mayer, and R. M. Sloanaker, *Astrophys. J.*, **119**, 456 (1954).

[15] Haddock, F. T., *Radio Astronomy* (*IAU Symposium No. 4*) (Cambridge, England, 1957), p. 192.

[16] Drake, F. D., and H. I. Ewen, *Proc. Inst. Radio Engrs.*, **46**, 53 (1958).

[17] Mayer, C. H., T. P. McCullough, and R. M. Sloanaker, *Astrophys. J.*, **126**, 468 (1957).

[18] Kuzmin, A. D., and V. L. Udaltsov, *Paris Symposium on Radio Astronomy* (Stanford University Press, 1959), p. 305.

[19] Mayer, C. H., and R. M. Sloanaker, *Astron. J.* (to be published).

[20] Dicke, R. H., and R. Beringer, *Astrophys. J.*, **102**, 375 (1946).

[21] Piddington, J. H., and H. C. Minnett, *Aust. J. Sci. Research* A, **2**, 63 (1949).

[22] Akabane, K., *Proc. Japan Acad.*, **31**, 161 (1955).

[23] Zelinskaja, M. R., and V. S. Troitzky, *Pub. of the Fifth Cosmogonical Conference* (Moscow, 1956), p. 99; Kajdanovsky, N. N., M. T. Turesbekov, and S. E. Khaikin, *Ibid.*, p. 347.

[24] Gibson, J. E., *Proc. Inst. Radio Engrs.*, **46**, 280 (1958).

[25] Troitzky, V. S., and S. E. Khaikin, *Radio Astronomy* (*IAU Symposium No. 4*) (Cambridge England, 1957), p. 155.

[26] Coates, R. J., *Astron. J.* (to be published).

[26a] Burke, B. F., and K. L. Franklin, *J. Geophys. Res.*, **60**, 213 (1955).

[27] Mayer, C. H., T. P. McCullough, and R. M. Sloanaker, *Astrophys. J.*, **127**, 1 (1958).

[28] Mayer, C. H., T. P. McCullough, and R. M. Sloanaker, *Astrophys. J.*, **127**, 11 (1958).

[28a] Mayer, C. H., "The Next Five Years in Radio Astronomy" Symposium (University of Michigan, 1959).

[29] Alsop, L. E., J. A. Giordmaine, C. H. Mayer, and C. H. Townes, *Paris Symposium on Radio Astronomy* (Stanford University Press, 1959), p. 69.

[30] Gibson, J. E., and R. J. McEwan, *Ibid.*, p. 50.

[31] McClain, E. F., and R. M. Sloanaker, *Ibid.*, p. 61; Sloanaker, R. M., *Astron. J.* (to be published).

[32] McClain, E. F., *Astron. J.* (to be published).

[33] Bolton, J. G., and J. A. Roberts, quoted by G. B. Field, *J. Geophys. Res.*, **64**, 1169 (1959).

[34] Epstein, E. E., *Nature*, **184**, 52 (1959).

[35] Drake, F., quoted by G. B. Field, *loc. cit.*

[36] Field, G. B., *loc. cit.*

[37] De Witt, J. H., and E. K. Stodola, *Proc. Inst. Radio Engrs.*, **37**, 229 (1949); Bay, Z., *Hung. Acta Phys.*, **1**, 1 (1946).

[38] Senior, T. B. A., and K. M. Siegel, *Paris Symposium on Radio Astronomy* (Stanford University Press, 1959), p. 29.

[39] Browne, I. C., J. V. Evans, J. K. Hargreaves, and W. A. S. Murray, *Proc. Phys. Soc.* (London), B **69**, 901 (1956).

[40] Yaplee, B. S., R. H. Bruton, K. J. Craig, and N. G. Roman, *Proc. Inst. Radio Engrs.*, **46**, 293 (1958); Bruton, R. H., K. J. Craig, and B. S. Yaplee, *Astron J.* (to be published).

[41] Price, R., *et al.*, *Science*, **129**, 751 (1959).

[42] Giordmaine, J. A., L. E. Alsop, C. H. Mayer, and C. H. Townes, *Proc. Inst. Radio Engrs.*, **47**, 1062 (1959).

[43] Bloembergen, N., *Phys. Rev.*, **104**, 324 (1956).

[44] Makhov, G., C. Kikuchi, J. Lambe, and R. W. Terhune, *Phys. Rev.*, **109**, 1399 (1958).

[44a] de Grasse, R. W., D. C. Hogg, E. A. Ohm, and H. E. D. Scovil, *J. Appl. Phys.* (to be published).

[45] Giordmaine, J. A., L. E. Alsop, C. H. Mayer, and C. H. Townes, *Astron. J.* (to be published).

[46] Maiman, T. H., *J. Appl. Phys.* (to be published).

[47] Alsop, L. E., J. A. Giordmaine, C. H. Mayer, and C. H. Townes, *Astron. J.*, **63**, 301 (1958); *Paris Symposium on Radio Astronomy* (Stanford University Press, 1959), p. 69.

[48] Kuiper, G. P., and A. P. Lenham (private communication).

[49] Kuiper, G. P., *The Atmospheres of the Earth and Planets*, 2d ed., (University of Chicago Press, 1952), p. 377.

[50] Townes, C. H., *Radio Astronomy* (*IAU Symposium No. 4*) (Cambridge, England, 1957), p. 92.

THE CONTROL OF THE FORMATION OF SPECIFIC PROTEINS IN BACTERIA AND IN ANIMAL CELLS

By Leo Szilard*

THE ENRICO FERMI INSTITUTE FOR NUCLEAR STUDIES, THE UNIVERSITY OF CHICAGO

Communicated January 19, 1960

In 1953, Monod and Cohen-Bazire as well as Cohn, Cohen, and Monod showed that an amino acid may repress the *last* enzyme in the biochemical pathway which leads to the formation of that amino acid.

Four years later, H. J. Vogel found that arginine, when added to a growing bacterial culture, represses the formation of acetyl ornithinase (one of the *early* enzymes along the biochemical pathway leading to arginine), which converts acetyl-ornithine into ornithine. This observation provided rather strong circumstantial evidence in favor of the view that enzyme repression may be part of the normal regulatory mechanism of enzyme formation in bacteria.

Subsequently, it occurred to Werner Maas that inducers which enhance the formation of an enzyme when added to a growing bacterial culture may perhaps be capable of doing so *only* because there is a repressor present in the cell, and that the inducer might perhaps do no more than inhibit some enzymes which are involved in the formation of the repressor. Thus the inducer would enhance the *formation* of an enzyme only because it reduces the concentration of the repressor in the cell. (Oral communication, April, 1957.)

At that time, the best investigated case of enzyme induction was the induction of the enzyme β-galactosidase. Milton Weiner helped my understanding of the induction of this enzyme greatly by pointing out that its induction must be considered in conjunction with the biochemical pathway leading from galactose to glucose-1-P. (Oral communication, January, 1957.)

The induction of β-galactosidase in a culture of bacteria growing on succinate or lactate, as the carbon source, is inhibited by adding glucose to the growing culture. From this I was led to infer that some metabolite, intermediate in the sequence of metabolites lying between galactose and glucose-1-P, is the precursor of the repressor of β-galactosidase. Further, in line with the above quoted suggestion of Werner Maas, I was led to surmise that certain galactosides may induce β-galactosidase, by inhibiting enzymes which lie on the biochemical pathway between glucose 1-P and the intermediate metabolite that may be the precursor of the repressor of this enzyme.

I believe that some such galactosides may in fact inhibit one of these enzymes and this may explain, in part, why the rate of formation of β-galactosidase rises faster than linearly with the intracellular concentration of the inducing galactoside. However, since I was not able to explain on any similar basis the induction of the degradative enzymes by their substrate, I was led to assume that the inducer must be able to exert an effect which goes beyond inhibiting the formation of a repressor. In particular, I was led to believe that a repressor may reduce the rate of formation of the enzyme by combining with an enzyme molecule which is still attached to its enzyme-forming site, and that it may thereby somehow prevent the attached enzyme molecule from leaving its enzyme-forming site.† According to this view the

repressor combines with a specific site, the controlling site, of the "attached" enzyme molecule, and an inducer may then enhance the formation of the enzyme by competing with the repressor molecule for this site.

I was further led to believe that the repressor of the enzyme β-galactosidase might be a molecule composed of two moieties. One of these (which we may call the metabolite moiety) might be a galactoside and the other (which we may call the *R* moiety) might perhaps be a polynucleotide. Certain galactosides would then enhance the formation of the enzyme β-galactosidase by competing for the controlling site of the attached enzyme molecule with the metabolite moiety of the repressor.

A model which was based on this mechanism of induction and repression of enzyme formation in bacteria was presented by me in a paper given at the annual meeting of the German Chemical Society in Berlin (Oct. 7, 1957) and in lectures, given in the subsequent six months, at various institutions actively interested in the problem of enzyme induction.

The model appeared to be capable of accounting not only for enzyme repression but also for some aspects of antibody formation in mammals. It was not then clear, however, whether it might provide a convincing explanation for the phenomenon of lasting immunity. Such lasting immunity manifests itself in the secondary antibody response which may be elicited in mammals such as the rabbit when it is given an injection of an antigen by which it had been immunized earlier. This secondary response can be elicited even if the second injection of the antigen follows the first injection of the antigen after a very long time interval and thus it involves a "memory" which fades away only very slowly.

In the postwar years the study of inducible enzymes received its impetus chiefly from Jacques Monod's studies of the induction of the enzyme β-galactosidase, at the Institut Pasteur in Paris. The induction of this enzyme turned out to be a very complex phenomenon, however, and until recently it could only be inferred that it involved enzyme repression.

Two years ago, when the model here discussed was first presented, it was supported only by scattered experimental facts. In particular the tenet that the *R* moiety might be a polynucleotide was based on rather tenuous circumstantial evidence.

In the last two years, however, very considerable progress has been made in the study of enzyme induction and enzyme repression. Thus an experiment by Arthur Pardee, Francois Jacob, and Jacques Monod has provided evidence in favor of the view that the phenomenon of enzyme repression may play a major role in the induction of β-galactosidase. Recent experiments performed by Luigi Gorini, at the Medical School of Harvard University, and by George Cohen, Francois Gros, Francois Jacob, Werner Maas, Jacques Monod, and Arthur Pardee, at the Institut Pasteur, support the view that enzyme repression may be the key to the understanding of the phenomenon of enzyme induction in general.

One of these recent experiments shows that a bacterial gene which is responsible for the repression of the enzyme β-galactosidase may exert its effect not by causing the synthesis of an enzyme, but rather by causing the synthesis of a molecule which is not a protein. This remarkable finding is consistent with our notion that this

gene might cause the formation of the R moiety of the repressor of β-galactosidase and that this R moiety might be a polynucleotide.

Apparently, the results of all these newer experiments are, so far, still consistent with the model formulated two years ago, and, in this limited sense, they lend support to the model.

REPRESSION AND INDUCTION OF THE FORMATION OF ENZYMES IN BACTERIA

1. *Enzymes Leading to Glucose-1-P.*—There are numerous repressible enzymes involved in the biochemical pathways which lead from a carbon source to glucose-1-P. In general, the formation of such enzymes is inhibited by glucose. This is quite consistent with the views on enzyme repression here adopted and may be readily understood on the basis of the considerations presented by Neidhardt and Magasanik (1956).

I propose to skip the discussion of this large class of enzymes in favor of discussing two other large classes of enzymes which we may designate as "special anabolic enzymes" and "degradative enzymes."

2. *Special Anabolic Enzymes.*—The enzymes which lie along the biochemical pathways that lead to the formation of an amino acid, a purine, or a pyrimidine, we shall designate as "special anabolic enzymes." We shall single out the enzymes, E_i, involved in the biosynthesis of the amino-acid arginine as being representative for the enzymes of this class.

One of these enzymes, ornithine transcarbamylase, which converts ornithine into citrulline, has been studied by Luigi Gorini and Werner Maas. In a certain strain of coli, the formation of this enzyme may be repressed by adding arginine to a growing bacterial culture. If the intracellular concentration of arginine is lowered in a mutant which cannot convert citrulline into arginine by growing it at a slow rate in a chemostat, with arginine as a controlling growth factor, then the rate of production of the enzyme is raised by a factor of about 25.

We shall refer to enzymes whose rate of production can be thus raised as "boostable" enzymes.

The high rate of enzyme production which may be obtained in the case of such a "boostable" enzyme by lowering the intracellular concentration of a controlling metabolite may represent the "full rate" at which an enzyme-forming site is capable of synthesizing the enzyme.

There are other strains of coli in which the rate of formation of ornithine transcarbamylase cannot be boosted by lowering the intracellular concentration of arginine or any other *known* metabolite. We shall not discuss these "unboostable" strains in the present paper.

We do not assume that the molecule responsible for the repression of ornithine transcarbamylase in the "boostable" strains is arginine itself. We rather assume that the repressor REP_i of the enzymes E_i is a composite molecule which consists of two moieties. One of these, the "metabolite" moiety, is arginine; the other is a moiety which we shall designate by R_i and to which we shall refer as the R-moiety. Thus we may write for the chemical formula on the repressor REP_i

$$REP_i = (\text{arginine} - R_i)$$

As stated above, the R moiety of such a repressor molecule might possibly be a polynucleotide.

Our model for the repression of the enzymes E_i, involved in the biosynthesis of arginine, is as follows:

We assume that the polypeptide chain of the enzyme molecule is synthesized along a specific enzyme-forming site, which determines the amino-acid sequence of the polypeptide. This polypeptide folds up to form the enzyme molecule, but this molecule remains attached, perhaps through a covalent bond, to the enzyme-forming site. If there are repressor molecules present in the cell which are specific for this enzyme, then the metabolite moiety of a repressor molecule may reversibly combine with the controlling site of the attached enzyme molecule (and the *R*-moiety might perhaps reversibly combine with the purine and pyrimidine base of the enzyme-forming site itself). We postulate that an "attached" enzyme molecule, which is so combined with a repressor molecule, cannot leave its enzyme-forming site and accordingly the formation of the enzyme may thus be repressed.

Concerning the mechanism of the action of the repressor we may assume—*pour fixer les idées*—that there is some universal enzyme U present in the cell which can split the covalent bond that ties newly-formed enzyme molecules to their enzyme-forming site. The repressor molecule, when it is combined with an attached enzyme molecule, sets up a "steric hindrance" and may thus prevent the universal enzyme U from splitting the covalent bond.

We postulate that the enzymes E_i, lying along a biochemical pathway that leads to an amino acid, have two specific combining sites, the "catalytic" site and the "controlling" site.

In the case of an enzyme which catalyzes an early step in the biosynthetic pathway, leading to an amino acid, a purine or a pyrimidine, there need be little chemical resemblance between the substrate of the enzyme and the amino acid, the purine, or the pyrimidine, which lies at the end of the biosynthetic pathway and which may be capable of repressing the formation of the enzyme. The substrate has a specific chemical affinity to the catalytic site of the enzyme, and the end product of the biosynthetic chain, the amino acid, the purine, or the pyrimidine, has a specific affinity to the controlling site. Therefore in the case of these "early" enzymes, the combining specificity of the catalytic site and of the controlling site might be quite different.

In the case of the enzymes which lie towards the end of the biochemical pathway, however, the substrate of the enzyme is likely to be a chemical analogue of the "end product" and we may expect it therefore to have specific chemical affinity, not only for the catalytic site but also for the controlling site of the enzyme.

3. *Degradative Enzymes E_j.*—The enzymes involved in the degradation of tryptophane to β-keto-adipic acid by *Pseudomonas fluorescens* may be taken to be representative for another large class of enzymes, the "degradative enzymes." There are seven enzymes involved in the degradation of tryptophane, and the formation of each of them can be enhanced by adding the substrate of the enzyme to the growing bacterial culture.

There is a vast array of compounds which can be oxidized by bacteria such as *P. fluorescens*. R. Y. Stanier estimated their number at more than 50 and estimated that at least 200 enzymes participate in their degradation. The formation of each of these enzymes may be expected to be enhanced by adding its substrate

to the growing bacterial culture, and we may therefore regard these "degradative enzymes" as "inducible" enzymes.

We postulate that the degradative enzymes E_j also have two specific combining sites, a catalytic site and a controlling site. Since in the case of the degradative enzymes the substrate of the enzyme is an inducer of the enzyme, we assume that the substrate of such a degradative enzyme has a substantial chemical affinity for the controlling site as well as the catalytic site. In the case of the degradative enzymes, E_j, we may therefore expect the two combining sites to be similar in their combining specificity for any given metabolite M.

The metabolite moiety of the repressor of a degradative enzyme might be either the substrate itself or else a metabolite further down the degradative pathway which is still a chemical analogue of the substrate.

If the metabolite moiety of the repressor is the substrate itself, and if the concentration of the repressor rises more slowly with increasing intracellular concentration of the substrate than the concentration of the substrate, then the substrate must be an inducer of the enzyme because it competes with the repressor for the attached enzyme molecule.

The concentration of the repressor would rise more slowly than the concentration of the substrate, for instance, if the limiting factor for the rate of production of the repressor were the rate of production of the R moiety of the repressor.

4. *The Coupling Enzymes C_i or C_j.*—We postulate that there may be present in the bacterial cells a class of enzymes to which we may refer as coupling enzymes, C_i and C_j, which couple a specific R moiety, R_i and R_j, to the metabolite M_i and M_j, and thus form the repressor REP_i and REP_j respectively.

Within the class of the degradative enzymes E^j, the corresponding coupling enzymes C_j might be close to being saturated with respect to the metabolite moiety of the repressor. With increasing intracellular concentration of the substrate, the concentration of the repressor would then rise more slowly than the concentration of the substrate and on this basis one may then expect the substrate to be an inducer of the enzyme.

If a compound $\bar{M}$ is a chemical analogue of the metabolite moiety M of the repressor REP, and if the cell cannot transform it into the metabolite moiety M, then such a compound may reduce the concentration of the repressor by inhibiting the coupling enzyme C and thereby enhance the formation of the enzyme E.

Equations Describing Our Model for Enzyme Repression and Induction.‡—In a bacterial culture, growing at a fixed rate, the total repressor concentration ρ_0, that establishes itself in the stationary state, is proportional to the rate at which the repressor molecules are formed.

We may compute ρ, the concentration of the free repressor molecules, from ρ_0, the total concentration of the repressor molecule J by writing

$$\rho = \rho_0 - z\frac{\rho/K}{1 + \rho/K} \tag{1A}$$

where K designates the equilibrium constant for the dissociation of the repressor molecule from the controlling site of the "unattached" enzyme molecules and z the concentration of the enzyme E in the cell.

In (1A) the first term represents the total concentration of the repressor in the

cell and the second term represents the concentration of those repressor molecules which are combined with the controlling site of an "unattached" enzyme molecule. For the sake of keeping our formulae simple we are disregarding here the fact that the repressor may also combine with the catalytic site of the "unattached" enzyme molecules. Accordingly (1A) must be amplified when this becomes relevant to the issue considered.

We may write (1A) also in the form of (1B)

$$z = \rho_0 \left(1 - \frac{\rho}{\rho_0}\right) + K \left(\frac{\rho_0}{\rho} - 1\right) \tag{1B}$$

We shall designate by τ the average time for which a newly-formed enzyme molecule remains tied to its enzyme-forming site, when it is *not* combined with a repressor molecule at its controlling site. We shall assume that τ is large compared to the time that it takes for the polypeptide to be formed and to fold up to form the attached enzyme molecule. In these circumstances we may say that there is practically always an enzyme molecule attached to the enzyme-forming site, and this enzyme molecule is either combined with a repressor molecule or it is not.

On the basis of our model we may then say that the rate of formation of an enzyme, when it is limited by the presence of a repressor molecule in the cell, is given by

$$\text{rate} = q/\tau \text{ per enzyme-forming site, per unit time} \tag{2}$$

where q is the probability that the attached enzyme molecule is *not* combined at its controlling site with a repressor molecule.

We may write for this probability q, in the presence of a repressor REP and an inducer $\bar{M}$

$$q = \frac{1}{1 + \mu/K_{\bar{M}}^* + \rho/K^*} + \frac{\mu/K_{\bar{M}}^*}{1 + \mu/K_{\bar{M}}^* + \rho/K^*} \tag{3}$$

μ and ρ are the intracellular concentrations of the inducer $\bar{M}$ and the free repressor REP, respectively; $K_{\bar{M}}^*$ and K^* are the equilibrium constants, for the reversible dissociation of the inducer molecule $\bar{M}$ and the repressor molecule REP, respectively, from the controlling site of the attached enzyme molecule.

In (3) the first term gives the fraction of the attached enzyme molecules which are not combined at their controlling site with either a repressor molecule REP or an inducer molecule $\bar{M}$. The second term represents the fraction of the attached enzyme molecules which are combined at the controlling site with an inducer molecule $\bar{M}$.

Formula (3) holds true if the average time that it takes an inducer molecule to dissociate from the controlling site of the attached enzyme molecule is short in comparison with τ.

We may write from (2) and (3) for the rate of enzyme formation per enzyme-forming site per unit time

$$\text{rate} = \frac{1}{\tau} \frac{1 + \mu/K_{\bar{M}}^*}{1 + \mu/K_{\bar{M}}^* + \rho/K^*} \tag{3A}$$

The concentration of an enzyme in a bacterium that grows at a fixed rate is pro-

portional to the rate at which the enzyme is formed. Accordingly, we may write for z, the intracellular concentration of the enzyme

$$z = z^* \frac{1 + \mu/K_{\bar{M}}^*}{1 + \mu/K_{\bar{M}}^* + \rho/K^*} \tag{4}$$

where z^* is the concentration which the enzyme might attain in the cell, in the absence of any repressor.

In the absence of the inducer $\bar{M}$ we may write

$$z = z^* \frac{1}{1 + \rho/K^*}. \tag{5}$$

Equations (4) and (5) give the concentration of the enzyme in the cell independent of how many enzyme-forming sites are present in the cell which synthesize the same enzyme. In (4) and (5), z^* represents the enzyme concentration which is obtained from these formulae when ρ, the repressor concentration, becomes zero.

It should be noted, however, that when the repressor concentration becomes very small and the concentration of the enzyme becomes correspondingly large, the repressor concentration may cease to be the limiting factor for the rate of enzyme production and something else may become rate-limiting. For this reason the enzyme concentration in the cell might not actually reach the value z^*, if the repressor concentration goes to zero.

We may now introduce into our formulae the repression factor λ which is defined by

$$\lambda = \rho_0/K^*.$$

We may then write (5) in the form

$$z = z^* \frac{1}{1 + \lambda\rho/\rho_0} \tag{5A}$$

and this we may also write in the form

$$\rho = \frac{\rho_0}{\lambda} \frac{1 - z/z^*}{z/z^*} \tag{5B}$$

We shall throughout the rest of our discussion invariably assume that we have

$$z^* \gg \rho_0. \tag{6}$$

The Simplified Equations.—For the enzymes E for which we may write

$$K \gg z^*$$

the second term in (1A) can be neglected and we may then write

$$\rho = \rho_0.$$

In this case (4) and (5) may be written in the form of

$$z = z^* \frac{1 + \mu/K_{\bar{M}}^*}{1 + \mu/K_{\bar{M}}^* + \rho_0/K^*} \tag{7}$$

and

$$z = z^* \frac{1}{1 + \rho_0/K^*} = \frac{z^*}{\lambda + 1} \tag{8}$$

When these simplified equations hold, then the rate of enzyme formation is independent of the concentration of the enzyme in the bacterium. Accordingly, if an inducer is added to a growing bacterial culture at a given point in time, the rate of enzyme formation will rise to a new value at the time when the inducer is added and from then on it will remain constant. This could be verified by studying the kinetics of the induction of the enzyme.

It may be seen from (7) that if the presence of the inducer $\bar{M}$ does not affect ρ_0, the concentration of the repressor molecules in the cell, then the rate of formation of the enzyme cannot rise any faster than linearly with the intracellular concentration of the inducer.

If it is found that the enzyme concentration rises faster than linearly with the intracellular concentration of the inducer, we may then expect either that the inducer inhibits an enzyme involved in the formation of the metabolite moiety of the repressor or that it inhibits the enzyme C which couples the metabolite moiety of the repressor to the R moiety of the repressor, or that it does both.

Predictions Based on the "Simplified" Equations.—On the basis of the model as described by the above given simplified equations we may expect the following:

(a) If the cells of a bacterial strain are incapable of converting $\bar{M}$ (a chemical analogue of the repressor's metabolite moiety) into M (the repressor's metabolite moiety itself), and if the concentration of M is fixed, then the chemical analogue $\bar{M}$ may enhance the formation of the enzyme, provided that it can get into the bacterial cell.

The chemical analogue $\bar{M}$ may be an inducer of the enzyme in such a bacterial strain, either because it competes with the metabolite moiety of the repressor for the controlling site of the enzyme molecule which is attached to its enzyme-forming site, or because it competes with the metabolite M for the coupling enzyme C which joins the metabolite moiety to the R moiety of the repressor, or for both of these reasons.

In the case of the bio-synthetic pathway leading to arginine the substrate of a *late* enzyme is a chemical analogue of arginine. Accordingly, we may expect such a substrate to induce the enzyme in mutant bacterial strains which cannot convert the substrate into arginine. Thus we may expect the enzyme ornithine transcarbamylase, which converts ornithine into citrulline, to be inducible by citrulline, in a mutant strain which cannot convert citrulline into arginine.

Luigi Gorini has observed that ornithine induces the enzyme ornithine transcarbamylase in such a mutant, if the intracellular concentration of arginine is kept *moderate* by growing the bacterium *at a fast rate* in a chemostat with arginine as a controlling growth factor. (Oral communications, 1959.) (If the intracellular concentration of arginine were kept low by growing the bacterium at a slow rate in the chemostat, then the enzyme level would be boosted to a high value and the inducing effect of ornithine would not be observable.) Since this mutant converts ornithine into citrulline, Gorini's observation is consistent with the views here presented.

(b) There might exist mutants in which the R moiety of the repressor is produced, but it is produced at such a low rate that its production may be the limiting factor for the production of the repressor when the intracellular concentration of the metabolite moiety of the repressor is not too low. On the basis of (7), we may then say that in such a mutant the formation of the enzyme should be enhanced by adding the repressor's metabolite moiety to the growing bacterial culture. Accordingly, for such a mutant the metabolite moiety of the repressor may be an inducer of the enzyme.

Thus, in such a mutant, arginine (for instance) should be an inducer of the enzyme ornithine transcarbamylase and it should be an inducer of this enzyme for one reason only, i.e. because it may compete with the repressor for the controlling site of the attached enzyme molecule.

(c) There may exist mutants which are not capable of producing the R moiety of the repressor. In such a mutant the enzyme may be produced at the full rate and accordingly the enzyme level would be very high. In such a mutant it should not be possible to repress the enzyme by adding the metabolite moiety of the repressor to the growing bacterial culture. Mutants of this type may be designated as "absolute constitutive strains."

Both Luigi Gorini and Werner Maas have obtained from a strain of coli, in which the enzyme ornithine transcarbamylase is repressible by arginine, mutants in which the enzyme is always maintained at a high level and is not repressible by arginine. (Oral communications, 1959.) Conceivably these might be mutants in which the R moiety of the repressor is not formed, i.e., they might be absolute constitutive strains.

The Case of $z^* \gg K$. — We may postulate here, for the sake of argument, a set of constants for "wild type" bacteria which might be as follows:

$$z^* = 10^{-4} \text{ mol/l}, \qquad \rho_0 = 10^{-6} \text{ mol/l};$$
$$K = 10^{-5} \text{ mol/l}; \qquad K^* = 10^{-10} \text{ mol/l}$$

The postulated value of $z^* = 10^{-4}$ mol/l would mean that a fully boosted enzyme amounts to about 10 per cent of the cell proteins.

The value of $\rho_0 = 10^{-6}$ mol/l postulated would be consistent with the assumption that there may be one thousand different repressors present in a bacterium and the assumption that the R moiety of these repressors is a polyribonucleotide of a molecular weight of about 2,000, without having to assume a larger amount of soluble RNA in the bacterium than is usually found in bacteria.

The postulated value of $K = 10^{-5}$ mol/l means that the free energy change for the combination of the repressor with the controlling site of an unattached enzyme molecule is about $\Delta F = 7{,}000$ cal/mol. This appears to be a reasonable value if we assume that only the M moiety of the repressor has a specific chemical affinity to the controlling site of the unattached enzyme molecule.

The postulated value of $K^* = 10^{-10}$ mol/l corresponds to a free energy change of $\Delta F = 14{,}000$ cal/mol for the combination of the repressor with the enzyme molecule that is attached to its enzyme-forming site. This appears to be a reasonable value if we assume that the M moiety of the repressor has a specific chemical affinity to the controlling site of the enzyme molecule and that the R moiety of the repressor

has a specific chemical affinity to the purine and pyrimidine bases of the enzyme-forming site itself.

For the above postulated set of constants we have

$$z^* \gg K$$

and accordingly the simplified equations do not strictly speaking hold.

Nevertheless, for this set of constants, ρ, the free repressor concentration, would be very close to ρ_0, because the enzyme is strongly repressed. We may write for the repression factor λ, for our set of constants,

$$\lambda = \rho_0/K^* = 10^4$$

and we have accordingly for the above postulated set of values

$$\frac{z^*}{K(\lambda + 1)} = 10^{-3} \ll 1.$$

In these circumstances ρ may be close to ρ_0.

Limiting ourselves, for the moment, to a set of constants where we have

$$K \gg \rho_0$$

we may now say the following:

If we have to deal with a *mutant* in which the repressor is produced at a very low rate, so that the repression factor λ is small, and if we have

$$\frac{z^*}{K\ (\lambda + 1)} > 1,$$

then ρ, the free repressor concentration, may be much smaller than ρ_0 and, accordingly, the enzyme level in the cell may then be rather high. This may be seen from (1A) as follows:

We may write for the second term in (1A)

$$z \frac{\rho/K}{1 + \rho/K} > \frac{z^*}{\lambda + 1} \frac{\rho/K}{1 + \rho/K} \approx \frac{z^*}{\lambda + 1} \frac{\rho}{K}$$

and thus we obtain from (1A)

$$\frac{\rho_0}{\rho} > 1 + \frac{z^*}{K(\lambda + 1)}$$

and from (5A) we obtain

$$z > \frac{1}{1 + \lambda/\{1 + z^*/[K(\lambda + 1)]\}} z^*.$$

Accordingly, strains of this type may maintain an enzyme level which may be high and which might come close to the fully boosted enzyme level z^* of an "absolute constitutive mutant."

Paraconstitutive Enzymes.—If for an enzyme we have

$$\rho_0 \gg K$$

and if the other constants fall within certain ranges, then the concentration of such

an enzyme may be maintained in the cell either at a low stable value or at a high stable value—in the absence of any inducer.

An enzyme for which this holds we shall designate as "paraconstitutive."

The concentration of such a paraconstitutive enzyme may be maintained indefinitely at a low level in a proliferating cell culture. But, if once the enzyme concentration is raised to a sufficiently high level and maintained there long enough to establish a stationary state, from there on a high rate of production of the enzyme may be permanently sustained—even in the absence of an external, or internal, inducer. Further, when such a cell, which sustains a high enzyme level, divides, then the daughter cells which it generates will also sustain a high enzyme level. Thus the property of sustaining a high enzyme level is hereditary even though the inheritance is not genic.

It is not possible to say whether paraconstitutive enzymes exist in bacteria. If they did exist, it would be somewhat difficult to recognize them, because if they have arisen in the normal course of evolution then it is likely that by now the enzyme would be sustained at a high level, and the paraconstitutive mutant would thus give the appearance of a constitutive mutant.

It might well be, however, that the condition $\rho_0 \gg K$ is not fulfilled for any of the bacterial enzymes. Perhaps, in order to have this inequality hold for an enzyme, it is not sufficient for the controlling site of the enzyme to have a specific combining affinity for the metabolite moiety of the repressor, but it is also necessary for it to have a specific combining affinity for one or more of the units which constitute the R moiety of the repressor.

Paraconstitutive Enzymes and Cellular Differentiation.—Even though the inherent instability of the enzyme-forming system which is described by our equations might play no role in bacteria, it may still be of great interest. It is conceivable that it might play a major role in certain types of cellular differentiation, in higher organisms such as mammals.

There is no need to assume (and in the case of amphibia there may indeed be reason to doubt) that the early cellular differentiation involved in the formation of ectoderm, mesoderm, and endoderm, is of this type. Still, cellular differentiation in the later phases of embryonal development, where an organizer is involved, might conceivably be based on the inherent instability of the enzyme-forming system here discussed. It is not possible, however, to substantiate this at present on the basis of available experimental evidence, and it may be very difficult to substantiate it even through experiments devised for the purpose.

Experimental confirmation of the view that the model here discussed may provide the molecular basis of a certain type of cellular differentiation in mammals might, however, be obtained in the case of antibody formation in mammals or birds. An antibody need not have any enzymatic activity, but we shall assume that it is in some way related to certain degradative enzymes E_j, present in the mammalian cell, and that the rate of formation of an antibody A_j is under the control of the repressor which is specific for the related enzyme E_j.

Whether an enzyme makes its appearance in cellular differentiation, provoked by an organizer, or whether a specific antibody is formed in response to the injection of an antigen, in either case we may assume that the event is triggered by a transient reduction of the concentration of a specific repressor.

If antibodies are paraconstitutive proteins, then, once the concentration of a particular antibody is raised to a sufficiently high level in a lymphatic cell, that cell and all its daughter cells may maintain a high rate of production of that antibody. This would then represent the kind of memory which may form the basis of the so-called secondary response.

The Enzyme-Forming System of the Mammalian Cell.—We assume that the enzyme-forming system in the mammalian cell is described by the same equations which we have postulated for the bacteria. There are certain differences, however, between the mammalian cells here discussed and the bacterial cells. Under physiological conditions bacterial cells as a rule proliferate. Accordingly, in bacteria there is no need for protein turnover, nor do we have any reason to assume that the R moieties of the repressors are hydrolyzed in bacteria at an appreciable rate. In these circumstances, in bacterial cells ρ_0, the total concentration of a particular repressor in the cell, and z^*, the concentration attained by an enzyme which is produced at the full rate, are both determined by the rate of two processes, i.e., the rate at which these entities are formed and the rate at which these entities are diluted through the growth of the bacteria.

In the case of mammalian cells which are not in a state of rapid proliferation, we may in general assume that ρ_0, the concentration of the repressor, and z^*, the concentration of an enzyme which is produced at the full rate, are also determined by the rate of two processes, i.e. the rate at which these entities are produced and the rate at which they are hydrolyzed.

The rate of hydrolysis of the proteins is presumably determined by the level of activity of the proteolytic enzymes in the cell. The rate of hydrolysis of the repressors is presumably determined by the level of activity of some hydrolytic enzyme H which may universally hydrolyze the R moieties of all of the repressors.

We shall assume that the R moiety of the various specific repressors is hydrolyzed in the cell at the same rate whether the specific repressor is free or is combined with the controlling site of an "unattached" enzyme molecule. This is not an unreasonable assumption because the repressor molecule combines with an unattached enzyme molecule in large part by virtue of the chemical affinity of the repressor's M moiety to the controlling site of the enzyme molecule. If the R moiety is indeed a polynucleotide, then the first, or the first few, bases of the polynucleotide may also combine with the controlling site of an unattached enzyme molecule, but the rest of the nucleotide will presumably remain freely exposed to the hydrolytic action of our hypothetical enzyme H.

We shall presently show that if the relevant constants fall within a certain range, quoted below, then according to equations (1) and (5) the enzyme concentration z exhibits the characteristics which we have attributed to paraconstitutive enzymes.

If we equate z given by (1B) and given by (5A), we obtain a cubic equation for ρ. For the below-quoted range of the constants this cubic equation has three positive roots which represent the self-sustaining free repressor concentrations. Accordingly, there may be three self-sustaining pairs of values for ρ and z which we shall designate (in the order of increasing values of z and decreasing values of ρ) with ρ_1, z_1, ρ_2, z_2, and ρ_3, z_3.

Of these, three self-sustaining pairs of values the first and the last pair, ρ_1, z_1 and

ρ_3, z_3 represent stable points. The intermediate pair ρ_2, z_2 represents an unstable point.

We shall refer to z_3 as a high stable enzyme concentration and to ρ_1 as the high stable repressor concentration. To ρ_2 we shall refer as the "critical" repressor concentration.

In the case of a paraconstitutive enzyme, if ρ, the free repressor concentration, is lowered below ρ_2, the critical free repressor concentration (for a period of time which is sufficiently long for the establishment of a stationary state), and if thereafter the free repressor concentration is permitted to find its own level, then the free repressor concentration will decrease to its low stable value ρ_3. Correspondingly, the enzyme concentration will rise to its high stable value z_3.

For any arbitrarily chosen value of ρ which we maintain in the cell long enough to establish a stationary state, we can determine from equations (1B) and (5A) whether the free repressor concentration would thereafter fall or rise in the cell when it is allowed to find its own level. In order to make this determination we substitute the arbitrarily chosen value ρ (to which we shall refer as the test value) into (1B) and (5A), and find from both of these expressions the corresponding value for z.

The rate of enzyme production, for a given free repressor concentration, is expressed by (5A) and if the value for z obtained from this expression is higher than the value for z obtained from (1B), then we may say that the repressor concentration will decrease when it is permitted to find its own level. In the opposite case we may say that the repressor concentration will increase when it is permitted to find its own level.

We propose to utilize below this simple rule, in order to establish the fact that there exist two stable self-sustaining values ρ_1 and ρ_3, if the constants fall within the range quoted below.

We shall now show that if we have

$$\frac{z^*}{K(\lambda - 1)} > 3 \tag{9}$$

and

$$\rho_0/z^* < 10 \tag{10}$$

then there is a stable point at which we have for the low self-sustaining free repressor concentration ρ_3

$$0 < \rho_3 < \rho_0/\lambda.$$

In order to show this we choose for our test concentration $\rho = \rho_0/\lambda$. Substituting this value of ρ into (5B) we obtain

$$\frac{z(\text{from 5B})}{z^*} = \frac{1}{2}$$

Substituting the same value for ρ into (1A) we obtain

$$\frac{z(\text{from 1A})}{z^*} = \frac{\rho_0}{\lambda}(1 + \lambda) + \frac{K(\lambda - 1)}{z^*}.$$

Do the versions you had in Boston have all these corrections?

Thanks. Will check.

JW

If we take (9) and (10) into account we see that the value for z (from 1A) is less than the value for z (from 5B). Therefore, ρ, when it is permitted to find its own level (after being held at $\rho = \rho_0/\lambda$ for an adequate period of time), will decrease and move to its low stable value, ρ_3.

For the corresponding high stable value of the enzyme concentration z_3 we may write

$$z^*/2 < z_3 < z^*.$$

Next, we propose to determine ρ_1, the high stable concentration of the free repressor, and ρ_2, the critical concentration of the free repressor. We obtain these self-sustaining values from (1B) and (5A) by writing

$$z \text{ (from 1B)} = z \text{ (from 5A)} \tag{11}$$

and by finding the roots of this equation.

Writing out (11) explicitly we obtain

$$\rho_0\left(1 - \frac{\rho}{\rho_0}\right) + K\left(\frac{\rho_0}{\rho} - 1\right) = z^* \frac{1}{1 + \lambda\rho/\rho_0} \tag{11A}$$

which we may also write in the form

$$\lambda = \frac{1}{\rho_0/z^*(1 - \rho/\rho_0)\rho/\rho_0 + K/z^* - K/z^*(\rho/\rho_0)} - \frac{1}{\rho/\rho_0}. \tag{11B}$$

If we have

$$\frac{\rho}{\rho_0}\frac{\rho_0}{z^*} \gg \frac{K}{z^*} \tag{12}$$

and

$$\frac{z^*}{\rho_0}\frac{1}{1 - \rho/\rho_0} \gg 1, \tag{13}$$

then we may simplify (11B) by leaving off the second term and we thus obtain

$$\lambda = \frac{1}{\rho_0/z^*(1 - \rho/\rho_0)\rho/\rho_0 + K/z^* - K/z^*(\rho/\rho_0)} \tag{14}$$

or

$$(\rho/\rho_0)^2 - (1 - K/\rho_0)\rho/\rho_0 + z^*/\rho_0\lambda - K/\rho_0 = 0 \tag{14A}$$

or

$$\frac{\rho_1}{\rho_0} = \frac{1 - K/\rho_0 + \left|\sqrt{[1 - K/\rho_0]^2 - 4[z^*/\rho_0\lambda - K/\rho_0]}\right|}{2} \tag{14B}$$

and

$$\frac{\rho_2}{\rho_0} = \frac{1 - K/\rho_0 - \left|\sqrt{(1 - K/\rho_0)^2 - 4[z^*/\rho_0\lambda - K/\rho_0]}\right|}{2}. \tag{14C}$$

The quantity under the square root in (14B) and (14C) is positive if we have

$$(1 - K/\rho_0)^2 > {}^4/_5 \tag{15}$$

and

$$\lambda > 5z^*/\rho_0. \tag{16}$$

We shall now, for the purposes of our discussion, assume a set of constants which satisfy the inequalities that we have assumed above and actually compute the ρ_1/ρ_0 and ρ_2/ρ_0 from (14B) and (14C) in order to obtain the values for ρ_1 and ρ_2.

For the purpose of our discussion we assume the following set of constants:

$$z^* = 10^{-3} \text{ mol/l}; \ \rho_0 = 10^{-8} \text{ mol/l}; \ K = 10^{-10} \text{ mol/l};$$
$$K^* = 10^{-14} \text{ mol/l}.$$

This set of values satisfies the inequalities assumed above (which represent a sufficient condition for an enzyme to be paraconstitutive) and, in particular, we obtain for this set of constants $\lambda = \rho_0/K^* = 10^6$ and $z^*/K(\lambda - 1) \approx 10$.

The following comment may be made concerning the particular values chosen for our constants:

$z^* = 10^{-3}$ mol/l means that if, even at zero repressor concentrations, the enzyme were formed at the rate corresponding to (5A), then the amount of enzyme in the cell would just about equal the total protein content of the cell.

$K = 10^{-10}$ mol/l corresponds to a free energy change of $\Delta F = 14{,}000$ cal/mol for the combination of a repressor molecule with the controlling site of an "unattached" enzyme molecule. It seems likely that both the metabolite moiety and the R moiety of the repressor would need to have a substantial chemical affinity to the controlling site of the unattached enzyme molecule in order to have a free energy change of this magnitude.

For the above quoted values of the constants we obtain from (14B) for the high stable repressor concentration $\rho_1 \approx 0.9\ \rho_0$ and from (14C) for the critical repressor concentration $\rho_2 \approx 0.11\ \rho_0$.

This means that it would be sufficient to lower the free repressor concentration to about one tenth of ρ_0 in order to trigger the enzyme-forming system and cause the cell thereafter to maintain, indefinitely, the enzyme at a high concentration, i.e. at a concentration lying somewhere between $z^*/2$ and z^*.

The set of values which we have assumed for our constants was selected because it appears conceivable that a quite similar set of values might hold for antibodies formed in the lymphatic cells of the adult rabbit that are capable of forming antibodies which are specific for an antigen injected into the rabbit.

These cells might be characterized—in comparison to the lymphatic cells of the newborn rabbit and the non-lymphatic somatic cells of the adult rabbit—by an increased level of activity of the hypothetical hydrolytic enzyme H. On this basis, we may assume that the value of ρ_0 and of the repression factor λ that holds for the lymphatic cells of the adult rabbit which are capable of forming antibodies is perhaps ten times lower than the corresponding values in those other cells, which are not capable of forming antibodies.

This possibility is discussed in detail in the following paper, "The molecular basis of antibody formation," which attempts to explain a number of phenomena in-

volved in antibody formation on the basis of the phenomenon of enzyme repression in bacteria.

It is conceivable that in attempting to build a theory of antibody formation on this foundation we may be building a house of cards, for in spite of the rapid progress made in the last two years with respect to enzyme repression in bacteria, many of the conclusions drawn from the experiments are still largely based on circumstantial evidence. This holds in particular for the conclusion, here adopted, that the repressor controls the rate at which the enzyme is formed by the enzyme-forming site rather than the rate of formation of the enzyme-forming site itself.

Clearly, we cannot attempt at present to say how antibodies are actually formed; at best we may be able to say how antibodies might conceivably be formed. But to be able to say even this much might be of some value.

I had the privilege of discussing the thoughts expressed in this paper with Dr. Maurice S. Fox, The Rockefeller Institute, New York, and it is a pleasure to acknowledge his help in clarifying the issues involved.

* The author started working on this paper while serving as a consultant to the Basic Research Program, National Institute of Mental Health, National Institutes of Health, U.S. Public Health Service, Department of Health, Education, and Welfare. In later phases the work was supported by a Research Grant of the National Institutes of Health.

† A similar model was proposed independently by O. Maaløe and presented at an informal seminar at the Cavendish Laboratory in Cambridge in 1958; it will be described in *Microbial Genetics* (Cambridge University Press, 1960).

‡ Notations:

REP	is the specific repressor which controls the rate of formation of an enzyme and which is composed of two moieties, an M moiety and an R moiety.
M	is a metabolite, which forms the metabolite moiety of the repressor.
R	is the R moiety of a repressor, which is specific for enzymes lying along a certain stretch of a given biochemical pathway.
K^*	is the equilibrium constant for the dissociation of a repressor molecule from the controlling site of the corresponding enzyme molecule that is attached to its enzyme-forming site.
K	is the equilibrium constant for the dissociation of a repressor molecule from the controlling site of the "unattached" enzyme molecule, present in the cell.
$K^*_{\bar{M}}$	is the equilibrium constant for the dissociation of a chemical analogue $\bar{M}$, of the metabolite M, from the controlling site of an enzyme molecule attached to its enzyme-forming site.
$K_{\bar{M}}$	is the equilibrium constant for the dissociation of the chemical analogue $\bar{M}$ from the controlling site of an unattached enzyme molecule contained in the cell.
ρ_0	is the concentration of the molecules of the repressor REP in the cell.
ρ	is the concentration of the free repressor molecules in the cell, i.e. of those repressor molecules which are not combined with an unattached enzyme molecule.
μ	is a concentration of the chemical metabolite $\bar{M}$ in the cell.
z	is the concentration of the "unattached" enzyme molecules in the cell.
z^*	is the concentration that the enzyme would attain in the cell, for $\rho = 0$, if we disregard the fact that factors, which our formulae do not take into account, may limit the rate of the formation of the enzyme for high values of z.
λ	is the repression factor defined by $\lambda = \rho_0/k^*$.

*THE MOLECULAR BASIS OF ANTIBODY FORMATION**

By Leo Szilard

THE ENRICO FERMI INSTITUTE FOR NUCLEAR STUDIES, THE UNIVERSITY OF CHICAGO

Communicated by Theodore Shedlovsky, January 19, 1960

In a preceding paper we have discussed the phenomenon of enzyme repression in bacteria and presented a model for a kind of cellular differentiation which might conceivably play a role in embryonic development. In the present paper we propose to discuss the molecular basis of antibody formation in the light of this model.

The Experimental Facts.—We shall list in the following the major immunological phenomena that we may regard as well established. Throughout this paper we shall restrict our discussion to one animal, the rabbit, and to one class of antigens, soluble proteins.

(1) When a soluble protein antigen is injected into an adult rabbit for the first time, the rabbit responds after about 5 days with the formation of antibodies which are specific for this antigen. Any remaining antigen will be rapidly eliminated from the circulation, and for a while there will be a substantial concentration of antibody present in the circulation. Subsequently the concentration of the antibody in the circulation will gradually decrease and after a while it may become no longer detectable. This is the so-called primary response.

(2) If, a few weeks after we have injected into the rabbit a soluble antigen, such as a foreign serum protein, we inject the same antigen again, then three days later the rabbit may respond with a copious production of antibody and the antigen will be rapidly eliminated from the circulation. The concentration of the antibody in the circulation may reach a high level, then fall off rather slowly and remain appreciable for a long time. This is the secondary response.

In response to the same amount of antigen injected, a much larger amount of antibody may be produced in the secondary response than in the primary response.

The secondary response can be elicited even a very long time after the antibody has disappeared from the circulation, subsequent to the first injection of the antigen. The readiness of the rabbit to exhibit such a secondary response represents some sort of a memory which fades away only very slowly.

(3) Albert Coons has found in the rabbit that if one evokes the secondary response in the manner described above, then, after 48 hours, clusters of cells which contain antibodies specific for the antigen may be found in the lymph nodes which are involved. The clusters found 4 days or 8 days after the injection are on the average larger than the clusters found after 48 hours. The cells which compose these clusters are small and round and have the appearance of plasma cells. Mitotic figures can be seen in the clusters, indicating that there is proliferation of the cells producing the antibody. The clusters vary in size; the larger ones consist of about a hundred or perhaps a few hundred cells.

(4) For a few days after birth, the rabbit is not capable of forming antibody in response to the injection of an antigen. If a newborn rabbit is injected with a *large* quantity of a soluble protein antigen, then later on when this rabbit becomes an adult and is capable of forming antibodies in general, it will still remain incapable of forming antibody against the antigen which was administered to it immedi-

ately after birth, even though by that time the concentration of the antigen in the circulation may have fallen to a very low level. This is the phenomenon of enduring immune tolerance.

(5) If an adult rabbit is given an X-ray dose of about 400 r to its whole body and a few days later an antigen is injected into the rabbit, then the rabbit will not form antibodies against this antigen. After a while the effect of the X-ray exposure will wear off and the rabbit is then again capable of forming antibodies.

If after the X-ray exposure, at the time when the rabbit is not capable of responding with the formation of antibody, a *large* quantity of an antigen, such as a foreign serum protein, is injected into the rabbit, then the rabbit will remain incapable of forming antibodies against this particular antigen, even after the effect of the X-ray exposure has worn off and the concentration of the antigen in the circulation has fallen to a level which is no longer detectable. Thus the X-rayed adult rabbit exhibits the phenomenon of enduring immune tolerance.

(6) If the antigen is injected into the rabbit prior to the exposure to the X-ray dose, then this exposure will not prevent the rabbit from forming antibodies to the antigen.

(7) If a rabbit has been pre-immunized with an antigen, then exposure of the rabbit to an X-ray dose of 400 r a few days prior to the injection of the antigen will not block the secondary response, i.e. in such a rabbit the injection of the antigen will evoke the secondary response even though the injection is given a few days following the administration of the X-ray dose.

The Enzymes of the Lymphatic Cells.—We postulate that, in general, the somatic cells of the rabbit contain a number of diverse biochemical pathways, j, $j + 1$ $j + 2$, etc., and that a number of enzymes lie along each such pathway. This might be represented symbolically by writing

$$M \begin{cases} M_j^1 \xrightarrow{E_j^1} M_j^2 \xrightarrow{E_j^2} M_j^3 \xrightarrow{E_j^3} \cdots\cdots M_j^k \xrightarrow{E_j^k} M_j^{k+1} \\ M_{j+1}^1 \xrightarrow{E_{j+1}^1} M_{j+1}^2 \xrightarrow{E_{j+1}^2} M_{j+1}^3 \xrightarrow{E_{j+1}^3} \cdots\cdots M_{j+1}^k \xrightarrow{E_{j+1}^k} M_{j+1}^{k+1} \\ M_{j+2}^1 \xrightarrow{E_{j+2}^1} M_{j+2}^2 \xrightarrow{E_{j+2}^2} M_{j+2}^3 \xrightarrow{E_{j+2}^3} \cdots\cdots M_{j+2}^k \xrightarrow{E_{j+2}^k} M_{j+2}^{k+1} \end{cases}$$

As this scheme indicates, the metabolites M_j; M_{j+1}; M_{j+2}; etc. of several of these stray biochemical pathways might have a common precursor M.

Let us now consider one of these enzymes, for instance E_j^k. We assume that this enzyme is under the control of the repressor

$$REP_j^k = \{M_j^k - R_j\}$$

We further assume that there is a coupling enzyme C_j^k present in the cell which joins the R moiety of the repressor, R_j, to the M moiety of the repressor, M_j^k. Symbolically this might be indicated by writing

$$M_j^k + R_j \xrightarrow{C_j^k} \{M_j^k - R_j\}.$$

We shall assume in our discussion that the coupling enzymes C are not under the control of any of the repressors here considered.

We shall further assume that both the catalytic site and the controlling site of all these degradative enzymes, E_j, can specifically combine with M_j, the substrate of the enzyme. (See preceding paper.)

The Genes G and the Antibodies A.*—We shall designate by G_j the genes which determine the identity of these degradative enzymes E_j, and we postulate that for each enzyme E_j there is only one corresponding gene G_j contained in each of the two haploid sets of chromosomes. The total number of genes of this category might perhaps be of the order of 10,000 per haploid chromosomal set.

One might be tempted at this point to assume that the enzymes E are themselves the antibodies. We prefer, however, to postulate the following: the genes G have a tendency to get doubled and in the course of evolution each gene G_j may have doubled many times. We assume that when a gene G undergoes doubling, the genes G^* which are formed will in general lack a part, presumably a small part, of the gene G. We assume in particular that the genes G^* differ from the genes G in two respects, which are as follows:

(a) the genes G^* lack the tendency of the genes G to undergo doubling;
(b) the proteins which are determined by the genes G_j^* resemble closely the enzyme E_j which is determined by the corresponding gene G_j but they may lack the catalytic activity of the enzyme. *We postulate that these proteins are the antibodies* A_j.

The controlling site of an antibody A_j has the same specific combining affinity to the metabolite M_j as has the controlling site of the enzyme E_j. Also the catalytic site of an antibody A_j may have the same specific combining capacity for the metabolite M_j as the catalytic site of enzyme E_j, to which it is related, *and if this is the case then we are dealing with a divalent antibody.*

The spontaneously occurring doubling of the genes G might be balanced by spontaneously occurring deletions of the genes G^*, and an equilibrium might be maintained on this basis, in the absence of genetic deaths. In such an equilibrium there might be present a number of genes G^* corresponding to each gene G. However, deletions of the genes G and their mutations to incompetence *would* have to be balanced by the occurrence of genetic deaths, in a state of mutational equilibrium.

There is a limit to the amount of genetic deaths which we may assume to occur per generation, because no species of mammals could remain in existence if the amount of genetic deaths were too high. This consideration does not permit us, however, to set an upper limit for the number of genes G^* present per gene G, because we are assuming that with respect to the genes G^* mutational equilibrium is maintained in the absence of genetic deaths.

We may set an upper limit for the total number of genes G^* on the basis of the amount of *DNA* present in the cell, but this comes out to be very high; *if we assume that the weight of the mammalian gene is about the same as the weight of the bacterial gene, then the amount of DNA in the mammalian cell would be sufficient to account for one million genes.*

The Nature of the Antigen.—For the purpose of our discussion an antigen P_j may be represented as a molecule which is composed of a non-antigenic protein molecule P_0 to which are coupled m identical groups $\bar{M}_j$ (to which we shall refer as a hapten). Accordingly, we may represent such an antigen P_j symbolically, by writing

$$P_j = \{P_0 - (\bar{M}_j)_m\}$$

One can prepare rather simple artificial antigens of this type by diazo-coupling

a hapten, some small molecule, arsanylic acid for instance, to a protein which is not antigenic in the rabbit. If m, the average number of such haptens per protein molecule, is made large enough ($m \geq 10$) we may have a good antigen which will elicit the formation of antibodies specific for the hapten.

If the hapten $\bar{M}_j$ is a chemical analogue of the metabolite M_j, then the antibody molecule A_j is capable of combining with the antigen molecule P_j by virtue of the specific chemical affinity of the catalytic site and of the controlling site of the antibody molecule A_j to the hapten $\bar{M}_j$.

In the case of a natural protein antigen, such as a foreign serum protein, we have a more complicated situation because one protein molecule might carry a certain number, m_1, of one kind of determinant group and also a certain number, m_2, of another kind of determinant group, etc. To these determinant groups we shall, for the sake of brevity, also refer as haptens.

More complex artificial antigens may be prepared by coupling a hapten to a natural protein which is itself antigenic in the rabbit.

The Rabbit Antibody-Antigen System.—If antibody which is obtained from the rabbit is mixed with the antigen for which it is specific, then within certain concentration limits a precipitate may be formed in which each antigen molecule may be combined with a number of antibody molecules, and each antibody molecule may be combined with two antigen molecules. The concentration limits within which such a precipitate is formed define the so-called equivalence zone where the supernatant over the precipitate contains only small quantities of both the antigen and the antibody. The free antigen concentration is exceedingly low in equilibrium with such a precipitate.

A precipitate may also be formed if the rabbit antibody is present in large excess. Such a precipitate may be represented as consisting of units in which a number of antibody molecules (the number depending on the size of the antigen molecule) are combined with one antigen molecule; the precipitate forms because such units stick to each other. The free antigen concentration is low in equilibrium with a precipitate of this type also.

No antigen-antibody precipitate is formed if antigen is present in great excess. Presumably in this case each divalent antibody molecule is combined with two antigen molecules. One of the antigen molecules is combined with the antibody molecule at the controlling site, and the other is combined with it at the catalytic site. Each antigen molecule is combined, however, with one antibody molecule only.

Proteins which may have a tendency to stick to gamma globulins may be co-precipitated when an antigen antibody precipitate is formed in their presence. An example for proteins which may be co-precipitated in this manner are the serum "complements"; which are "fixed" when an antigen-antibody precipitate is formed in their presence.

The Coupling Enzyme-Antigen System.—If the hapten $\bar{M}_j$ of the antigen P_j is a chemical analogue of the metabolite M_j, then the antigen can reversibly combine with the coupling enzyme C_j by virtue of the specific chemical affinity of the hapten to a part of the catalytic site of the coupling enzyme.

We postulate that the coupling enzymes resemble those antibodies of the rabbit which form a precipitate with antigen when the antibody is in excess. Accordingly, at low antigen concentrations a number of coupling enzyme molecules might be

combined with one antigen molecule and such units may then stick to each other and form a precipitate. We may assume that the free antigen concentration can be very low in equilibrium with such a precipitate.

The "Sensitive" Lymphatic Cells.—We assume that the cells of the lymphatic system go through a maturation process that carries the cell from its initial form, presumably the stem cell, to its mature form, presumably the plasma cell. When a lymphatic cell reaches a certain phase in this maturation process it becomes "sensitive" in the sense that it becomes capable of responding to the exposure to a soluble antigen with the formation of a specific antibody. We assume that what renders the cell sensitive, when it reaches this phase of its maturation process, is a general lowering of the repression factors to a value of perhaps $\lambda = 10^6$. (For definition of the repression factor see preceding paper.) This might be brought about by an increase in the activity of an enzyme which can universally hydrolize the R moieties of the repressors. In the preceding paper we have postulated the existence of such an enzyme and designated this hypothetical enzyme as the "hydrolase."

The set of constants assumed in the preceding paper, for the enzyme-forming system of the mammalian cell, we assume to hold for the antibody-forming system of the "sensitive" lymphatic cells. In the immature form of the lymphatic cells and in the rest of the somatic cells the concentration of the repressors ρ_0 and the corresponding repression factors λ presumably have a much higher value.

The Primary Response.—We assume that when a soluble antigen is injected intravenously or intraperitoneally into the rabbit, it penetrates into the cytoplasm of all the lymphatic cells. We further assume that if the antigen stays in the circulation long enough, the free antigen concentration in the lymphatic cells will be the same as the free antigen concentration in the circulation. This means that the chemical potential of the antigen inside the cytoplasm of the lymphatic cell is the same as the chemical potential of the antigen in the circulation.

According to the views here adopted, the primary response comes about in the following manner: when a soluble antigen P_j is injected into the rabbit it will diffuse into the lymphatic cells and precipitate the coupling enzyme C_j. As the result of this, the rate at which the repressor REP_j is formed will be reduced, and the concentration of this repressor will begin to fall. As the concentration of the repressor falls, the rate of formation of the antibodies A_j will increase.

Antibody molecules A_j present in the cell bind molecules of the repressor REP_j because of the specific affinity of the repressor molecule to their controlling site. Accordingly, in a sensitive cell, as the concentration of the antibody molecules A_j rises and the concentration of the repressor molecules REP_j falls, at some point in time the enzyme-forming system will lock and from then on the cell will produce the antibody molecules A_j at a high rate, even in the absence of antigen.

This sustained antibody production, by the cells in which the enzyme-forming system has locked in the primary response, represents a kind of memory, and it may account for the sustained immunity manifested by the rabbit.

Possibly a cell might lock simultaneously for the production of antibodies specific for two different haptens. But once a cell has locked for the production of an antibody, which is thereafter produced at a high rate, then subsequently a new stationary state establishes itself in the cell. The cell is then no longer "sensitive,"

so that if it is exposed to another antigen it will not lock for the production of the corresponding antibody.

The Complexities of the Primary Response.—When the primary response is elicited in the rabbit by injecting an antigen which consists of a non-antigenic protein P_0 to which are coupled m haptens $\bar{M}_j$, there will combine with an antigen molecule not only molecules of the coupling enzymes C_j but also molecules of the enzyme E_j and of the antibodies A_j.

The phenomena accompanying the primary response are even more complicated if the artificial hapten is coupled not to a protein which is non-antigenic in the rabbit but, for instance, to a foreign serum protein which *is* antigenic in the rabbit. When such an antigen diffuses into the lymphatic cells, various coupling enzymes corresponding to the various determinant groups carried by the antigen molecule, and also the corresponding enzymes E and antibodies A may combine with the antigen and form a precipitate.

On this basis it is possible to explain why a conjugated protein carrying an artificial hapten elicits more antibody directed against the artificial hapten if the protein is a foreign protein which is a good antigen in the rabbit, rather than if it is one of the rabbit's own serum proteins.

The Secondary Response.—We shall postulate that the cells of the lymphatic system contain a hypothetical enzyme S which, when present at high concentration, will inhibit cell division. We shall further postulate that this hypothetical enzyme S resembles complement, inasmuch as it can be co-precipitated if an antigen-antibody precipitate is formed in its presence.

When an antigen P_j is injected into a rabbit for the first time, a certain number of the sensitive lymphatic cells will lock and henceforth produce the antibodies A_j at a high rate. When a lymphatic cell locks and produces such proteins at a high rate, it will from then on produce most other proteins, including the hypothetical enzyme S, at a low rate. Thus, following the locking of the lymphatic cell in the primary response, the concentration of the enzyme S will fall, and it may reach a new stationary level within a few days or weeks.

If, about four weeks after the first injection of the antigen P_j, the same antigen is injected into the rabbit again, it will diffuse into the lymphatic cells and it will form a precipitate with the antibodies A_j in those lymphatic cells which have locked at the time of the first injection of the antigen. By the process of co-precipitation a certain quantity of the enzyme S will thereby be fixed, and, inasmuch as at the time of the second injection the level of this enzyme in the locked cells is low, the concentration of the enzyme may fall to the point where it can no longer inhibit cell division.

Thus, the second injection of the antigen will lead to proliferation of those cells which have locked at the time of the first injection of the antigen. This is our explanation of the secondary response.

If the views here adopted are correct, we may expect that the secondary response would be elicited by any compound carrying a hapten, which forms a precipitate with the antibody that is directed against this hapten, whether or not the compound is capable of eliciting the primary response.

The finding of compounds which are weak antigens, in the sense that they will

elicit only a weak primary response, but are good antigens, in the sense that they will elicit the full secondary response, would lend support to our theory.

A conjugated protein, obtained by coupling an artificial hapten to rabbit serum albumin, is supposed to be a very weak antigen in the rabbit, in the sense that it does not elicit in the primary response the formation of an appreciable quantity of antibody directed against the artificial hapten. On the other hand, a conjugated protein obtained by coupling an artificial hapten to a foreign serum globulin, which is antigenic in the rabbit, is supposed to be a very good antigen in the sense that it will elicit in the primary response the formation of a substantial quantity of antibody directed against the artificial hapten. (Oral communication, Herbert Anker, 1959.)

On this basis, our theory predicts that if we pre-immunize the rabbit with a conjugated foreign serum globulin and evoke the secondary response with the conjugated rabbit serum albumin, we should obtain in the secondary response a substantial quantity of antibody directed against the hapten. If, however, we pre-immunize the rabbit with the conjugated rabbit serum albumin and evoke the secondary response with the conjugated foreign serum globulin, then we should obtain in the secondary response a less substantial production of the antibody directed against the hapten.

In interpreting the results of an experiment of this type, one must keep in mind that when an antigen is injected for the second time one obtains not only a secondary response but also a "primary response," in which sensitive lymphatic cells will lock for the formation of the specific antibody. It should be possible, however, to distinguish these two responses, because the release of the antibody into the circulation from the secondary response presumably precedes its release from the "primary response."

The Decay of the Primary Response.—In the primary response the release of antibody into the circulation does not persist long at a substantial rate after the antigen has been eliminated from the circulation. It is conceivable, though by no means certain, that, as far as the release of antibody into the circulation is concerned, the phenomena which characterize the secondary response may play a part in the primary response also.

When a cell locks for the production of an antibody in the primary response the concentration of the antigen present in the circulation might be high enough to lead to the formation of an antibody-antigen precipitate in the locked cell and to a co-precipitation of the enzyme *S*. This might cause a proliferation of the locked cell as described above, in connection with the secondary response.

The locked cells which divide may disintegrate as fast as they are produced and release their antibody content into the circulation.

Soon after the antigen disappears from the circulation, this enforced proliferation of the locked cells may cease, but we may assume that the locked cells will keep on dividing, even though rather slowly, and releasing their protein content into the circulation. The amount of antibody produced which is specific for any given antigen may not be appreciable, but the total gamma globulin production of the adult animal may be a measure of the rate at which the locked lymphatic cells divide and disintegrate.

Newborn rabbits are not capable of forming antibodies and we may perhaps

assume that in the lymphatic cells of the newborn rabbit hydrolase activity is low, and therefore the repression factors λ are high. On this basis we may understand why lymphatic cells of the newborn rabbit cannot lock for the production of an antibody when they are exposed to an antigen.

The fact that in the young rabbit, just as in many other young animals, the rate of production of gamma globulin is low supports the view here adopted that the gamma globulins are produced by the locked lymphatic cells. The lymphatic cells which have not locked might not divide at all or might divide exceedingly slowly.

Immune Tolerance Induced in the Newborn Rabbit.—If a large amount of an antigen P_j is injected into a newborn rabbit, which cannot form antibodies, the antigen will diffuse into the lymphatic cells and there will be a condition of antigen excess both with respect to the coupling enzymes C_j and the antibodies A_j.

At the time, perhaps two weeks after birth, when some of the lymphatic cells of the rabbit become "sensitive" and capable of forming antibodies, the antigen concentration in the circulation will still be high.

The presence of a high concentration of the antigen P_j will prevent the locking of these cells with respect to the production of the antibodies A_j, because the haptens $\bar{M}_j$ of the antigen P_j compete with the repressor REP_j for the controlling site of the antibodies A_j.

The concentration of the antigen in the circulation of the rabbit will slowly fall and after several months it might reach a very low value. Nevertheless, the rabbit may still exhibit at that time specific immune tolerance with respect to the antigen. We may attempt to account for this phenomenon as follows:

If an antigen molecule is combined with the controlling site of the "attached" enzyme molecule we may assume that it will set up a steric hindrance and repress the formation of the antibody molecule in much the same way as would the specific repressor molecule.

We shall designate the enzyme-forming site which is specific for the formation of an antibody A_j as the ribosome B_j*. For the purpose of our discussion we may assume that corresponding to each gene G_j* which determines an antibody A_j there is present in the cell one and just one ribosome B_j*. Since we have assumed that there are a number of genes G_j* which correspond to the gene G_j, there will also be a number of ribosomes B_j* for each gene G_j. (The antibodies A_j which are made by the different ribosomes B_j* may differ somewhat from each other in their specific combining capacity with respect to the metabolite M_j and the hapten $\bar{M}_j$.)

We shall assume that each antibody A_j is formed inside the corresponding ribosome B_j*, and that the ribosome is a semi-closed structure.

We assume that water, salts, and small protein molecules, including the hypothetical enzyme U postulated in the preceding paper, may all diffuse freely in and out of the ribosome. The antibody molecule A_j which is produced in the ribosome can, however, not diffuse out of the ribosome, and its concentration will therefore rise until the osmotic pressure inside the ribosome exceeds the osmotic pressure in the cytoplasm outside of the ribosome. At that point water will begin to diffuse into the ribosome and as the hydrostatic pressure inside the ribosome increases, the ribosome may open up sufficiently to permit escape of a few antibody molecules. On the basis of such a model we may expect that even in cells which are not locked

for the production of an antibody each ribosome contains the antibody, for which it is specific, at a high concentration.

The concentration of the antigen injected into the newborn rabbit will remain high in the circulation for an extended period of time, and during this time enough antigen P_j will diffuse into the ribosome B_j^* to form an antigen-antibody precipitate. The "attached" antibody molecule A_j in the ribosome may be combined at its controlling site with an antigen molecule and may form part of the precipitate. Because the concentration of the free antigen in equilibrium with such a precipitate is low, the precipitate may still persist in the ribosome at the time when the concentration of the free antigen in the circulation has fallen so low as to be undetectable. In this manner we may account for enduring immune tolerance.

Accordingly, enduring immune tolerance requires the presence of the antigen in the lymphatic cells, but does not require the antigen to be present in the circulation at a detectable concentration.

Specific immune tolerance could not endure for long if the lymphatic cells of the rabbit which have *not* locked for the production of any antibody were to divide at a substantial rate, because new ribosomes B_j^* are presumably formed by the genes G_j^* when the cell divides, and antibody production in these new ribosomes would not be blocked. (Cells which have locked for the production of an antibody may be assumed to undergo divisions at an appreciable rate, but these cells are not capable of responding to the exposure of an antigen with the formation of the specific antibody, and would therefore not abolish immune tolerance.)

The Case of the X-Rayed Rabbit.—We may attribute the inability of the rabbit to respond with the formation of antibody, if the antigen is injected several days after the rabbit has been exposed to an X-ray dose of 400 r, to the inability of its lymphatic cells to lock for the formation of an antibody.

On this basis we may expect that, if a large quantity of an antigen is injected into the rabbit, several days after the rabbit has been exposed to an X-ray dose of 400 r the rabbit will exhibit enduring immune tolerance with respect to this antigen.

If an X-ray dose of 400 r is administered to the rabbit after the injection of an antigen, then by the time the X-ray exposure takes effect many of the lymphatic cells of the rabbit will have locked for the production of antibody directed against the antigen. These locked cells will proceed to form antibody, unaffected by the X-ray exposure. Accordingly, in this case the X-ray exposure will not prevent the rabbit from responding to the injection of the antigen with the formation of antibody.

Since the antibody released into the circulation in the secondary response is released by cells that have locked for the formation of the antibody at the time of the primary response, or by their descendants, there is no reason to expect that exposing the pre-immunized rabbit to an X-ray dose of about 400 r should inhibit the secondary response.

Concluding Remarks.—If the model for cellular differentiation, presented in the preceding paper, should in fact correctly describe the molecular basis of antibody formation, then we could be rather confident that the above given explanations for the major immunological phenomena are essentially correct. This holds in particular for the role we have attributed to the "locking" of sensitive lymphatic cells in the primary response and for the notion that the primary response and the second-

ary response are basically different phenomena. We cannot be equally confident, however, of the correctness of various assumptions which relate to details and which we introduced for the sake of the concreteness of the discussion. Among these are the assumptions which relate to the mechanisms by which the antigen lowers the repressor concentration and the assumptions which relate to the structure of the ribosomes B^*. As far as such details are concerned it might well be that our assumptions will have to be modified later on, in the light of future experimental data.

In the process of formulating the thoughts expressed in this paper I had the privilege of discussing the subject with Dr. Maurice S. Fox, The Rockefeller Institute, New York; Dr. Howard Green and Dr. Baruj Benacerraf, New York University College of Medicine; and Dr. Herbert Anker, The University of Chicago. It is a pleasure to acknowledge their helpful suggestions and criticism.

* This paper is the continuation of a paper entitled "The Control of the Formation of Specific Proteins in Bacteria and in Animal Cells," pages 277–292 of this issue of these PROCEEDINGS. The concepts, notations, and equations of the first paper carry over to this paper.

† This work was supported by a research grant of the National Institutes of Health, U. S. Public Health Service.

---

*PURIFICATION OF A NERVE-GROWTH PROMOTING PROTEIN FROM THE MOUSE SALIVARY GLAND AND ITS NEURO-CYTOTOXIC ANTISERUM**

BY STANLEY COHEN†

DEPARTMENT OF ZOOLOGY, WASHINGTON UNIVERSITY, ST. LOUIS

Communicated by Viktor Hamburger, January 4, 1960

Introduction.—We have reported the isolation of a protein from snake venom which specifically promotes the growth of sensory and sympathetic nerve cells, both in tissue culture and in the living chick embryo.[1,2,3] The discovery of a similar factor in the salivary glands of the mouse, rat, and hamster,[1] extended the investigation to include mammals.

The first part of this paper is concerned with (*a*) the purification and nature of the nerve-growth factor in the submaxillary gland of the mouse, and (*b*) its effect, when injected into the mouse, on the gross chemical composition of the sympathetic ganglia.

In the course of this study we were able to prepare an antiserum to the purified growth factor isolated from the salivary gland. The antiserum inhibited, in tissue culture, the biological activity of the antigen. This gave us an opportunity to examine a question raised in our previous work concerning the possible physiological role (if any) of the growth factor in the normal organism. If a similar factor operates in the normal mouse, then the injection of the antiserum might interfere with its function. We have indeed found that the subcutaneous injection of this antiserum *in vivo* results in a specific atrophy and destruction of the sympathetic

nerve cells not only of the mouse, but also of the rat, cat, and rabbit. The cytological effects on the nerve cell of both the growth factor and the specific antiserum are described in two communications by Levi-Montalcini and Booker (in this issue of the PROCEEDINGS). These observations suggest, but do not prove, that the growth factor or an antigenically similar molecule is involved in the maintenance of the nerve cells of the sympathetic system.

Apart from this point, the more or less complete elimination of the sympathetic nervous system by a specific antiserum opens up new areas for physiological research.

Materials and Methods.—The submaxillary glands were isolated from adult (over 22 gm body weight) male Swiss mice. The carboxymethyl cellulose (CM-cellulose) and diethylaminoethyl cellulose (DEAE-cellulose) preparations have been described.[3]

The assay for nerve-growth promoting activity was made using sensory ganglia from 8–9 day chick embryos explanted in hanging drop tissue cultures. The amount of fiber outgrowth was observed after 18 hr of incubation. The details of the procedure have been presented elsewhere.[1,3] The assay was sensitive to twofold changes in concentration of the active material; smaller changes were not detectable.

The protein determinations were made using the Folin phenol reagent[4] with bovine albumin as a standard. The total nucleic acid content of the ganglia was estimated by the ultraviolet absorption of a hot acid extract.[5] It was assumed that both DNA and RNA have an ϵ (P) of 9850 at 268.5 mμ. The protein was determined on the residue after the hot acid extraction. The DNA content of ganglia was determined by a fluorometric procedure.[6]

Experimental Results.—Distribution of the growth factor: In a series of experiments the concentration of the factor in the submaxillary gland, obtained from both male and female mice at various ages, was examined. The glands were excised, homogenized in isotonic sodium chloride, and aliquots were assayed for nerve growth promoting activity in tissue culture. The results are shown in Table 1. Up

TABLE 1

NERVE GROWTH FACTOR CONTENT OF THE SUBMAXILLARY GLAND OF MICE DURING MATURATION

Age, Days	Protein Required for a 3+ Response, μg per ml	
	Female	Male
0–17	>8,000	>8,000
25	4,000	1,000
32	1,000	200
41	50	6
44	100	3
50	6	1.5

Aliquots of crude homogenates of the submaxillary gland were assayed for biological activity.

to approximately 17 days of age only traces of activity could be detected. During the period of 25 to 50 days of age, when adult levels are reached, there is a several thousandfold increase in the specific activity of the homogenates. In all age groups the submaxillary gland from male mice showed a higher specific activity than did the corresponding gland of female mice.

Homogenates of the submaxillary gland isolated from adult rats and hamsters

were active, but possessed a specific activity of only $^1/_{1,000}$ of that of the adult male mouse gland. Activity was also detected in the saliva of a mouse injected with pilocarpine to induce salivation. Only traces, if any, could be detected in crude homogenates of the submaxillary gland of the cow at levels up to 5 mg of protein per ml of tissue culture medium.

The sublingual salivary gland of the mouse has regularly shown a specific activity of approximately $^1/_{100}$ of that of the submaxillary gland. In one of three attempts the parotid gland was found to contain a trace of activity.

The presence of the growth factor in certain rodent tumors has been extensively reported.[7-11] Evidence has been obtained that a similar activity may be present in very low concentrations in other normal mouse tissues. Levi-Montalcini *et al.*[9] have reported its presence in the heart muscle of embryonic mice. Traces of activity have occasionally been found in homogenates of the striated muscle of adult mice,[10] and in one of four attempts it has been detected in the blood serum of a normal mouse. Although at levels of 5 mg of protein per ml of tissue culture medium crude homogenates of a variety of other mouse tissues have shown no detectable activity,[1] Bueker[12] has detected some activity in partially purified preparations of thymus, kidney, and muscle. Its presence has recently also been noted in the serum and in the urine of the mouse (R. Levi-Montalcini).

Where examined, the specific activity of tissues other than the salivary gland was never more than $^1/_{5,000}$ of the latter.

It has not been ascertained whether the growth factor is synthesized in the salivary gland or is produced elsewhere and is concentrated in that organ. In any case, there is a striking parallelism between the distribution of the activity as shown in Table 1 and the cytological changes which occur in the salivary gland of the mouse during its post-natal development.[13]

Purification of the growth factor: Adult male mice (22 gm body weight or over) were killed using chloroform. The submaxillary glands were excised and frozen until a sufficient quantity had been accumulated (8 gm wet weight from 70–80 mice). The frozen tissue was homogenized for 2 min with 50 ml of cold distilled water in a Waring blendor. The homogenate was centrifuged for 10 min. The supernatant fluid was decanted and the residue was stirred with 22 ml of distilled water and recentrifuged. The supernatant fluids were combined and the residue discarded. All centrifugations in this procedure were performed at 0–2° at 15,000 $\times$ *g* in an International centrifuge.

To 9 volumes of the combined supernatant fluids was added 1 volume of a stock streptomycin solution. (Stock streptomycin sulfate solution: 0.2 *M*, adjusted to pH 7.8 with NaOH.) The final pH of the mixture was between 6.9 and 7.1. The mixture was allowed to stand in the refrigerator for 3 hr and then was centrifuged for 5 min. The clear red supernatant was retained and the residue (nucleoproteins) was discarded.

Absolute alcohol was then added in a ratio of 0.07 ml per ml of supernatant fluid. The mixture was allowed to stand for 15 min at 0° and was then centrifuged. The small precipitate was discarded. To the supernatant was added absolute alcohol, 0.33 ml for each ml of *original* solution. The mixture was allowed to stand for 45–60 min at −5°, and was then centrifuged for 10 min. The supernatant fluid was discarded. The precipitate contained most of the red pigment and the

growth factor. To the precipitate was added 25 ml of distilled water and the pasty residue was stirred until uniformly dispersed. We found it convenient to freeze and store the material overnight at this stage.

The frozen mixture was then thawed and centrifuged; the precipitate was discarded. The supernatant was fractioned by the addition of a saturated ammonium sulfate solution, pH 7.3. The fraction precipitating between 52.5 and 71 per cent saturation was retained. (A time interval of 15 min at 0° was allowed for the precipitation after each addition of the ammonium sulfate solution.) The active precipitate was dissolved in 25 ml of distilled water to form a clear red solution. The solution was dialyzed, with stirring, for 36 hr against repeated changes of distilled water. The mixture was then centrifuged and the slight precipitate was discarded.

A short column of CM-cellulose was prepared as follows: 1 gm of the powder, in a 2 cm diameter column, was washed with a mixture of 0.5 *M* NaOH, 0.5 *M* NaCl, and then with 0.005 *M* NaCl until the eluate was free of alkali. The dialyzed ammonium sulfate fraction was then passed through the column at a flow rate of 3–4 drops per minute. Under these conditions the active material was not absorbed. The cellulose was washed with 2 column volumes of distilled water and the water clear eluates were combined (CM-1 fraction). All of the red pigment remained adsorbed to the column.

A column of DEAE-cellulose was prepared. 3 gm of the powder, in a 2 cm diameter column, were successively washed with solutions containing (*a*) 0.5 *M* NaOH, 0.5 *M* NaCl, (*b*) 0.1 *M* NaCl, (*c*) 0.1 *M* phosphate buffer, pH 6.0, and (*d*) 0.005 *M* NaCl. The CM-1 fraction was then passed through the column followed by 80 ml of 0.01 *M* NaCl. The eluates were discarded. The active material was then eluted with 70 ml of 0.12 *M* NaCl (DEAE fraction).

A second column of CM-cellulose was prepared. 3.5 gm of the powder, in a 2 cm diameter column, were successively washed with solutions containing (*a*) 0.5 *M* NaOH, 0.5 NaCl, (*b*) 0.01 *M* NaCl, (*c*) 0.1 *M* sodium acetate buffer pH 4.38, and (*d*) 0.01 *M* NaCl. The DEAE fraction was now passed through the column. The column was then washed with 40 ml of 0.1 *M* NaCl and then with 100 ml of 0.3 *M* NaCl. All the eluates thus obtained were discarded. The active material was then eluted with 70 ml of 0.75 *M* NaCl (CM-2 fraction).

A third column of CM-cellulose was prepared as follows: 500 mg of the powder in a 1 cm diameter column was washed as directed above for the CM-2 fractionation, except that the final wash is made with 0.1 *M* NaCl instead of 0.01 *M* NaCl. The CM-2 fraction was dialyzed overnight against 0.1 *M* NaCl and passed through the column. The column was then washed successively with 15 ml of 0.1 *M* NaCl, 15 ml of 0.3 *M* NaCl, and 20 ml of 0.35 *M* NaCl. These eluates were discarded. The active material was then eluted with 15 ml of 0.75 *M* NaCl. This solution is stable at least for several weeks when kept frozen, although a gradual flocculation of the active material occurs.

Typical yields and biological activities at the various fractionation steps are shown in Table 2. A 100-fold purification was achieved with an over-all yield which varied between 10 and 20 per cent.

Properties of the growth factor: The biological activity of the purified material

was nondialyzable, heat labile (5 min at 90°), destroyed by acid (0.1 *N* HCl for 1 hr at 26°), and stable to alkali (0.1 *N* NaOH for 1 hr at 26°).

The ultraviolet absorption spectrum of the material showed a peak at 279 mμ, a trough at 251–252 mμ, and a 280/260 absorption ratio of 1.53.

TABLE 2

PURIFICATION OF THE NERVE GROWTH FACTOR FROM THE SUBMAXILLARY GLAND

Fraction	Total Protein, mg.	Protein Required for 3+ Response, μg per ml
Homogenate	1,800	1.5
Alcohol	450	0.6
Ammonium sulfate	190	0.3
CM-1	146	0.3
DEAE	54	0.15
CM-2	14	0.045
CM-3	3	0.015

The preparation of each fraction is described in the text.

The behavior of the material was examined in a Spinco analytical ultracentrifuge using a Waugh-Yphantis partition cell. The result is shown in Figure 1. Only a single peak was detectable, with an s_{20} of 4.33 S; the molecular weight was estimated to be on the order of 44,000. The centrifugation was continued until the boundary passed into the lower segment of the cell. The concentration of protein in the upper compartment was found to be 4 per cent of that of the starting material, and it contained approximately 4 per cent of the biological activity. The remaining protein and biological activity was recoverable from the lower compartment.

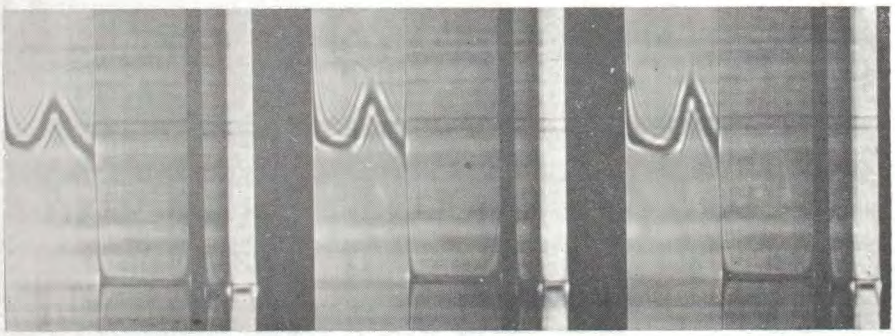


FIG. 1.—Ultracentrifugation pattern of the purified protein at 59,780 rpm. The protein concentration was 2.6 mg per ml. in 0.1 *N* NaCl containing 0.01 *M* phosphate buffer, pH 7.6. The pictures were taken at 8 minute intervals.

Upon acid hydrolysis (6 *N* HCl for 10 hours in an autoclave) and two-dimensional paper chromatography of 150 μg aliquots, the amino acid pattern obtained was found to be qualitatively identical to a similar chromatogram prepared with crystalline bovine albumin. Less than 0.3 per cent hexose was present in the preparation as determined by the orcinol procedure with galactose as a standard at 540 mμ.[14]

Two additional lines of evidence support the view that the salivary gland factor, like the snake venom factor, is a protein. First, the biological activity is destroyed

upon incubation with proteolytic enzymes, and second, the salivary factor is antigenic and the antiserum thus obtained inhibits its biological activity.

The biological activity of the purified material is completely destroyed upon incubation with crystalline pepsin or chymotrypsin. In these experiments 40 μg of the CM-3 fraction were incubated with either 0.4 μg of pepsin in 0.2 ml of 0.02 M sodium acetate buffer pH 3.3, or 8 μg of chymotrypsin in 0.2 ml of 0.02 M phosphate buffer pH 7.6. The incubations were carried out for 4 hr at 30° and aliquots then were assayed for biological activity. Under these conditions, over 95 per cent of the activity was destroyed, whereas no diminution of activity was detected in control tubes lacking the enzymes. Other controls were run in which additional amounts of the growth factor were added to the enzymatic digestion mixtures after incubation had been completed. No inhibition of the added factor was detected, indicating that the digestion mixture did not interfere with the assay system. Crystalline trypsin was less effective in destroying the biological activity. Under conditions identical to those of the chymotrypsin experiment, 8 μg of trypsin only destroyed approximately 50 per cent of the activity.

The preparation of a specific antiserum and its biological effects are discussed in a later section.

Comparison with the snake venom factor: Although the biological properties of the previously isolated venom protein and the mouse salivary gland protein are very similar, the specific activity of the most purified mouse factor was approximately 10 times greater than that of the best venom preparation. Other differences are also apparent. A comparison of the isolation procedures will show that their behavior on the ion-exchange columns was quite different. The ultracentrifugation pattern of the venom protein showed a single peak with an s_{20} of 2.2 S, whereas the s_{20} of the mouse protein was found to be 4.33. It should be remembered, however, that during the purification of the venom protein, but not of the mouse factor, a 90-min exposure to urea was included. There also appear to be antigenic differences between the two proteins as described in a later section. The biological activities of both proteins were resistant to the rather drastic alkali treatment used.

Biological activity of the growth factor: It has been reported that in tissue culture the salivary gland factor will stimulate the growth of nerve fibers from sensory ganglia isolated from chick, mouse, and rat embryos.[1,2] It will be shown in a separate communication (R. Levi-Montalcini) that sensory ganglia isolated from human embryos will also respond.

Previous tissue culture experiments, using the snake venom protein, have shown that concomitant with the stimulation of nerve fiber outgrowth, there is an increased incorporation of lysine into protein and of adenine into ribonucleic acid. No data were presented to distinguish between net synthesis and turnover.

In the present experiments it is shown that the injection of the salivary gland growth factor into newborn mice results in a marked net increase in the protein, ribonucleic acid, and desoxyribonucleic acid content of the superior cervical ganglion of the mouse. The details of the experiment and the results are shown in Table 3. It may be seen that after 12 days of injection, the protein content of the experiment was more than six times greater than that of the control ganglion, and more than two times greater than that of the normal adult (male). The DNA

content of the experimental ganglion was approximately twice that of the control and again much greater than that of the normal adult. The approximate RNA phosphorus content of the ganglia may be estimated by subtracting the average DNA phosphorus content of the ganglion (fifth column, Table 3) from the total nucleic acid phosphorus (fourth column, Table 3). The RNA value for the experimental ganglia (0.39 μg) is approximately three times greater than that of the control ganglia (0.12 μg) and more than twice the value for the normal adult (0.16 μg).

The detailed cellular changes accompanying these gross analytical differences are described in a separate paper (R. Levi-Montalcini).

The injection of the CM-3 fraction at the levels indicated in Table 3 did not result in any observable difference in the body weight from that of control mice or in other symptoms. However, attempts to inject less purified fractions resulted in a variety of side effects. The daily injection of the ammonium sulfate or CM-1 fractions (Table 2) into newborn mice resulted (in addition to the effect on the nerve cells) in the following gross anatomical changes: (*a*) precocious opening of the eyes (at 6–7 days instead of the usual 12–14 days); (*b*) precocious eruption of the teeth

TABLE 3

EFFECT OF THE INJECTION OF THE GROWTH FACTOR ON THE PROTEIN, RNA, AND DNA CONTENTS OF THE SUPERIOR CERVICAL GANGLION OF THE NEWBORN MOUSE

		Content per Ganglion*		
Age	Treatment	Protein, μg	Total Nucleic Acid, μg P	DNA, μg P
12 days	Control	15 (13–17)	0.18 (0.17–0.20)	0.056 (0.048–0.062)
12 days	Experimental	98 (86–106)	0.51 (0.46–0.57)	0.12 (0.10–0.13)
Adult	Control	36 (33–40)	0.23 (0.21–0.25)	0.066 (0.053–0.076)

Daily subcutaneous injections of 10 μg. of the CM-3 fraction per gm. body weight were made into the experimental newborn mice.

* Each set of values shown is the average obtained from four experimental animals. The figures in parentheses show the range of values obtained. The protein and RNA analyses were carried out on the same ganglion. The DNA analyses were made on separate ganglia of identically treated mice.

(at 5–6 days instead of the normal 8–10 days; (*c*) a marked stunting of the animals with an inhibition of normal hair growth. These results suggested the presence of other physiologically active components in the submaxillary gland of the adult mouse. Preliminary experiments indicate that the factor(s) responsible for these effects is heat stable but is nondialyzable, and is precipitable with ammonium sulfate. It is completely separable from the nerve growth factor.

Preparation and properties of a rabbit antiserum to the growth factor: One mg of the CM-3 fraction was injected into the foot pads of each of two rabbits using Freund's adjuvant (0.5 ml of isotonic sodium chloride containing the antigen, 0.4 ml of Bayol F with 40 μg of Mycobacterium butyricum, and 0.1 ml of Arlacel A). The antibody titer was assayed weekly. The assay, based on the inhibition of the biological activity of the growth factor in tissue culture, was performed as follows: 0.2 μg of the most purified material (CM-3 fraction) in 0.2 ml of isotonic sodium chloride was incubated with 0.2 ml of a series of two-fold dilutions of the rabbit serum. The mixture was incubated at 26° for 1 hr, diluted to 1 ml with isotonic sodium chloride and aliquots were tested for nerve growth promoting activity in tissue culture.

In this manner antibody was detected in both injected rabbits. Rabbit A reached a maximum titer in 4 weeks. The biological activity of 0.2 μg of the growth factor was completely inhibited by 0.001 ml (or more) of antiserum. The maximum titer in rabbit B was reached in 6 weeks; the titer of the antiserum was approximately one-half of that in rabbit A. The rabbits have thus far been kept for 10 weeks following the initial injection with no detectable decrease in titer. Serum obtained from both rabbits prior to immunization showed no inhibitory effects. In all cases the animals were bled from the ear vein.

The following exploratory experiment indicated that the observed inhibition of biological activity was due to the presence in the antiserum of normal precipitating antibodies. To a series of tubes containing 1 ml of antiserum (rabbit B) were added increasing amounts (1–10 mg) of crude antigen (alcohol fraction, Table 2) in isotonic sodium chloride. The mixture was allowed to stand at 26° for two hr and then the precipitate which had formed was centrifuged. Aliquots of the supernatant fluid were assayed for biological activity. Activity was absent in all tubes containing 3 mg or less of the crude antigen. The precipitate (from the 3 mg tube) was washed twice with isotonic sodium chloride and finally dispersed in 0.9 ml of distilled water. Then 0.1 ml of 1 *N* NaOH was added and the solution was allowed to stand for 1 hr at 30°. It was neutralized with 1 *N* HCl to pH 7 using phenol red as an internal indicator. Over 50 per cent of the initial activity was recovered in this solution. Control solutions to which alkali had not been added were inactive. Since a similar alkali treatment of the growth factor did not alter its biological activity or its ability to be inhibited by the antiserum, it appears that the regeneration of biological activity by treatment of the antigen-antibody precipitate with alkali was due to alterations of the antibody molecules. No precipitation occurred in control experiments using normal rabbit serum.

From preliminary experiments, there also appears to be some cross reactivity between the rabbit antiserum and the nerve growth promoting protein present in snake venom. Defining one unit of biological activity as that amount/ml required to show a 3+ response in tissue culture, 1 ml of the antiserum inhibited the biological effect of 83 units of snake venom activity (500 μg of crude venom, Agkistrodon piscivorus). This mixture, although unable to inhibit the biological effect of any further additions of venom, was still capable of neutralizing the effect of approximately 8,000 units of salivary protein (120 μg of the CM-3 fraction).

We have previously reported that the nerve growth promoting effect of snake venom was inhibited by a commercial preparation of antisnake venom serum. 100 μg of the antiserum preparation inhibited 50 μg (approximately 8 biological units) of the crude venom. In the quantities employed, the preparation did not inhibit the biological effect of the mouse salivary factor. In these experiments, amounts of antivenom up to 1,000 μg had no inhibitory effect on 4 biological units of activity derived from the mouse.

Effect of antiserum on the sympathetic chain ganglia: Up to this point in our studies there was no evidence that the salivary growth factor played any role in the normal maintenance of the sympathetic system. If such a factor was present in the general circulation of the normal animal, it was conceivable that its removal or depletion by the injection of the specific antiserum might result in some observable effect on the nerve cells.

The daily subcutaneous injection of the antiserum from rabbit A into newborn (or adult) mice at a level of 0.05 ml per 1.5 gm of body weight resulted in a rapid and extensive destruction of the nerve cells of the sympathetic chain ganglia. The injection of normal rabbit serum had no effect. No external abnormalities were observed in the mice, and after 21 days of injection the body weights of the experimental and control mice (either injected with normal serum or uninjected) were very similar.

The biological evidence for the destruction of the sympathetic system is presented in a separate communication (R. Levi-Montalcini, these PROCEEDINGS, this issue). The same antiserum causes very similar destructive effects when injected into the newborn rat, cat, or rabbit. These results suggest that there is in the general circulation of the species examined a nerve growth factor similar (identical?) in chemical structure and biological activity to that isolated from the mouse submaxillary gland. It is also possible that the antiserum interacts with the antigen (or antigen-like material) on the surface of or within the nerve cell.

The finding that the antibodies produced in the rabbit destroy the rabbit's own sympathetic chain ganglia makes the question of the identity of the mouse salivary factor with the hypothetical rabbit growth factor of great interest.

The role of the salivary glands with respect to the nerve growth factor is not clear. The possibility that the growth factor is produced elsewhere in the organism and is merely concentrated and stored in the salivary glands must be considered (see R. Levi-Montalcini and B. Booker, this issue).

Summary.—A protein with specific nerve-growth stimulating properties has been purified from the submaxillary gland of the mouse. Upon examination in an ultracentrifuge, only one component was detectable with a sedimentation constant of 4.33 S. The protein, when injected into mice, resulted in a marked increase in the protein, RNA, and DNA contents of the sympathetic chain ganglia. A rabbit antiserum to the growth factor was prepared and was found to inhibit the effect of the growth factor in tissue culture and to have specific neurocytotoxic activity when injected into a variety of mammalian species.

The author is greatly indebted to Dr. A. Holtzer for the ultracentrifugal analysis, to Dr. H. Eisen for aid in the preparation of the antiserum, and to Dr. E. Robins for aid in the DNA analyses. The technical assistance of Miss Jean Macnish is gratefully acknowledged.

* This work has been supported by a grant from the National Science Foundation and by a contribution from an Institutional grant of the American Cancer Society to Washington University. A preliminary report has been published in *Federation Proc.*, **18**, 205 (1959).

† Present address: Department of Biochemistry, Vanderbilt University, Nashville, Tennessee.

[1] Cohen, S., *Chemical Basis of Development*, ed. W. D. McElroy and B. Glass (Baltimore: Johns Hopkins Press, 1958), pp. 665–676.

[2] Levi-Montalcini, R., in *Chemical Basis of Development*, ed. W. D. McElroy and B. Glass (Baltimore: Johns Hopkins Press, 1958), pp. 646–664.

[3] Cohen, S., *J. Biol. Chem.*, **234**, 1129–1137 (1959).

[4] Lowry, O. H., N. J. Rosebrough, A. L. Farr, and R. J. Randall, *J. Biol. Chem.*, **193**, 265–275 (1951).

[5] Logan, J. E., W. A. Mannell, and R. J. Rossiter, *Biochem. J.*, **51**, 470–482 (1952).

[6] Kissane, J. M., and E. Robins, *J. Biol. Chem.*, **233**, 184–188 (1958).

[7] Bueker, E. D., *Anat. Rec.*, **102**, 369–390 (1948).

[8] Levi-Montalcini, R., and V. Hamburger, *J. Exper. Zool.*, **116**, 321–362 (1951).

[9] Levi-Montalcini, R., H. Meyer, and V. Hamburger, *Cancer Research*, **14**, 49–57 (1954).
[10] Cohen, S., and R. Levi-Montalcini, *Cancer Research*, **17**, 15–20 (1957).
[11] Bueker, E. D., *Cancer Research*, **17**, 190–199 (1957).
[12] Bueker, E. D., I. Schenklein, and J. Bane, *Anat. Record*, **133**, 256 (1959).
[13] Harvey, H., *Physiol. Zool.*, **25**, 205–222 (1952).
[14] Winzler, R. J., in *Methods of Biochemical Analysis*, Vol. 2, ed. D. Glick (New York: Interscience Publishers, Inc., 1955) p. 279.

---

*THE ACCOMMODATION OF NONCOMPLEMENTARY BASES IN HELICAL POLYRIBONUCLEOTIDES AND DEOXYRIBONUCLEIC ACIDS**†

BY JACQUES R. FRESCO‡ AND BRUCE M. ALBERTS

DEPARTMENT OF CHEMISTRY, HARVARD UNIVERSITY

Communicated by Paul Doty, December 28, 1959

It is now well established that deoxyribonucleic acid* is the molecular counterpart of the genetic apparatus. In this two-stranded helical polynucleotide the perfect crystalline geometry which normally prevails requires that adenine residues in one chain be hydrogen-bonded to thymine residues in the other; similarly, guanine residues can only be hydrogen-bonded to cytosine residues.[1–3] Thus, one chain is necessarily the complement of the other, and it appears likely that each chain serves as the template for the synthesis of its complement.[4–6]

Current views on the molecular basis of mutations hold that they are due to a variety of alterations in the nucleotide sequence within the two-stranded DNA helix. Presumably, many of these alterations arise from mistakes made during its replication. It appears from studies of fine structure genetics[7,8] that such mistakes could involve the substitution of noncomplementary bases, and also the addition or deletion of one or a sequence of nucleotides, during the synthesis of a progeny chain on its template. In view of these plausible mechanisms of mutation, we have examined the possibilities whereby noncomplementary base pairs can be accommodated within the two-stranded helical framework of DNA. We first investigated the effects of varying proportions of noncomplementary bases incorporated into pairs of complementary polyribonucleotides which are known to form two-stranded helices like DNA. The results of such experiments allowed us to exclude the notion that noncomplementary bases remain within the interior of the helix. Instead, they suggested that noncomplementary nucleotides of opposite chains rotate out of the helix in such a manner as to enable normal hydrogen-bonded base pairing of subsequent regions of nucleotides which are in register. This structural alternative was then explored by model building and found to be readily plausible.

Experimental Approach.—Polyadenylic and polyuridylic acids* are single stranded polyribonucleotides[9, 10] containing base residues equivalent to the complementary pair, adenine-thymine, present in DNA. Indeed, in neutral saline solution they form a 1 : 1 two-stranded helical complex which has essentially the same structure as DNA.[11–13] Under appropriate conditions, a second strand of poly U can be induced to wrap around this poly(A+U) helix, so that a three-stranded complex is formed in which the molar ratio of adenine to uracil is 1 : 2.[13]

Mixing curves: The interaction of polynucleotide strands to form helical complexes is accompanied by a marked decrease in ultraviolet absorbance.[10, 11, 13, 15] For long chains, this hypochromic change can be expected to reflect in a linear manner the number of nucleotides involved in the interaction. Thus, by titrating one species against another, it is possible to locate the mixture of maximum hypochromicity, and thereby to accurately determine the molar ratio of the reacting species in the complex being formed.[13]

In the present investigation, such mixing curves were used in order to study quantitative aspects of the interaction of poly A or poly U with a series of single stranded poly AU copolymers.[16] Complex formation here necessitates juxtaposition of the mismatched bases, adenine-adenine and uracil-uracil, at certain levels of the helix. The manner in which these pairs are structurally accommodated will influence the molar ratio at the point of maximum hypochromicity.

The underlying assumption behind these interaction experiments is, of course, that polynucleotide chains have the capacity to explore and find the partners which permit the complete fulfillment of their hydrogen bonding potentialities. This was previously shown for the interaction of poly A and poly U.[13, 17] The results to be described below also bear out this assumption. Even those single-stranded AU copolymers which exhibited a high degree of intramolecular hydrogen bonding (as evidenced by a large reversible hyperchromic change on heating) were found to interact optimally with homopolymer to form multistranded complexes.

Absorbance-temperature profiles: Helical macromolecules, being highly ordered, are found to denature or "melt" over relatively narrow temperature ranges.[18, 19] In the case of polynucleotides, the profile of this transition can be followed spectrophotometrically by measuring the increase in ultraviolet absorption (reversal of hypochromicity) as a function of temperature. In a given solvent, the temperature of the midpoint of this transition (T_m) will reflect the relative stability of the complex.[15] This property was assessed for the complexes formed between poly A or poly U and several poly AU copolymers in order to evaluate the effect of the mismatchings on the strength of the interaction.

Methods.—Polynucleotide samples: Samples of poly A and poly U, and samples of poly AU differing in their content of adenylic and uridylic residues were synthesized in this or other laboratories as previously described,[20] employing the reaction catalyzed by polynucleotide phosphorylase.[21]

Polymers were generally isolated from their polymerization reaction mixtures by precipitation with ethanol, and were purified by reprecipitation with ethanol from clarified neutral saline solution, followed by extensive dialysis against neutral saline containing versene or citrate. Stock solutions of polymers were stored at −20°C.

Base analysis of polymers: Duplicate determinations of the ratio of adenylic to uridylic residues in the copolymers were made according to a modification of a method of Markham and Smith.[22] About 0.5 mg of polynucleotide was hydrolyzed in an alkali resistant glass test tube in 0.4 *N* NaOH at 37°C for 18 hours. The hydrolysate was neutralized and divided into two parts for chromatography on Whatman No. 1 paper. Descending chromatograms were developed at 4°C with a solvent containing saturated aqueous $(NH_4)_2SO_4$ [79 vol], water [19 vol.], and isopropanol [2 vol.]. At this low temperature sharper spots were obtained, so

long as the chromatography paper was dry when the run was started. After thorough drying of the paper, the adenylate and uridylate spots and corresponding paper blanks were eluted quantitatively and their amounts determined spectrophotometrically.

Polymer concentration determination: Duplicate aliquots of stock solutions used for mixing curves were hydrolyzed in 0.4 *N* NaOH at 37°C for 18 hours. It was found necessary to incubate similar flasks containing 0.4 *N* NaOH in order to provide proper blanks. The hydrolysates were then diluted to a constant volume and final acid concentration of 0.1 *N* with HCl. Knowing the nucleotide composition and the extinction coefficients of the monomers at 259 mμ, the molar nucleotide residue concentration of the homopolymers and copolymers was calculated from the absorbance at 259 mμ.

Mixing curves: Polymer stock solutions were made up to the same nucleotide residue concentration. For two-stranded complex formation, the solvent used was either 0.15 *M* NaCl + 0.015 *M* sodium citrate, pH 7, or 0.15 *M* NaCl + 0.045 *M* sodium cacodylate, pH 6.9—the latter being preferred because of its ability to deter bacterial contamination. For each homopolymer-copolymer combination, a series of mixtures was made such that the total number of nucleotide residues was kept constant while the ratio of homopolymer to copolymer was varied. These mixtures were allowed to equilibrate at a constant temperature, and their absorbance at 259 mμ then determined, against a solvent blank, in a Beckman DU spectrophotometer adapted with a thermostated cell chamber. Additional mixtures, with polymer ratios clustered about the observed minimum, were then used to precisely locate the optimally interacting mixture. To detect any hypothetical three-stranded structure which might form, similar mixing curves were performed in solvent also containing 0.05 *M* $MgCl_2$.

TABLE 1

ANALYTICAL PROPERTIES OF SINGLE-STRANDED POLYRIBONUCLEOTIDES

Polymer	Mole % Adenylic Residues	$S^\circ_{20,w}$*	Approximate Molecular Weight
Poly A	100	9.0	600,000†
Poly U	0	4.3	150,000†
Poly AU "90"	90	3.0	50,000†
Poly AU "66"	66	1.4	8,000‡
Poly AU "53"	53	3.9	40,000‡
Poly AU "37"	37	2.9	25,000‡

* These mean sedimentation constants were determined in 0.15 *M* NaCl + 0.015 *M* sodium citrate, pH 7.
† Extrapolated from S° versus M.W. calibration curve for Poly A.
‡ Extrapolated from S° versus M.W. calibration curve for RNA.

Absorbance-temperature profiles: Absorbance measurements were made at 259 mμ on solutions contained in quartz stoppered cuvettes with a thermostated Beckman DU spectrophotometer controlled to ±0.3°C.

Sedimentation constants: Sedimentation velocity measurements were made at about 22°C in a Spinco Model E Ultracentrifuge using the ultraviolet absorption optical system. The mean $S^\circ_{20,w}$ was calculated from the moving boundaries traced with a Spinco analytrol.

Model building: Pauling–Corey space-filling nucleotide models,[23] (1″ = 2 Å) were used to explore possible configurations for the helical homopolymer-copolymer complexes.

Results.—Properties of polymers: In Table 1 are presented some analytical properties of the single-stranded polynucleotides used in the interaction studies. The compositional data are subject to an average deviation of ±1.5 per cent. Note that the identification number following each copolymer is derived from the mole per cent of adenylic residues that it contains. Approximate molecular weight values were derived from the sedimentation constants using either the calibration scale of S° versus molecular weight for RNA[24] or that for poly A.[9] It is recognized that these extrapolations may be subject to errors of as much as 50 per cent. Nevertheless, it is apparent that all the samples are of sufficiently high molecular weight so that hypochromicity can serve as a linearly proportional measure of complex formation.

Homopolymer-copolymer interactions: A priori, one might conceive of two possible ways in which noncomplementary base pairs could be accommodated into the DNA type of helical structure.

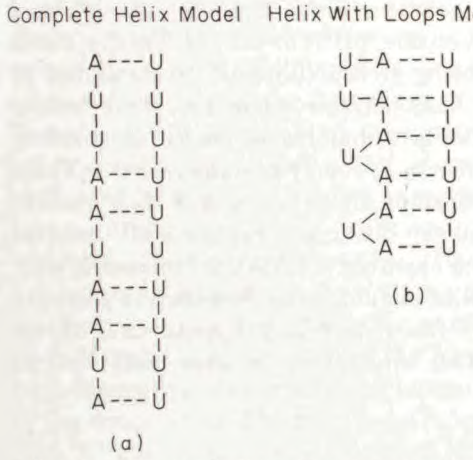


FIG. 1.—Structural alternatives for accommodating noncomplementary residues in DNA-like helices. (*a*) In any case of the Complete Helix Model the molar ratio of poly U:poly AU will always be 1:1 for the two-stranded complex. If a second strand of poly U is added, this ratio becomes 2:1. (*b*) In the Helix-With-Loops Model the molar ratio of poly U:poly AU varies with copolymer composition. In the example shown, this ratio is 6:10 for the two-stranded complex and 12:10 when a second strand of poly U is added.

The first possibility is that such nonmatching bases could be held *within* the helix either with or without hydrogen bonding. Conceivably this would involve occasional distortions of the helix to compensate for the steric variations involved in pyrimidine-pyrimidine and purine-purine pairings.

The alternative is that these noncomplementary nucleotide residues could in some manner rotate out of the helix to allow a continuity of complementary base pairs along its entire length.

These two possibilities are illustrated schematically for poly (AU + U) in Figure 1*a* and *b*. From Figure 1 it is clear that the overall composition of the two complexes will be different depending on the method by which nonmatching bases are accommodated. If these are retained within the helix (Fig. 1*a* "Complete Helix" model), the mixture of maximum hypochromicity in a mixing curve will always contain equimolar amounts of homopolymer and copolymer for the two-stranded complexes poly (AU + A) and poly (AU + U). In the alternative case, where the nonmatching residues in the copolymer do not reside within the helix (Fig. 1*b* "helix-with-loops" model), the homopolymer content of the complex will be *less* than 50 moles per cent. As is apparent from Figure 1 (*b*), the exact composition of such a complex can be calculated from the proportion of noncomplementary bases to be accommodated. If complex formation is complete, this scheme predicts that the mixing curve minimum will lie at the point where the

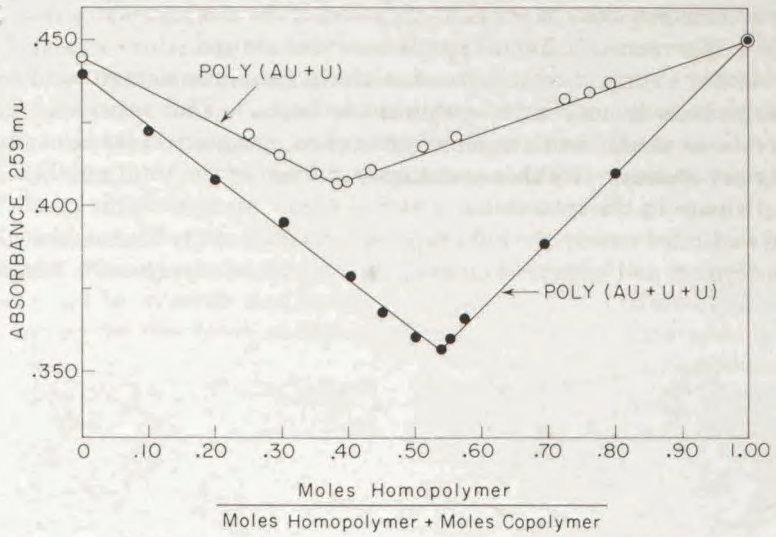


FIG. 2.—Mixing curves for poly AU "66" + poly U. *Open circle* points are for two-stranded complex formation at 21°C in 0.15 *M* NaCl + 0.045 *M* cacodylate, pH 6.9. *Filled circle* points are for three-stranded complex formation at 17°C in the same solvent + 0.05 *M* $MgCl_2$. The composition at the point of maximum hypochromicity did not change when the temperature was lowered to 4°C.

moles of homopolymer equals the moles of *complementary* residues in the copolymer.

Similar considerations can be used to analyze mixing curves involving the formation of the three-stranded complexes, poly (AU + U + U).

Mixing curves, such as those in Figure 2, were obtained on combinations of the copolymers and poly U or poly A. The composition of the various homopolymer-copolymer complexes were determined from the mixtures of maximum hypochromicity, and are compared in Table 2 with the theoretical values calculated for the two models described above. Two sets of the data included were derived from mixing curves published in another connection by Steiner.[25] It can be seen from Table 2 that in every case where two- or three-stranded complexes were found, their compositions agreed very closely with those expected for the model of the helix-with-loops. This is also evident from the examples in Figure 3 which show that *in every combination, maximum complex formation occurred at the point where*

TABLE 2

COMPOSITION OF HELICAL POLYRIBONUCLEOTIDE COMPLEXES

	Mole % of Homopolymer in Mixture of Maximum Hypochromicity					
	2-Stranded Complexes			3-Stranded Complexes		
		Theoretical			Theoretical	
Polymer Mixture	Experimentally Found	Helix With Loops	Complete Helix	Experimentally Found	Helix With Loops	Complete Helix
Poly A + Poly U	50	X	50	67	X	67
Poly AU "90" + Poly U	...	..	..	65 ± 1	64.5	67
Poly AU "66" + Poly U	38 ± 1	40	50	54 ± 1	57	67
Poly AU "53" + Poly U	34 ± 1	34.5	50	...	..	..
*Poly AU "62" + Poly U	...	..	..	57	55	67
*Poly AU "82" + Poly U	...	..	..	64	62	67
Poly AU "37" + Poly A	38 ± 3	39	50	X	X	X

* These sets of data were derived from the work of Steiner.[25]
Dots in place of a value indicate the data were not available, while an *X* indicates the value is not meaningful.

the moles of homopolymer either equals the moles of the complementary residue in the copolymer (two-stranded helix), *or equals twice that amount* (three-stranded helix).

These results clearly demonstrate that the noncomplementary residues of the copolymer strands do not remain within the helix. The only other way to explain our observations would be to assume significant compositional heterogeneity among the copolymer chains. In this event only a fraction of the total number of chains could participate in the interaction with the homopolymer. This possibility was evaluated and ruled out by the following considerations: (1) Chemical degradation of AU copolymers and isotopic studies of their enzymatic synthesis[20, 26] have shown

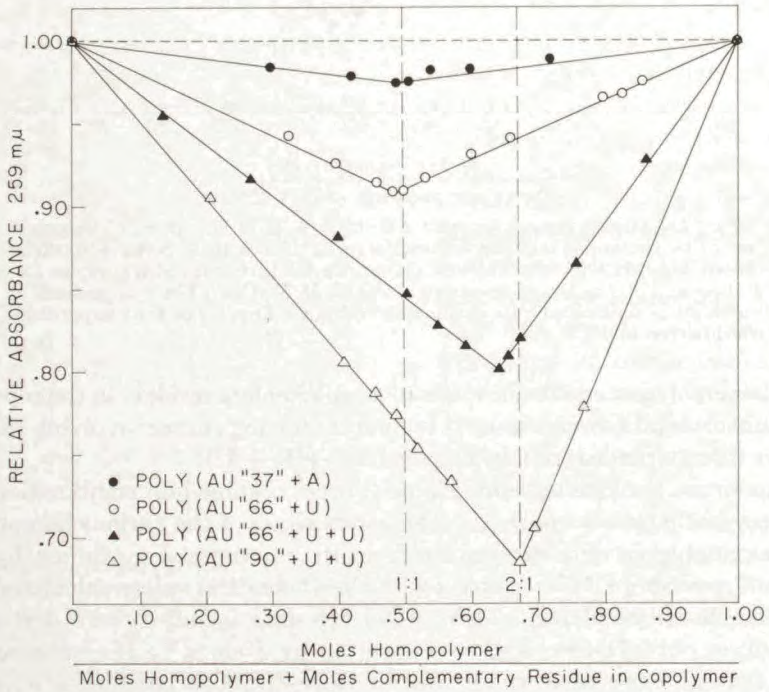


FIG. 3.—Mixing curves for the formation of homopolymer-copolymer polyribonucleotide complexes. Relative absorbance is the ratio of the absorbance of the mixture to that of the average of the unmixed constituents. It should be noted that the depth of these mixing curves will depend in part on the initial hypochromicity of the reacting species. The extreme shallowness of the (AU "37" + A) curve can be explained by the fact that both poly A and the AU copolymers are highly hypochromic, whereas poly U is not.

that the sequence of adenylic and uridylic residues is essentially random. Moreover, the chain lengths of our samples are sufficient to average out small compositional differences. (2) The self-consistency of all the interaction data argues strongly for a quantitative reaction. It is especially reflected by the equivalence of the amount of homopolymer required to form the poly (AU "66" + U) two-stranded complex, and the additional amount required to form the three-stranded complex. This rules out the possibility that the original copolymer solutions contained any stable two-stranded helical complexes which could not be titrated. (3) The fact that the hypochromicity increases in a *linear* manner as the copolymer

is titrated with homopolymer indicates that all the available copolymer molecules have an equal capacity for interaction. If some copolymer molecules had a preferential tendency to interact because of more favorable residue sequence or composition, the initial phase of the titration would result in a greater hypochromic change than that occurring when the titration was nearer to completion. In this event, the mixing curve would have a readily detectable concave character extending to the point of maximum hypochromicity.

Model building: Having concluded that the noncomplementary residues in the copolymer must loop out of the helix, we then proceeded to examine how this condition could be satisfied structurally. A poly (A + U) space-filling helix was built according to the DNA coördinates.[27] It was found that when a uridylic

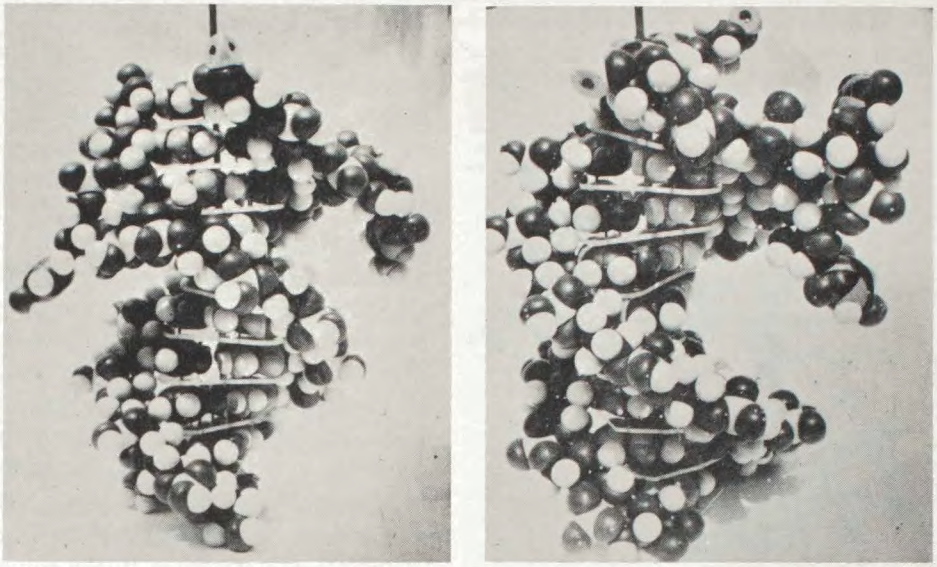


FIG. 4.—(*a*) A poly (A + U) helix containing a single nucleotide loop in each chain. This portrays the situation which might occur in DNA if cytosine and thymine are bases located in opposite chains at the same level, while all the other residues are in register. Note that the loops point away from the backbone and do not obstruct either groove.

FIG. 4.—(*b*) A poly (A + U) helix containing in the A-chain a looped region of two uridylic residues.

residue is incorporated into the A-chain, it can be readily looped out of its position within the helix, merely by rotation about its two adjacent phosphodiester bonds. This leaves the uracil base pointing radially out from the helix axis, and allows an adjacent nucleotide residue to move into the vacancy created without strain. (Fig. 4*a*). In addition, similar loops containing two, three or more nucleotides are also possible (Fig. 4*b*, *c*). Indeed, there appears to be no structural limitation on the number of nucleotide residues which can be incorporated into a loop. It should be noted, however, that whereas a loop of one residue is rigidly fixed in position except for the rotation about its phosphodiester bonds, larger loops become increasingly more flexible.

Exactly the same considerations are involved for any other noncomplementary base residues which might be incorporated into either chain. In all cases, the

regularity of the helix in the vicinity of the loop is unaffected, both the 3.4 Å separation and 36° translation of successive nucleotides being maintained. Furthermore, the loops do not interfere with either the "deep" or "shallow" groove, which explains why it is possible to add a second poly U chain to the poly (AU + U) complexes.

The only significant alteration in the helical backbone is that for each loop the separation of one pair of PO^- groups is reduced from 7 Å to approximately 6. However, it is apparent that other thermodynamic considerations such as the maximization of hydrogen bonding and the increased entropy brought about by loop formation tend to offset this small increase of charge repulsion. An additional factor favoring loop formation would seem to be that removing noncomplementary bases from the interior of the helix enables them to form hydrogen bonds with solvent molecules from which they would be otherwise inaccessible.

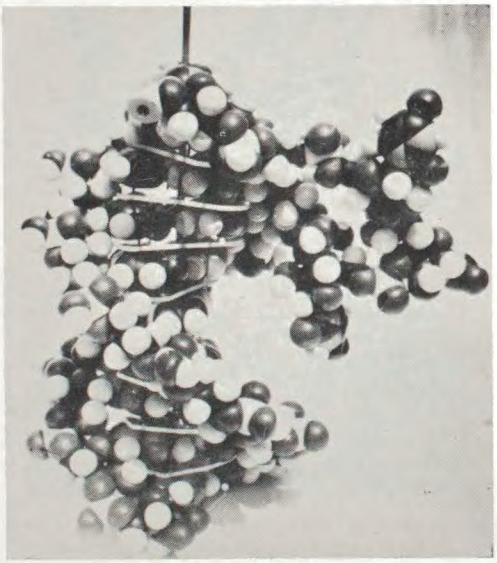


FIG. 4.—(*c*) A poly (A + U) helix containing in the A-chain a looped region of three uridylic residues.

Although the stereochemical considerations just described require further examination with the more precise models in use by crystallographers, it would appear that the broad structural features of the helix-with-loops model are correct.

Stability of homopolymer-copolymer complexes: The introduction of imperfections into a two-stranded helix can be expected to produce a weaker, more heterogeneous complex. It is not surprising therefore that the homopolymer-copolymer complexes examined melt more broadly and at lower temperatures than the perfect poly (A + U) helix. For example, in the saline-citrate solvent, whereas poly (A + U) melts almost entirely between 57 and 62°, poly (AU "53" + U) melts from 5 to 46° and has a T_m of about 24°.[28] The latter helix contains 31 per cent unpaired, looped out bases. Since its complete formation requires several hours at 2°, it would seem that a limit to the number of tolerable imperfections is being approached under these experimental conditions. In fact, for an AU copolymer containing 51 per cent adenylic residues, no interaction with poly U could be observed. In any case, the number of mismatchings which can be incorporated into a DNA-like helix is surprisingly large.

Discussion.—The helix-with-loops model adds a dimension of freedom to configurational considerations of helical polynucleotides. In the case of RNA, the model offers a means for satisfying the requirement for the short helical regions which have been recently suggested.[15] In addition, it involves the generation of a new type of tertiary structure which could have biological significance. A molecular structure for RNA incorporating these features will be described in a subsequent report.

There are several contexts in which the helix-with-loops model might be significant for DNA. In view of the similarity of essential structural features between the poly (A + U) helix and DNA, it seems likely that any base pair mismatchings arising during DNA synthesis would also be accommodated by loop formation. From the foregoing it is apparent that the looping mechanism does not require any significant alteration in the structural parameters of the poly (A + U) helix. It also does not result in significant crowding of the grooves, which in the case of DNA must remain unobstructed in order to contain protamine or histone.[29] The homopolymer-copolymer system does not provide an entirely analogous model to a DNA molecule with defective base pairs. Since one of the strands of the synthetic helix is a homopolymer, this strand need never form a loop in order to keep all nucleotides in register. Further, this helical complex is the resultant of an interaction between two *already existing* polynucleotide chains. In DNA, on the other hand, not only is there a specific sequence of residues, but it is believed that the helix is formed by one chain being synthesized in a linear fashion upon its complementary template chain.[4–6] Under these conditions, the accidental addition to the growing chain of a nucleotide which is not complementary to its partner in the template chain will lead to one of three obvious consequences. Any of these would appear to be a possible molecular counterpart for point mutations. These models showing how mutational events might be accommodated are represented schematically in Figure 5.

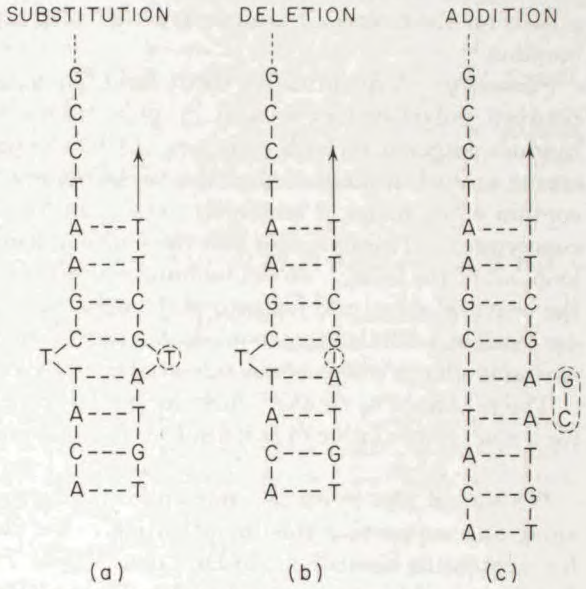


FIG. 5.—Hypothetical models for point mutations. In each case, the template chain is the one on the left. Note that while the templates are identical in each case, the sequence in the growing chains varies, depending on the kind of "mistake" made during replication. The "mistake" in the growing chain is indicated by a dotted circle.

In the first case, Figure 5*a* (compare with Fig. 4*a*), both the erroneous base and its noncomplementary partner have looped out of the growing helix, thus enabling the succeeding regions to pair normally. This type of accommodation merely involves the *substitution* of one residue for another, and results in no difference in chain length between the chains.

In Figure 5*b*, however, the erroneous base has paired with a succeeding base on the template, causing the intervening template residue(*s*) to loop out of the helix. Chain growth then continues, leading to a progeny chain which is shortened by one or more residues. Conceivably, such a *deletion* in the growing chain could also be caused by the presence of a pre-existing distortion in the template chain, rendering some of its residues inaccessible.

In the last case, Figure 5*c*, the errors made on the growing chain have been removed from the helix to enable succeeding chain growth to continue normally. This *addition* of residues to the growing chain results in a progeny chain longer than its template.

While it would seem that the *substitution* mechanism could produce reversible mutations (including those induced by base analogues in bacteriophage[7, 8]), the *addition* and *deletion* mechanisms could account for those mutational events which have been found to be irreversible.

It is worth noting that these models for point mutations can serve equally well to explain the incorporation into DNA of unnatural or unusual nucleotides incapable of forming satisfactory hydrogen bonds with any of the naturally occurring residues.

Finally, it is important to recognize that the helix-with-loops model may provide a basis for the molecular interpretation of such other genetic phenomena as recombination.[30]

Summary.—A quantitative study has been made of the helical complex formation between polyriboadenylic acid or polyuridylic acid and copolymers containing residues common to both members of this complementary pair. The interaction occurs in such a manner that the two-stranded helical complexes formed always contain equal moles of homopolymer residues and complementary residues in the copolymers. This indicates that the noncomplementary residues in the copolymers loop out of the helix. Model building shows that this can be done without altering the essential structural features of the helix, and that loops of one or more residues are feasible. While these loops do weaken the helix, it is apparent that the number of mismatchings which can be tolerated in a DNA-like helix is quite large.

The relevance of these findings to DNA is considered, and hypothetical schemes for the accommodation of point mutations by forming such loops are presented.

We should like to express our appreciation to Professor Paul Doty for encouraging and supporting this investigation. We are also indebted to Dr. E. Freese for stimulating discussions, to Dr. Leon Heppel, Dr. R. C. Warner, and Dr. A. Rich for the poly AU samples, and to Mr. Richard Blake for capable assistance. This work has been aided by grants from The American Heart Association, the United States Public Health Service, C-2170 and the National Science Foundation, G-7849.

* The following abbreviations have been used: RNA = ribonucleic acid; DNA = deoxyribonucleic acid; A = adenine; U = uracil; C = cytosine; G = guanine. The prefix *poly* is used to indicate a homo or copolymer of nucleotide(s) of the indicated base(s). Polynucleotide complexes are indicated by the prefix *poly* followed in parentheses by the summated homo or copolymer chain symbols.

† This paper is No. III in a series entitled *Polynucleotides*, of which the last was by J. R. Fresco, *J. Mol. Biol.*, **1**, 103 (1959).

‡ Established Investigator of the American Heart Association.

[1] Watson, J. D., and F. H. C. Crick, *Nature*, **171**, 737 (1953).

[2] Crick, F. H. C., and J. D. Watson, *Proc. Roy. Soc.* (London), *A***233**, 80 (1954).

[3] Wilkins, M. H. F., W. E. Seeds, A. R. Stokes, and H. R. Wilson, *Nature*, **172**, 759 (1953).

[4] Watson, J. D., and F. H. C. Crick, *Nature*, **171**, 964 (1953).

[5] Meselson, M., and F. W. Stahl, these PROCEEDINGS, **44**, 671 (1958).

[6] Bessman, J. M., I. R. Lehman, J. Adler, S. B. Zimmerman, E. S. Simms, and A. Kornberg, these PROCEEDINGS, **44**, 633 (1958).

[7] Benzer, S., and E. Freese, these PROCEEDINGS, **44**, 112 (1958).

[8] Freese, E., *Brookhaven Symposia in Biology*, **12**, 63 (1959).

[9] Fresco, J. R., and P. Doty, *J. Am. Chem. Soc.*, **79**, 3928 (1957).

[10] Fresco, J. R., and E. Klemperer, *Ann. N. Y. Acad. Sci.*, **81**, 730 (1959).

[11] Warner, R. C., *J. Biol. Chem.*, **229**, 711 (1957).

[12] Rich, A., and D. R. Davies, *J. Am. Chem. Soc.*, **78**, 3548 (1956).

[13] Felsenfeld, G., and A. Rich, *Biochim. et Biophys. Acta*, **26**, 457 (1957).

[14] Thomas, A., *Biochim. et Biophys. Acta*, **14**, 231 (1954).

[15] Doty, P., H. Boedtker, J. R. Fresco, R. Haselkorn, and M. Litt, these PROCEEDINGS, **45**, 482 (1959).

[16] Breslow, E., and R. C. Warner, *Federation Proc.*, **18**, 197 (1959).

[17] Felsenfeld, G., *Biochim. et Biophys. Acta*, **29**, 133 (1958).

[18] Doty, P., these PROCEEDINGS, **42**, 791 (1956).

[19] Doty, P., *Collection Czechoslov. Chem. Commun.*, **22**, 5 (1957).

[20] Heppel, L. A., P. J. Ortiz, and S. Ochoa, *J. Biol. Chem.*, **229**, 695 (1957).

[21] Grunberg-Manago, M., P. J. Ortiz, and S. Ochoa, *Biochim. et Biophys. Acta*, **20**, 269 (1956).

[22] Markham, R., and J. D. Smith, *Biochem. J.*, **49**, 401 (1951).

[23] Pauling, L., and R. B. Corey, *Arch. Biochem. Biophys.*, **65**, 164 (1956).

[24] Doty, P., H. Boedtker, J. R., Fresco, B. D. Hall, R. Haselkorn, *Ann. N. Y. Acad. Sci.*, **81**, 693 (1959).

[25] Steiner, R. F., *Ann. N. Y. Acad. Sci.*, **81**, 742 (1959). Contrary to Steiner's interpretation, his mixing curves have been analyzed in terms of the formation of a *three*-stranded complex. That this was the case is evident from the degree of hyperchromic change which he observed upon heating a solution of the complex.

[26] Ortiz, P. J., and S. Ochoa, *J. Biol. Chem.*, **234**, 1208 (1959).

[27] Langridge, R., W. E. Seeds, H. R. Wilson, C. W. Hooper, M. H. F. Wilkins, and L. D. Hamilton, *J. Biochem. Biophys. Cyt.*, **3**, 767 (1957).

[28] It is important to note that the homopolymer-copolymer complexes melt at temperatures low enough for the single-stranded copolymer chain (and the poly A chain) to reform a considerable number of hydrogen bonds within itself. Therefore, the experimentally determined profile of the complexes must be adjusted as follows in order to obtain a true measure of their stability:

where x = mole fraction of complex melted; t = temperature; a(t) = absorbance of the complex as a function of temperature; b(t) = absorbance of an equimolar amount of non-interacted constituent chains (calculated from their separate profiles); and c = absorbance of the completely formed complex [minimum value of a(t)];

$$a(t) = c[1 - x] + x[b(t)]$$

$$x = \frac{a(t) - c}{b(t) - c}$$

[29] Zubay, G., and P. Doty, *J. Mol. Biol.*, **1**, 1 (1959).

[30] Levinthal, C., in *The Viruses*, ed. F. M. Burnet and W. M. Stanley (New York: Academic Press, 1959), vol. 2, p. 281.

STUDIES ON SOLUBLE RIBONUCLEIC ACID (S-RNA) OF RABBIT LIVER, I. AMINO ACID ACCEPTOR SPECIFICITY AND MOLECULAR WEIGHT

By Werner A. Klee and G. L. Cantoni

LABORATORY OF CELLULAR PHARMACOLOGY, NATIONAL INSTITUTE OF MENTAL HEALTH, BETHESDA

Communicated by David Shemin, January 4, 1960

Cytoplasmic or soluble RNA (S-RNA) exhibits the unique biological property of functioning as an acceptor for acyl-activated amino acids and as a donor of the amino acyl group to microsomal proteins.[1, 2] It has been established that the amino acid is linked to the polynucleotide chain through the 2′ or 3′ hydroxyl group of the terminal nucleotide having an unesterified 3′ hydroxyl group, [3, 4] and furthermore that the terminal nucleotide is adenylic acid.[3, 5] For a given S-RNA preparation there are a finite number of acceptor sites, presumably one for each polynucleotide chain and it has been shown that various amino acids can be bound independently of one another, but in fixed amounts, to a given S-RNA preparation.[2, 7, 8] From this observation it has been concluded that the number of acceptor sites for any one amino acid is smaller than the total number of acceptor sites. In a few instances it has been possible to achieve a partial separation of the accepting species

TABLE 1

Sedimentation Coefficients Calculated from Partition Cell Experiments*

	$S_{20, w}$	
	C^{14} = RNA − Amino Acid†	O.D. = Total RNA
Leucine	4.4 ± 0.6 (6)	4.3 ± 0.5 (6)
Proline	4.2 ± 0.7 (7)	4.3 ± 0.5 (8)
Valine	4.0 ± 0.7 (4)	4.5 ± 0.7 (4)

* The figures in parentheses indicate the number of experiments which were averaged. All sedimentation coefficients have been corrected to standard conditions. The ionic strength varied from 0.03 to 0.20, the temperature from 2 to 22°C and the concentration of RNA from 0.01 to 0.1 gm/100 ml. None of these variations were found to cause large changes in the measured sedimentation coefficients. The pH was approximately 7.0. No experiments were discarded in calculating the average values given and mean deviations are indicated.

Amino acid-labeled S-RNA was prepared by incubating 15–30 mg of rabbit liver S-RNA,[12] in approximately 10 ml, with the appropriate amino acid activating enzyme[13] in the presence of ATP, 10 mM; $MgCl_2$, 20 mM; NaCl 2.8 mM; K phosphate buffer pH 7.6, 2.8 mM; and C^{14} proline, leucine, or valine, 0.05 mM. The nonreacted amino acid was removed by precipitating the S-RNA-amino acid with 6 per cent perchloric acid and exhaustive acid washing followed by extraction with NaCl-phosphate buffer pH 7.4 and dialysis of the labeled RNA. The S-RNA-amino acid preparation thus obtained is capable, underap propriate experimental conditions, of transferring the bound amino acid to microsomal protein without dilution with free amino acid.

S-RNA from one another.[9, 10] Any given S-RNA-amino acid preparation therefore consists of a mixture of polynucleotide chains only some of which are charged with the specific amino acid while others, which are uncharged, will act as acceptors for other amino acids in the presence of the appropriate enzymes and substrates. Thus, it is established that S-RNA exhibits specificity toward different activated amino acids but the basis for this specificity is unknown.

The possibility that specificity for different amino acids might be related to the length of the polynucleotide chain was investigated in the ultracentrifuge by means of the moving partition cell of Yphantis and Waugh.[11] This technique provides a powerful tool for the study of the relationship between molecular size and biological activity. Inasmuch as each S-RNA species can be charged with an isotopically

labeled amino acid, both the sedimentation coefficient of the amino acid-labeled S-RNA component and that of the total S-RNA present can be determined independently in the same experiment.

The sedimentation coefficients, (in Table 1) were obtained from partition cell experiments using the equation developed by Yphantis and Waugh.[11] The weight average s values for the total RNA present in the solution were calculated from ultraviolet absorption measurements, while the values of s for the individual species were calculated from C^{14} determinations of the same ultracentrifugal samples.

Average values of the sedimentation coefficients of three S-RNA preparations charged respectively with leucine, proline, or valine are listed in Table 1. It is clear that in each case the sedimentation coefficient of the species which carries the amino acid is the same as that of the total S-RNA; moreover, it can be seen that there are no significant differences in s among the three species examined.

On the assumption that the sedimentation coefficient of S-RNA is a measure of its size, it may be concluded from these studies that the specificity of S-RNA as an acceptor for different amino acids is not related to molecular weight. Ultracentrifugal studies with U. V. optics[14] have shown that this preparation of S-RNA exhibits a reasonably smooth distribution of sedimentation coefficients around a single sharp peak at 4.2S, with 85 per cent of material sedimenting with s of less than 8.0. While this distribution of sedimentation coefficients is due in large part to heterogeneity with respect to chain length, the preparation is relatively more homogeneous in this respect than other RNAs.

It would appear therefore that the basis for the biological specificity of S-RNA must reside in its nucleotide composition or in the sequence in which the units are arranged.

[1] Hoagland, M. B., P. C. Zamecnik, and M. L. Stephenson, *Biochim. Biophys. Acta*, **24**, 215 (1957).

[2] Hoagland, M. B , M. L. Stephenson, J. F. Scott, L. I. Hecht, and P. C. Zamecnik, *J. Biol. Chem.*, **231**, 241 (1958).

[3] Zachau, H. G., G. Acs, and F. Lipmann, these PROCEEDINGS, **44**, 885 (1958).

[4] Preiss, J., P. Berg, E. J. Ofengand, F. H. Bergmann, and M. Dieckmann, these PROCEEDINGS, **45**, 319 (1959).

[5] Hecht, L., M. L. Stephenson, and P. C. Zamecnik, *Biochim. Biophys. Acta*, **29**, 460 (1958).

[6] Singer, M., and G. L. Cantoni (in preparation).

[7] Berg, P., and E. J. Ofengand, these PROCEEDINGS, **44**, 78 (1958).

[8] Schweet, R. S., F. C. Bovard, E. Allen, and E. Glassman, these PROCEEDINGS, **44**, 173 (1958).

[9] Holley, R. W., B. P. Doctor, S. H. Merrill, and F. M. Saad, *Biochim. Biophys. Acta*, **35**, 272 (1959).

[10] Smith, K. C., E. Cordes, and R. S. Schweet, *Biochim. Biophys. Acta*, **33**, 286 (1959).

[11] Yphantis, D. A., and D. F. Waugh, *J. Phys. Chem.*, **60**, 623, 630 (1956).

[12] Cantoni, G. L., and R. Morrison (to be published).

[13] Gelboin, H., and G. L. Cantoni (to be published).

[14] Luborsky, S., and G. L. Cantoni (to be published).

*THE MECHANISM OF BACTERIAL FRAGILITY PRODUCED BY 5-FLUOROURACIL: THE ACCUMULATION OF CELL WALL PRECURSORS**

By Alexander Tomasz† and Ernest Borek

DEPARTMENT OF BIOCHEMISTRY, COLLEGE OF PHYSICIANS AND SURGEONS, COLUMBIA UNIVERSITY

Communicated by David Rittenberg, January 22, 1960

In a previous communication we have reported that there is an early phase in the bacterial action of 5-fluorouracil (FU) on *E. coli* K_{12} which produces an "osmotic imbalance" in the cells.[1]

Further study of this phenomenon revealed that FU exerts its lethal action only on growing bacteria.[2] Inhibition of growth during the time of FU treatment by metabolic inhibitors or by omission of growth factors from the media of auxotrophs prevented the development of osmotic imbalance.

When exponentially growing bacteria were treated with FU and incubated on nutrient agar plates for various times, 90–95 per cent of the cells did not give rise to colonies. However, it was possible to recover these cells by a transfer from the nutrient agar plates to sucrose-supplemented agar provided the replica plating was done *before* a critical 25 minutes of incubation on the nutrient agar. After 25 minutes of incubation, 90 per cent of the cells could no longer be recovered by this method, possibly since they had already disintegrated on the nutrient plates.

When the FU-treated bacteria were plated on a thin layer of agar, observation under a phase contrast microscope revealed a series of anomalous cytological changes which culminated in the sudden disintegration of the cells.[3]

The disintegration of FU-treated bacteria could also be demonstrated in fluid medium: after 25–30 minutes of incubation in broth, about 90 per cent of the cells abruptly disintegrated and sedimented out of the medium. The timing of these events suggests that a great part of the population must have been synchronized, possibly by the FU treatment itself (thymine starvation). The disintegration of the cells at the end of a normal generation time suggests a possible connection between the division process and the events of disintegration.

The fate of the bacteria treated with FU depends fully upon the conditions of growth during a critical period *following* the exposure to the drug. Maximum rate of growth during this time inevitably leads to cellular disintegration unless the osmotic pressure of the medium is raised before the cells reach some irreversible stage in the process of disintegration. Suppression of the metabolic rate during this critical period also "rescues" the cells from FU-induced death. This can be accomplished by keeping the nutrient plates at low temperatures for prolonged periods or by plating on minimal medium. Slow rate of metabolism apparently enables the cells to "heal" the lesion introduced by FU and thus to restore full viability. The length of the critical period during which the cells need the protection of high osmotic environment was found to be 60 minutes. There was no cell division during this time.

The prevention of cellular disintegration by high osmotic milieu suggested the involvement of some cell wall abnormality. Our recent findings that FU-treated

cells also exhibit an increased sensitivity toward heat and mechanical stress could also be interpreted as consequences of diminished rigidity of the cell wall. (FU-treated cells also show high UV sensitivity.[4])

In order to test this hypothesis we have searched for the accumulation of cell wall precursors,[5] and found a significant increase of N-acetylhexosamine esters[6] in the FU-treated cells. Table 1 summarizes the results of experiments designed to establish a possible correlation between the accumulation of N-acetylhexosamine esters and the presence of osmotic imbalance in bacteria. The data clearly establish such a correlation.

TABLE 1

Incubation medium*	Supplement added	μM-s of N-acetylhexosamine esters accumulated per 10^{12} cells	Osmotic effect‡
Complete	None	3.8	1
Complete	FU(100 μg/ml)	33.6	21
Complete	FU (5 μg/ml)†	15.0	1.5–2
No glucose	FU(100 μg/ml)	1.0	1
No glucose	None	5.3	1
Complete	FU(100 μg/ml+ uracil (100 μg/ml)	2.0	1
Complete	FU(100 μg/ml+ thymine (100 μg/ml)	28.0	18
Complete	2-thioracil (100 μg/ml)	2.5	1
E. coli, B, complete	FU(100 μg/ml)	1	1

* Bacteria at half-maximum growth in exponential growth phase in synthetic medium (Gray and Tatum[7]) were incubated with FU for 60 minutes at 37°C.

† 5 μg/ml FU is just above the threshold concentration which induces "osmotic imbalance" under the standard conditions of incubation.

‡ Osmotic effect was quantitatively expressed as the ratio of numbers of colonies recovered on sucrose supplemented plates to the number of colonies recovered on nutrient agar plates: S/N; in normal bacteria S/N = 1.

The accumulation showed linear increase with incubation time: 4μM-s at 0 minutes, 8.5 μM-s at 30 minutes and 16 μM-s at 60 minutes of incubation (expressed per 10^{12} cell.). Preliminary experiments with an amino acid auxotroph of *E. coli* K_{12} (C-600-25, Leu$^-$, Threo$^-$) showed that resting populations of these bacteria (produced by amino acid starvation) are also able to accumulate these compounds in the presence of glucose and FU.

In attempts to isolate the accumulated compounds, large batches of FU-treated bacteria were extracted and fractionated on Dowex-1-Cl columns according to the method of Strominger.[6] 90 per cent of the N-acetylhexosamine esters adsorbed were recovered in two peaks, a major and a smaller one, both eluted with 0.05 *M* NaCl–0.01 *M* HCl (Fig. 1). The peaks were located on the basis of UV absorbance and the quantitative Elson-Morgan reaction. No N-acetylhexosamine containing component came off the column with any of the successive eluents.

The two peaks were not homogeneous. Paper chromatography resolved each peak to at least 5 components all having typical nucleotide spectra in the UV. Two of the components of the major peak on strong acid hydrolysis yielded diaminopimelic acid, glutamic acid, alanine, and UV-absorbing spots but no hexosamine. Another component of the same peak on strong acid hydrolysis yielded a UV-absorbing component which had UV spectra and chromatographic mobility identical with those of an authentic sample of FU. The fourth—and largest—component of the major peak contained N-acetylhexosamine, uracil but no amino acids.

It will be of interest to determine at what site FU interferes with the assembly of the cell wall mucocomplex. It appears likely that small quantities of FU become

metabolized to some cell wall precursor and this product may inhibit the whole enzyme complex of cell wall synthesis. This may lead to the accumulation of relatively large amounts of the normal precursor(s). The restoration of cells to viability would then involve the slow removal, by some means, of this interfering compound from the synthetic pathway.

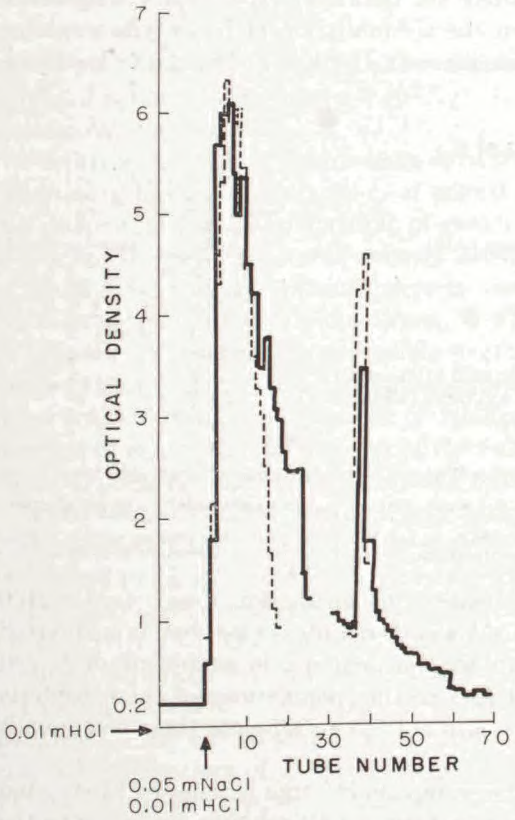


FIG. 1.—Isolation of the nucleotide linked N-acetylhexosamine esters on Dowex-1-Cl. 15 liters of bacteria at half maximum growth in synthetic medium were treated with FU(100 μg/ml) for one hour and then harvested, extracted, and fractionated on an ion-exchange column.[7] The figure only shows the part of elution diagram where the N-acetylhexosamine esters were eluted. Solid lines indicate UV absorbance at 260 mμ, dotted lines show the quantitative Elson-Morgan reaction.

These findings seem to confirm our earlier suggestion[1] that the mechanism of FU-induced "osmotic imbalance" involves a metabolic imbalance between cytoplasmic and cell wall syntheses. This condition is initiated by an early injury of the cell wall synthesizing mechanism by FU and is accompanied by relatively uninhibited cytoplasmic growth. As a result, after the removal of the FU from the medium the bacteria may resume a sort of unbalanced growth which soon leads to the disintegration of the cells.[8, 9]

* This work was supported by a grant (E-1181) from the National Institutes of Health, U. S. Public Health Service, and by a contract (AT (30–1) 2358) from the U. S. Atomic Energy Commission.

† Predoctoral Fellow of the National Institutes of Health, U. S. Public Health Service (EF-9085).

[1] Tomasz, A., and E. Borek, these PROCEEDINGS, **44**, 929 (1959).

[2] The action of FU resembles in this respect the action of penicillin and of a number of other antibiotics.

[3] Tomasz, A., and E. Borek, *Federation Proc.* (1960).

[4] (to be published).

[5] Recently, Otsuji and Takagaki have reported the accumulation of these compounds in 6-azauracil treated bacteria, *Journal of Biochem. (Japan)*, **46**, 791 (1959).

[6] Strominger, J. L., *J. Biol. Chem.*, **224**, 509 (1957).

[7] Gray, C. H., and E. L. Tatum, these PROCEEDINGS, **30**, 404 (1944).

[8] Resumption of the DNA synthesis may have a decisive role in making the unbalanced growth of the organisms irreversible.

[9] The 60 minutes' incubation time with FU—a standard condition used in our experiments—may represent the critical time up to which the above mechanism of action of the drug predominates. On prolonged incubations inhibitions of other phases of pyrimidine metabolism may become decisive.

ACTION SPECTRA OF CHROMATIC TRANSIENTS AND THE EMERSON EFFECT IN MARINE ALGAE

BY L. R. BLINKS

HOPKINS MARINE STATION OF STANFORD UNIVERSITY, PACIFIC GROVE, CALIFORNIA

Communicated January 28, 1960

Chromatic transients are the changes in oxygen evolution rate recorded on altering the color of light incident on a tissue, even though the intensities are adjusted to give equal steady rates of photosynthesis at both wavelengths. These were first observed[1] on exposing a red alga (*Porphyra*) alternately to red light (675 mμ) and green light (560 mμ). They have been reported[2] in a green alga (*Ulva*) on alternating illumination between (a) 490 and 540 mμ; and (b) 640 and 688 mμ. The location of these regions coincided fairly closely to the absorption *in vivo* of several pigments: chlorophyll *a* at 675–688 mμ; mixed chlorophylls at 540 mμ; chlorophyll *b* at 640–650 mμ; phycoerythrin at 560 mμ, and carotenoids at 490 mμ. (Alterations of wavelength within the absorption region of a single pigment produce little or no transient.)

The earlier studies were made by rapid change of setting on a monochromator, and the regions were limited by output energy and action spectra of the tissue to a few pairs of wavelengths. In order to obtain a more accurate delineation of the entire action spectrum for the transients, two sources of light have now been employed, one a fixed or reference wavelength, derived from a separate lamp with interference filter, the other the high-energy monochromator previously described.[3] The images of the two lamp filaments were focused carefully upon the tissue, usually an algal thallus one cell (or a few cells) thick, tightly held against a bright platinum electrode by means of a cellophane strip.[3] *Anabaena*, a blue green alga, was studied by lifting mats of filaments which had grown out very uniformly at the surface of sea water, and spreading them as smoothly as possible over the electrode.

Oxygen arriving at the electrode was reduced to H_2O_2 at an applied potential of 0.5 volt, the current being recorded by a Speedomax potentiometer connected across a fixed resistance (usually 1,000 ohms) in the circuit. Flowing or recirculated sea water, usually equilibrated against 5 per cent CO_2 in air, quickly established a base line which remained very steady in the dark, frequently at around

2 or 3 μamp, due to the passage of O_2 across the tissue. It was increased in the light to as much as 8 or 10 μamp, due to the arrival of photosynthetically produced O_2 at the electrode, the level being dependent upon light intensity. This is therefore read as a *rate* of photosynthesis and, by means of the electrochemical equivalent of H^+ ions oxidized, can be made an absolute measure of O_2 diffusing to the electrode. Furthermore, due to the short diffusion distance (a few microns only, the thickness of the cell wall), the new equilibrium value is quickly established, in a matter of one or 2 minutes (Fig. 1). This makes it possible to follow transients fairly sensitively.

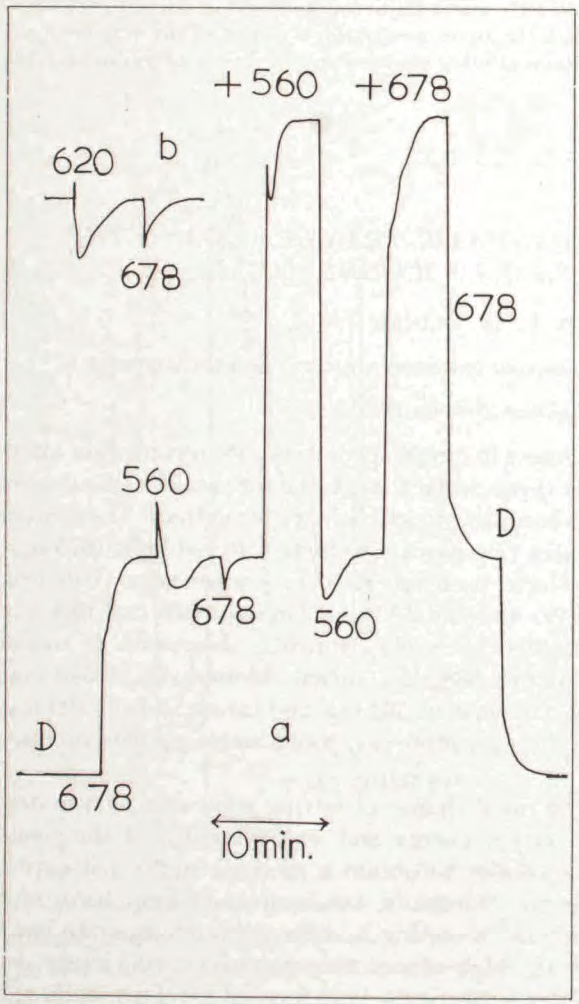


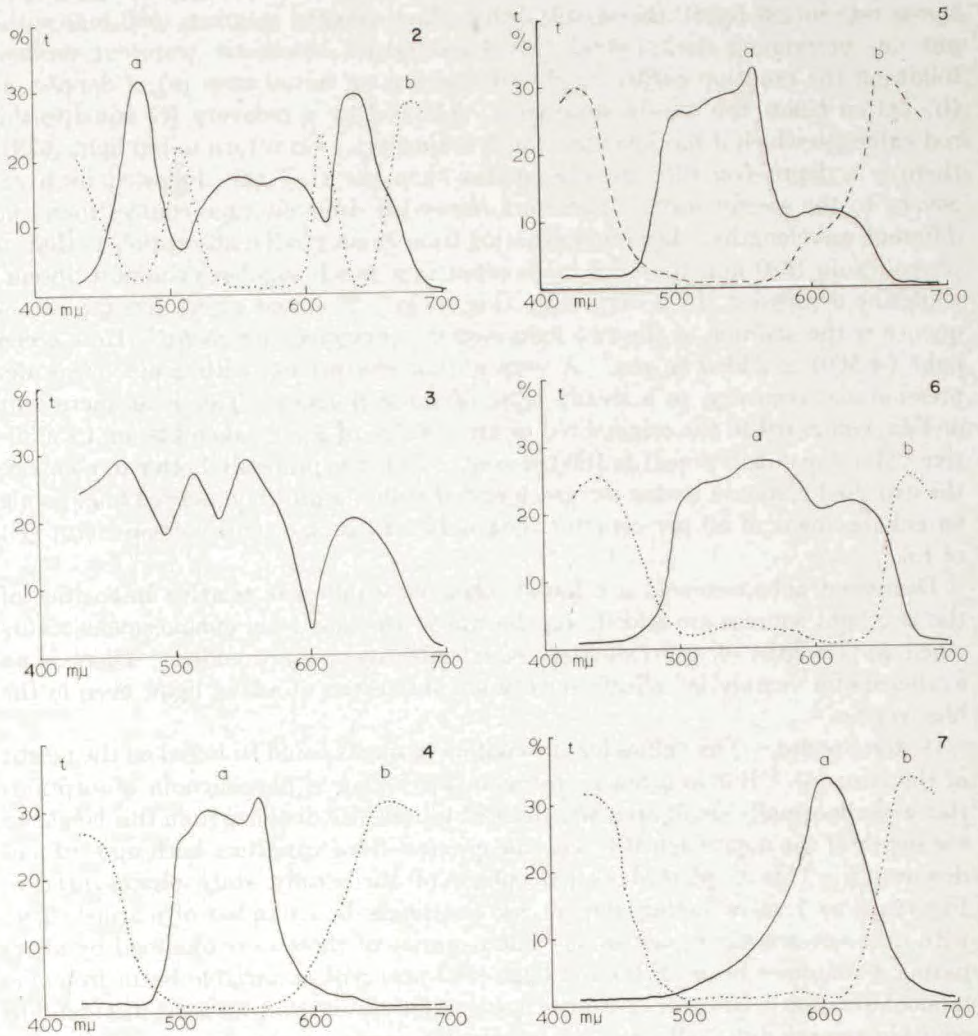
FIG. 1*a*.—Chromatic transients and the Emerson enhancement due to alternation and addition of red (678 mμ) and green light (560 mμ), in the red alga *Porphyra Nereocystis*. *b*.—Chromatic transients on alternation of 678 and 620 mμ. Explanation in text.

One precaution in recording chromatic transients is that the tissue (or the light beam) be very carefully restricted to the surface of the electrode. If the tissue projects beyond its edges, there may be a slow diffusion of O_2 from the sides to the electrode (despite good flow of sea water) which gives spurious transients if the beams of light do not exactly coincide. Careful adjustment of the beams and tissue to the electrode size or, in some cases, masking with black paper or black cellophane obviated this "edge effect" (which may be readily tested by alternating an identical wavelength from the two sources).

Another source of spurious chromatic transients is poor synchronization of the light shutters. While electrical switching partially obviated this trouble, it was found best to utilize a sliding shutter which very accurately interrupted one beam as it exposed the other. A check with photocells is desirable.

Emerson Effect.—This phenomenon, discovered by the late Robert Emerson,[4, 5] signifies the more than additive effect of two superposed wavelengths; thus the far red (700 mμ), which is usually inefficient in the photosynthesis of green plants,

becomes much more effective when shorter wavelengths are given simultaneously. This is ascribed to the low activity of chlorophyll *a*, which is markedly enhanced when light absorption by chlorophyll *b* or *c*, phycocyanin, phycoerythrin, fucoxanthin, or other carotenoids occurs simultaneously. Since two alternating light



Action spectra of chromatic transients (t):
FIG. 2.—*Enteromorpha tubulosa:* reference beam (*a*) 702 mμ; (*b*) 647 mμ. FIG. 3.—*Punctaria occidentalis;* reference beam 702 mμ. FIG. 4.—*Porphyra Thuretii;* reference beam (*a*) 702 mμ; (*b*) 566 mμ. FIG. 5.—*P. Nereocystis;* (same). FIG. 6.—*P. perforata;* reference beam (*a*) 702 mμ; (*b*) 614 mμ. FIG. 7.—*Anabaena* sp.; (same).

sources were found desirable to trace the transient action spectra, it was a simple matter to *combine* two wavelengths (ordinarily adjusted to give equal photosynthesis separately) and observe the enhancement. (Had such a double source been employed earlier, the enhancement would no doubt have been observed some time ago.)

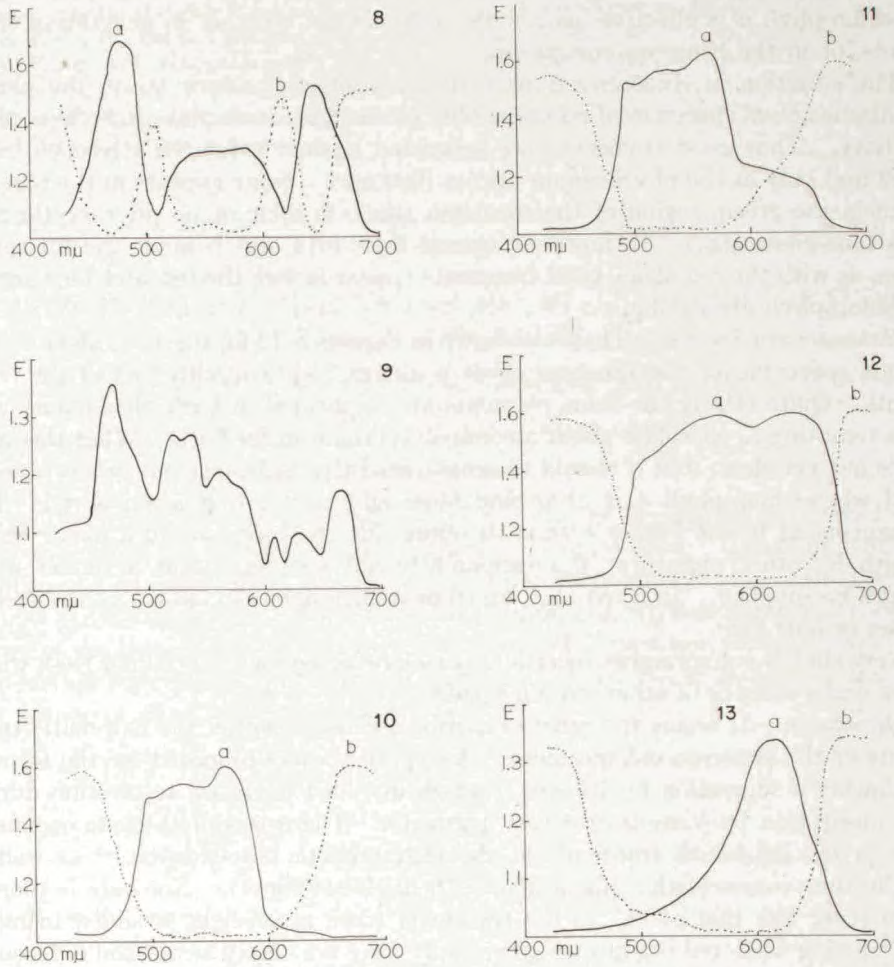
Recording.—Figure 1 shows a characteristic sequence of exposures in a red alga (*Porphyra Nereocystis*). The initial level of current (2 μamp) is due to oxygen arriving at the electrode across the tissue in the dark (D). Red light (678 mμ) near the absorption peak of chlorophyll *a* is then given; the polarographic current is increased to about twice the dark value. This represents the steady photosynthetic rate in red light; the wavelength is then changed to green (560 mμ) without an intervening dark period. A characteristic chromatic transient ensues; following the notation earlier employed[2] there is an initial cusp (a), a depression (b)—often below the steady state level—followed by a recovery (c) equal to the red value (to which it has been previously adjusted). On return to red light (678), there is a depression (d)—usually smaller than the cusp (a)—followed by a recovery to the steady state. There are somewhat different time courses found at different wavelengths; thus on alternating from chlorophyll *a* absorption to that of phycocyanin (620 mμ) the cusp (a) is often very much smaller, or almost absent, while the depression (b) is very large (Fig. 1, *b*). The next event in a typical sequence is the *addition* of the two light sources, previously *alternated*. Here green light (+560) is added to red. A very abrupt rise occurs, with a new cusp, depression and recovery, to a steady state of about 6 μamp. This is an increment of 4 μa, compared to the original red or green value of 2 μa; taken just on its additive value the enhancement is 100 per cent. But it is probably better to compare the expected response (twice the green or red value) with the observed one, giving an enhancement of 50 per cent for the combined lights, or an Emerson factor (E) of 1.5.

Decreased enhancements are found when very different relative intensities of the two light sources are added; on the whole, the best total enhancement occurs when wavelengths of approximately equal effectiveness are added. There is no evidence of a "catalytic" effect[6] at very low intensities of added light, even in the blue region.

Action Spectra.—The values for chromatic transients could be based on the height of the cusp (a). But in a few cases (as in the region of phycocyanin absorption) this was abnormally small, so it was decided to take the distance from this height to the depth of the depression (b); i.e., the greatest total variation, both upward and downward. This is plotted as percentage of the steady state photosynthesis. Figures 2 to 7 show action spectra for transients in a number of marine algae, with different accessory pigments. The majority of these were obtained by alternating a reference beam of far red light (702 mμ) with a variable beam from the monochromator. In these cases, the maxima for chromatic transients are found to coincide remarkably well with the absorption peaks of the accessory pigments. Thus in the green alga (*Enteromorpha*) the highest activity was found at 640–650 mμ (chlorophyll *b* absorption) and 480–490 mμ (carotenoid absorption). (The latter could conceivably be due partly to chlorophyll *b*, and the somewhat lower activity in the middle of the spectrum must also represent predominant absorption by chlorophyll *b*.) The peaks for the brown alga (*Punctaria*) must represent chlorophyll *c* (630 and 580 mμ), fucoxanthin (520–540 mμ), and other carotenoids (480 region); again, chlorophyll *c* might be contributing to the latter maximum.

The red algae, having no chlorophyll *b* or *c* (chlorophyll *d* seems to be nearly absent from most red algae as well), show little or no activity in the regions charac-

terizing such pigments; but they do display transients in the region 620–650 mμ depending upon the phycocyanin (and allophycocyanin) content. *Porphyra Thuretii* has the least of these pigments (it is a deep red color), and shows little or no transient activity until the phycoerythrin region is approached (wavelengths less than 600 mμ, with maximum at 560 mμ). *P. Nereocytsis* (a more purple species) has a shoulder indicating some phycocyanin activity (620 mμ), though



Action spectra for enhancement (Emerson effect, E):
FIG. 8.—*Enteromorpha.* FIG. 9.—*Punctaria.* FIG. 10.—*Porphyra Thuretii.*
FIG. 11.—*P. Nereocystis.* FIG. 12.—*P. perforata.* FIG. 13.—*Anabaena.*
(Wavelengths as in FIGS. 2–7 for the corresponding algae.)

again the major activity is at 560 mμ. Only in *P. perforata* (of a slate gray color) does the transient activity become very large in the phycocyanin region; here it extends well toward 650 mμ, corresponding to the high content of allophycocyanin in this species. It should be noted that the transient activity is very slight in the blue end of the spectrum (400–500 mμ) for all these species; quite clearly, the carotenoids are unable to generate transients against the far red (nor, obviously,

can chlorophyll *a* in this region of its absorption). However, as Figure 4 indicates, the blue end of the spectrum is perfectly capable of generating good transients when alternated with green (or orange) light absorbed by the *phycobilins*. This is clearly shown in several of the figures, where a reference beam of 566 or 614 mμ was employed. Against such a reference beam good activity is shown in *both* ends of the spectrum (the intensity of blue light has to be very high, due to its low photosynthetic efficiency in red algae).[3] It must be stressed that *either* absorption region of chlorophyll *a* is effective against the phycobilins, whether in generating transients, or in the Emerson enhancement.

The situation in *Anabaena* is particularly interesting, since (as in the photosynthetic action spectrum of a marine blue green alga[3]) it displays low chlorophyll activity. Thus good transients are generated against a far red reference beam (702 mμ) only at the phycocyanin maxim (620 mμ). None appears in the blue, or even in the green, region of the spectrum (there is little or no phycoerythrin in this blue-green alga). If, however, orange light (614 mμ) is made the reference then, as with the red algae, good transients appear in *both* the red and blue region of chlorophyll absorption.

Enhancement Spectra.—These are shown in Figures 7–12 for the same algae. The action spectrum for the Emerson effect is almost identical with that of the transients. Quite clearly the same pigments are implicated in both phenomena, and it is tempting to speculate about a common mechanism for both. What this may be is not yet clear; but it should be emphasized that enhancement occurs equally well when chlorophyll *a* is absorbing blue light as when it absorbs red. The enhancement in the former case is therefore due to absorption of a *longer* wavelength by other pigments; it is apparently not necessary that a *shorter* wave length be supplied. In a red alga, green or orange light can enhance the effect of violet or blue light.

Very similar enhancement spectra are being reported for a unicellular fresh water alga[7] and a number of other marine algae.[8]

Discussion.—It seems too early to ascribe a cause to either the chromatic transients or the Emerson enhancement. A hypothesis was proposed for the former[2] (following a suggestion by Emerson) which involved increased respiration during the absorption by various accessory pigments. There is something to commend this in the light-dark transients at the characteristic wavelengths,[1, 2] as well as in the time course of the enhancements themselves (Fig. 1). Not only is there a cusp (very like that of "a" in the transient) when green light is added to red—and missing when red is added to green; but there are nearly as marked differences when the supplementary light is removed. On turning off the red light (leaving only green), there is a marked depression (enhanced respiration?), while this is not observed when green is turned off (leaving only red). Experiments at higher and lower temperature, and with a variety of respiratory and photosynthetic inhibitors, are under way to clarify these effects.

Summary.—Action spectra are presented for chromatic transients and the Emerson effect ("enhancement") in the photosynthesis of a number of marine algae. When far red light (700 mμ) is altered or supplemented with other wavelengths, the greatest effects occur at the absorption maxima of the accessory pigments: chlorophyll *b* and carotenoids in green algae; chlorophyll *c* and fucoxan-

thin in brown algae; phycobilins in red and blue-green algae. Both effects also occur equally well when the chlorophyll *a* is absorbing in the blue end of the spectrum (435 mμ).

[1] Blinks, L. R., "Chromatic Transients in the Photosynthesis of Red Algae," in *Research in Photosynthesis* (New York: Interscience Publishers, Inc., 1957).
[2] Blinks, L. R., *Plant Physiol.*, **34**, 200 (1959).
[3] Haxo F., and L. R. Blinks, *J. Gen. Physiol.*, **33**, 389 (1950).
[4] Emerson, R., R. Chalmers, and C. Cederstrand, these PROCEEDINGS, **43**, 133 (1957).
[5] Emerson, R., and R. Chalmers, *Phycological Soc. of America News Bulletin*, **11**, 51 (1958).
[6] Warburg, O., S. Krippahl, and W. Schroeder, *Z. Naturforsch.*, **10B**, 631 (1955).
[7] Meyers, J., and C. S. French, *J. Gen. Physiol.*, **43**, (in press) 1960.
[8] Haxo, F. T., in *Comparative Biochemistry of Photoreactive Pigments*, ed. M. B. Allen (New York: Academic Press, in press).

SIGNIFICANT STRUCTURES IN LIQUIDS, III. PARTITION FUNCTION FOR FUSED SALTS

BY CHARLES M. CARLSON, HENRY EYRING, AND TAIKYUE REE

DEPARTMENT OF CHEMISTRY, UNIVERSITY OF UTAH

Communicated January 19, 1960

Very little has been done in the past in the way of developing partition functions to predict the thermodynamic properties of fused salts. Using the work of Walter and Eyring,[1] Wheeler[2] formulated a partition function for molten alkali halides and he, as well as Parlin and Eyring (unpublished), calculated successfully many of the thermodynamic properties of salts. The partition function used here is a further step in the application of significant structures as developed earlier.[3] For a mole of alkali halide molecules it is

$$f = \left\{ \frac{e^{\frac{E_s}{2RT}} \left(\frac{V}{V_s}\right)^{1/3}}{(1 - e^{-\theta/T})^3} \left[1 + n_h \cdot e^{\frac{-aE_s(V/V_s)^{1/3}}{2n_h RT}} \right] \right\}^{\frac{2V_s}{V} N} \times$$

$$\left\{ \frac{(2\pi mkT)^{3/2} eV}{Nh^3} \frac{8\pi^2 IkT}{h^2} \frac{1}{(1 - e^{-h\nu/kT})} \right\}^{\left(1 - \frac{V_s}{V}\right) N} \quad (1)$$

$$n_h = n\left(\frac{V}{V_s} - 1\right) \quad (2)$$

The various parameters are explained as follows: E_s is the potential energy of the solid at the melting point; θ is the Einstein temperature of the solid; V_s is the volume of the solid per mole at the melting point; V is the molar volume of the liquid; n and a are parameters to be fitted to the experimental liquid data; m, I, and ν are the mass, the moment of inertia, and the ground state vibrational frequency, respectively, of the gaseous diatomic alkali halide molecule; T is the absolute temperature, R the gas constant, N Avogadro's number, k is Boltzmann's constant, and h is Planck's constant.

The two significant structures described by the partition function are solid-like and gaslike. In the solid-like structure as far as the partition function is concerned, the alkali metal ions are assumed to be equivalent to the halide ions. In other words, the alkali metal and halide ions are considered to be vibrating with a common Einstein frequency. The solid-like portion of the partition function is raised to the power $2(V_s/V)\ N$ because a mole of alkali halide crystal contains $2N$ particles when all of the ions are assumed to be equivalent. Also E_s/N is the potential energy per alkali halide molecule. Since the desired potential energy is the potential energy per ion, E_s must be divided by 2. The gaslike significant structure is composed of diatomic alkali halide molecules whose moments of inertia and ground state vibrational frequencies are assumed to be the same as for the vapor phase. To account for the long range nature of the coulombic interionic potential, the potential energy for the solid E_s has been multiplied by the factor $(V/V_s)^{1/3}$.

Calculations of melting point and boiling point data and critical constants have been carried out for four alkali halides, NaCl, KCl, NaBr, and KBr. The method of calculation was the same as that of Eyring, Ree, and Hirai.[3]

The parameters E_s and θ for the solid can be determined by various techniques. The value of θ may be calculated from the equation $\theta = 3\theta_D/4$ where θ_D is the

TABLE 1

	NaCl	KCl	NaBr	KBr
V_s, cc	30.19[4, *]	41.57 cc[4]	36.02 cc[4]	48.06 cc[4]
E_s, kcal/mole	56.07[5]	54.15[5]	51.91[6]	51.53[6]
θ, °K	215[7]	170[7]	145[6]	118[6]
I(gm cm^2)	1.291×10^{-38}[8]	2.195×10^{-38}[8]	1.856×10^{-38}[8]	3.468×10^{-38}[8]
$\omega = \nu/c$, cm^{-1}	380[9]	305[9]	302[10]	231[9]
n	9	6	7	5.5
a	0.1000	0.03000	0.05300	0.02300

* The reference numbers for experimental quantities are listed in the table.

Debye characteristic temperature determined experimentally at low temperatures. With θ known a value for E_s is chosen in the solid partition function to give an observed property of the solid at the melting point such as the vapor pressure or the energy of sublimation. Alternatively since the Debye temperature of a solid is usually lower at the melting point than for low temperatures, two independent experimentally determined parameters of the solid at the melting point can be used to find both E_s and θ.

For NaCl and KCl θ and E_s were determined by the first method. That is, three fourths of the experimentally determined θ_D was used for θ, and then the vapor pressure of the solid at the melting point was used along with the already determined θ to find E_s. For NaBr and KBr θ and E_s were determined by using the experimentally determined energy of sublimation and the vapor pressure at the melting point. The results obtained by the two methods will in general be slightly different but lead to about equally good values for the liquid properties. This is true since the parameters n and a in the liquid partition function can be varied to offset small deviations in the values of E_s and θ.

The values used for the various parameters are given in Table 1.

All of the properties calculated for the salts are listed in Tables 2, 3, and 4. As one can observe, the melting temperature was predicted for NaCl and KCl, while

for NaBr and KBr the melting temperature was fitted exactly by adjusting the parameters n and a.

In Table 2, T_m, V_m, and ΔS_f are the melting temperature, volume of the liquid, and the entropy of fusion, respectively. In Tables 3 and 4 these same properties carry the subscripts B and c to indicate the boiling point and the critical point respectively. References to experimental quantities are again listed by the particular value. The critical constants are, of course, not known experimentally.

Thus, the agreement with the observed data for all of the salts investigated is reasonably good, and the order of magnitude of n is what might be expected from previous work. There are one or two points which need to be discussed, however. First, as can be seen from recent publications,[4, 11] the experimental value of V_s is uncertain. Moreover, a recent publication[12] indicates that the vapors of the alkali halides are strongly associated to four atom and even six atom complexes. In the present treatment only diatomic molecules were assumed to constitute the

TABLE 2

MELTING-POINT PROPERTIES OF THE ALKALI HALIDES

		NaCl	KCl	NaBr	KBr
T_m, °K	Calc	1,070	1,023	(1,023)	(1,008)
	Obs	1,074[6]	1,049[6]	1,023[6]	1,008[6]
V_m, cc	Calc	38.14	49.06	43.84	56.13
	Obs	37.74[4]	48.80[4]	44.08[4]	56.03[4]
ΔS_f, eu	Calc	7.75	5.40	6.16	4.83
	Obs	6.3[6]	5.8[6]	5.96[6]	6.94[6]

TABLE 3

BOILING-POINT PROPERTIES OF THE ALKALI HALIDES

		NaCl	KCl	NaBr	KBr
T_B, °K	Calc	1,750	1,684	1,671	1661
	Obs	1,738[6]	1,680[6]	1,665[5]	1653[6]
V_B, cc	Calc	51.15	71.20	60.15	81.81
	Obs	Unreported	Unreported	Unreported	Unreported
ΔS_v, eu	Calc	21.55	21.63	21.02	20.89
	Obs	23.5[6]	23.1[6]	23.2[6]	22.4[6]

TABLE 4

CRITICAL CONSTANTS OF THE ALKALI HALIDES

	NaCl	KCl	NaBr	KBr
T_c, °K	3,600	3,092	3,364	3,060
V_c, cc	293	431	342	482
P_c, atm	235.5	135.5	186.1	118.3

gaslike significant structure. Taking account of polymers of the salt molecules in the gaseous part of the partition function requires no new parameters but should improve the partition function.

Recent literature also has given new experimental values for the ground state vibrational frequencies of the diatomic alkali halides.[10] In this case, however, it has been verified that the new values affect the calculated results but slightly. In conclusion it can be said that although some significant structures have been neglected and uncertainties in the values of some experimental parameters exist, nevertheless the results prove that the general method of approach can be very fruitful and readily applied to calculate the thermodynamic properties of salts.

Very recently, Blomgren[13] applied the significant structure theory of liquids to molten KCl in a slightly different manner from our approach. But he obtained

reasonable agreement with experiment for the molar volume. An extensive review was made for fused salts by Blomgren and Van Artsdalen.[14]

The authors wish to thank the National Science Foundation and the Office of Ordnance Research, United States Army for support of this work.

[1] Walter, J., and H. Eyring, *J. Chem. Phys.*, **9**, 393 (1941).

[2] Wheeler, I. B., Jr., B.A. Thesis, Princeton Univ., Department of Chemistry (1942).

[3] Eyring, H., T. Ree, and N. Hirai, these PROCEEDINGS, **44**, 683 (1958); Fuller, E. J., T. Ree, and H. Eyring, *ibid.*, **45**, 1594 (1959).

[4] Vogel, E., H. Schinke, and F. Sauerwald, *Z. anorg. u. allgem. Chem.*, **284**, 131 (1956).

[5] Zimm, B. H., and J. E. Mayer, *J. Chem. Phys.*, **12**, 362 (1944).

[6] *American Institute of Physics Handbook* (New York: McGraw-Hill Book Company, Inc., 1957), Table 4j-1.

[7] Clusius, Von Klaus, J. Goldmann, and A. Perlick, *Z. Naturforsch.*, **4a**, 424 (1949).

[8] Honig, A., M. Mandel, M. L. Stitch, and C. H. Townes, *Phys. Rev.*, **96**, 629 (1954).

[9] Herzberg, G., *Molecular Spectra and Molecular Structure, I. Diatomic Molecules* (Englewood, N. J.: Prentice-Hall, Inc., 1939), Table 36.

[10] Rice, S. A., and W. Klemperer, *J. Chem. Phys.*, **27**, 573 (1957).

[11] Landon, C. J., and A. R. Ubbelohde, *Trans. Far. Soc.*, **52**, 647 (1956).

[12] Miller, R. C., and P. Kusch, *J. Chem. Phys.*, **25**, 860 (1956).

[13] Blomgren, G. E., *Ann. N. Y. Acad. Sci.*, in press.

[14] Blomgren, G. E., and E. R. Van Artsdalen, *Annual Review of Physical Chemistry*, Volume 10, (Stanford, Calif.: Annual Review Inc., 1959).

---

*SIGNIFICANT STRUCTURES IN LIQUIDS, IV. LIQUID CHLORINE**

BY TOM R. THOMSON,† HENRY EYRING, AND TAIKYUE REE

DEPARTMENT OF CHEMISTRY, UNIVERSITY OF UTAH

Communicated January 29, 1960

Earlier investigators[1, 2] attained considerable success in fitting the liquid state through the use of the "holes-in-solid" model. Extending this theory, Eyring and co-workers[3, 4] have recently proposed the theory of significant structures in liquids and have thus obtained a relatively simple and accurate partition function for normal liquids such as neon, argon, krypton, xenon, benzene, methane and nitrogen, and also for fused salts and molten metals.

According to the significant structure theory, a liquid molecule possesses both solid-like and gaslike degrees of freedom. The relative contribution of the two types is given by V_s/V and $(V - V_s)/V$, respectively, where V_s is the molar volume of the solid at the melting point and V is the molar volume of the liquid at various temperatures. Thus, the partition function for the liquid is given by

$$f_L = (f_s)^{NV_s/V}(f_g)^{N(V-V_s)/V} \tag{1}$$

where f_s and f_g are the partition functions for the solid-like and gaslike parts.

The halogens seemed a particularly interesting group of elements on which to apply the theory, and chlorine was chosen to be the first of the halogen group because of its general interest and the availability of ample data against which calculated values might be checked.

Partition Function for Liquid Chlorine.—In writing the various terms of the respective partition functions of the solid-like and gaslike parts, certain assumptions had to be made concerning the degrees of freedom of the chlorine molecule in these two states. The unusually high entropy of fusion reported by Giauque and Powell[5] and the absence of transition peaks in the heat capacity curve for solid chlorine given by the latter indicates that the chlorine molecule probably does not rotate freely in the solid state. Also the density data on liquid chlorine[6, 7] suggests that rotation is inhibited in the liquid state. This question is discussed further below.

Rather than complicate the partition function by considering libration-type degrees of freedom, the solid-like part was treated as a five-degree Einstein oscillator, with the internal vibration being the sixth degree of freedom. Free rotation was assumed in the gaslike part of the partition function.

The resulting partition function for the liquid, then, assumed the following form:

$$f_L = \left\{ \frac{e^{E_s/RT}}{(1 - e^{-\theta/T})^5} \frac{1}{1 - e^{-h\nu/kT}} (1 + n_h e^{-a'/n_h RT}) \right\}^{NV_s/V} \left\{ \frac{(2\pi mkT)^{3/2}}{h^3} \frac{8\ \pi^2 IkT}{2h^2} \frac{1}{1 - e^{-h\nu/kT}} \frac{eV}{N} \right\}^{N(V-V_s)/V} \tag{2}$$

Equation (2) contains two parameters which have the following connotations. n_h represents the number of "holes" or equilibrium sites accessible to a molecule in addition to its single most stable position. This could also be considered to be the moles of holes per mole of normal sites. The latter description can be equated to the total volume available for holes divided by the volume per mole of holes, or

$$n_h = \frac{(V - V_s)}{(V_s/n)} \equiv n(x - 1) \tag{3}$$

where n is the number of holes whose combined volumes equal the volume of one molecule, or $(1/n)$ is the fraction of the volume of a single molecule required per new equilibrium site. The term x is a reduced volume used to express the ratio (V/V_s).

The second parameter a' represents the energy put into the system by expansion, and is related to the heat of sublimation E_s by the expression

$$a' = a''E_s \tag{4}$$

The strain energy, or energy contributed per hole, E_h, then, is $a''E_s/n_h$. Substituting the value for n_h from equation (3), we then obtain,

$$E_h = \frac{a''E_s}{n(x - 1)} = aE_s/(x - 1) \tag{5}$$

The degeneracy term, then, becomes

$$1 + n(x - 1)\ e^{-aE_s/RT(x-1)}$$

and the partition function takes its final form, which now includes the two new parameters n and a:

$$f_L = \left\{ \frac{e^{E_s/RT}}{(1 - e^{-\theta/T})^5} \frac{1}{1 - e^{-h\nu/kT}} [1 + n(x - 1)e^{-aE_s/RT(x-1)}] \right\}^{N/x}$$
$$\left\{ \frac{(2\pi mkT)^{3/2}}{h^3} \frac{8\pi^2 IkT}{2h^2} \frac{1}{1 - e^{-h\nu/kt}} \frac{eV_s}{N} x \right\}^{N(1-1/x)} \quad (6)$$

The Helmholtz free energy A is perhaps the most useful function related to the partition function, as it is readily converted into the other thermodynamic functions. Since it involves the logarithm of the partition function, it was found convenient to adopt the following abbreviations for component terms:

$$A = -\frac{RT}{x}(\sigma_1 + \sigma_2) + RT\left(1 - \frac{1}{x}\right)(\gamma + \ln x) \quad (7)$$

where,
$$\sigma_1 \equiv \frac{E_s}{RT} - 5\ln(1 - e^{-\theta/T}) - \ln(1 - e^{-h\nu/kT}) \quad (8a)$$

$$\sigma_2 \equiv \ln\left\{1 + n(x - 1)\exp\left[\frac{-aE_s}{RT(x - 1)}\right]\right\} \quad (8b)$$

$$\gamma \equiv \ln\left[\frac{(2\pi mkT)^{3/2}}{h^3} \frac{8\pi^2 IkT}{2h^2} \frac{1}{1 - e^{-h\nu/kT}} \frac{eV_s}{N}\right] \quad (8c)$$

It will be noted that σ_1 and γ are free of any x terms, and hence can be treated as constants, if T is kept constant.

The observed $x_m = 1.198$ ($V_s = 34.341$, $V = 41.145$) at the melting point (171.4°K) is abnormally high, since most solids increase about 10 per cent upon melting. This value of x_m, however, is probably correct, although a small uncertainty exists due to the fact that density data for both phases had to be extrapolated to the melting point. The anomality for chlorine is probably due to some transition in the solid beginning at a temperature near the melting point. Thus, we had to choose a molar volume for the solid state larger than that observed and more of the order of what it might be for the complete transition mentioned above. By a trial-and-error method, we obtained $x_m = 1.05$.

Equation (6) was solved for σ_1 and σ_2 for $x_m = 1.05$ ($V_s = 39.1757$ cc/mole), according to the method developed by Fuller[8] in fitting benzene. This yielded a value of 14.3 for n, a θ-value of 41.48°K, an E_s value of $-6{,}075.9$ cal/mole and an a-value equal to 0.0012977.

Results.—(*a*) *Properties at the boiling and the critical points:* The equation was tested at the boiling point (67 degrees above the melting point) and yielded the following results, listed and compared with observed values in Table 1:

TABLE 1

BOILING-POINT DATA FOR CHLORINE

	Calc.	Obs.	Error, %
Liquid volume, cc/mole	44.856	45.321	−1.03
Vapor pressure, atm.	0.9984	1.0000	−0.161
Temperature, °K	(239.05)	239.05	...
Entropy of Vaporiz'n, e.u.	20.46	20.40	0.27

Critical point properties were calculated by setting the first and second derivatives of P with respect to V equal to zero, P being equal to $-(\partial A/\partial V)_T$. The

results are shown in Table 2. The relatively larger error compared to similar calculations previously reported for the inert gases[3, 4] is somewhat to be expected considering the longer liquid range (245 degrees) of chlorine. The error is large enough, however, to conclude that the theory still needs some modification to take care of the critical point.

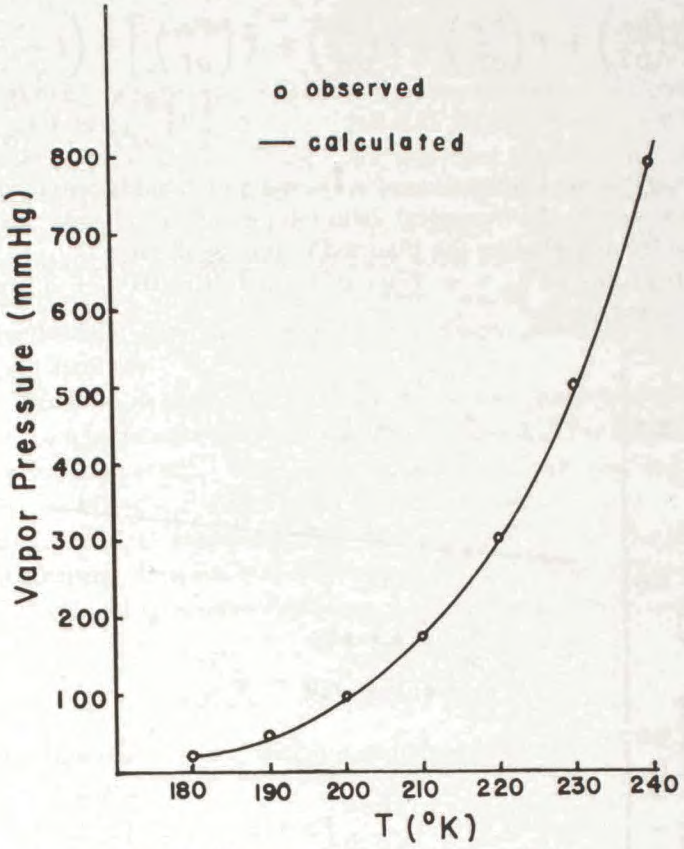


FIG. 1.—Vapor pressure versus temperature.

(b) *Vapor pressures and molar volumes:* A further check on the accuracy of the function was made for temperatures between the melting and boiling points of chlorine. Figure 1 shows a comparison of calculated and observed values for the vapor pressure over the liquid range indicated. The observed data is from the

TABLE 2

CRITICAL POINT PROPERTIES FOR CHLORINE

	Calc.	Obs.	Error, %
Critical temperature, °K	463.5	417.16	11.1
Critical volume, cc/mole	131.2	123.8	5.98
Critical pressure, atm.	104.74	76.1	37.7

work of Giauque and Powell.[5] In Figure 2 calculated molar volumes are compared with those observed by Johnson and McIntosh[7] over the range from the melting point to the boiling point.

(c) *Heat capacity:* The heat capacity of liquid chlorine was calculated by differentiating the expansion for the liquid entropy, equation (9), with respect to temperature at constant volume, and multiplying the derivative by T, i.e.,

$$S = \frac{R}{x}\left[\sigma_1 + T\left(\frac{\partial\sigma_1}{\partial T}\right)_x + \sigma_2 + T\left(\frac{\partial\sigma_2}{\partial T}\right)_x\right] + R\left(1-\frac{1}{x}\right)\left[\gamma + T\left(\frac{\partial\gamma}{\partial T}\right)_x + \ln x\right] \quad (9)$$

$$C_V = \frac{RT}{x}\left[2\left(\frac{\partial\sigma_1}{\partial T}\right)_x + T\left(\frac{\partial^2\sigma_1}{\partial T^2}\right)_x + 2\left(\frac{\partial\sigma_2}{\partial T}\right)_x + T\left(\frac{\partial^2\sigma_2}{\partial T}\right)_x\right] + \left(1-\frac{1}{x}\right)\left[2\left(\frac{\partial\gamma}{\partial T}\right)_x + T\left(\frac{\partial^2\gamma}{\partial T^2}\right)_x\right] \quad (10)$$

Here the first and second derivatives of σ_1, σ_2 and γ are readily obtained from equation (8); consequently the numerical values are easily calculated. Especially the values for the terms including the Planck-Einstein oscillators in $\sigma_1 + T(\partial\sigma_1/\partial T)_x$, $2(\partial\sigma_1/\partial T)_x + T(\partial^2\sigma_1/\partial T^2)_x$, $\gamma + T(\partial\gamma/\partial T)_x$, and $2(\partial\gamma/\partial T)_x + T(\partial^2\gamma/\partial T^2)_x$ are facilitated by using tables.[9]

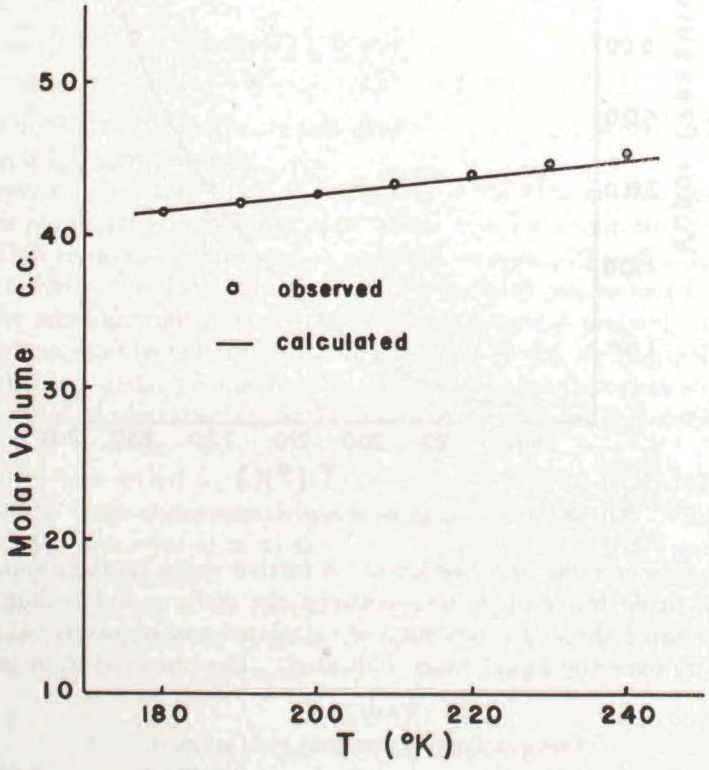


FIG. 2.—Molar volume versus temperature.

Since the partition function yields C_V rather than C_p, it was converted to the latter through the use of equation (11):

$$C_p - C_V = \frac{TV\alpha^2}{\beta} \quad (11)$$

Here α is the coefficient of thermal expansion for liquid chlorine, and β is its compressibility. These two coefficients are as follows:

$$\alpha = \frac{1}{V}\left(\frac{\partial V}{\partial T}\right)_p \tag{12}$$

$$\beta = -\frac{1}{V}\left(\frac{\partial V}{\partial P}\right)_T \tag{13}$$

The literature is quite lacking in data for these coefficients. Richards and Stull[10] reported a value of 118×10^{-6} atm.$^{-1}$ for β at 20°C and over a pressure range from 9.9 to 98.7 atmospheres. Their work indicates that β decreases with pressure. Generally speaking, it also increases with temperature, although this is more directly due to the effect of temperature on density. The reported figures could hardly be extrapolated to conditions existing below the boiling point without considerable uncertainty. This is true, to a lesser extent, for the coefficient of expansion, which would have to be derived by differentiating empirical equations given for liquid densities.

Since the difference in the heat capacities at constant pressure and constant volume amounts to a large correction (about 35%), it was decided to calculate it from the partition function itself. This would constitute an extreme test of the function, since the errors in C_V, α, and β would be compounded.

The values for β were obtained by calculating $(\partial P/\partial V)_T$ from the partition function and substituting its reciprocal into equation (13). The coefficient of expansion, α, was calculated by a more circuitous route involving the following equation:

$$\left(\frac{\partial V}{\partial T}\right)_P = -\left(\frac{\partial P}{\partial T}\right)_V \Big/ \left(\frac{\partial P}{\partial V}\right)_T \tag{14}$$

The necessary equations for calculating α and β are given below:

$$P = \frac{RT}{V_s x^2}\left[-\sigma_1 - \sigma_2 + x\left(\frac{\partial \sigma_2}{\partial x}\right)_T + \gamma + (x-1) + \ln x\right] \tag{15}$$

$$\left(\frac{\partial P}{\partial T}\right)_V = \frac{R}{V_s x^2}\left\{-\left[\sigma_1 + T\left(\frac{\partial \sigma_1}{\partial T}\right)_x\right] - \left[\sigma_2 + T\left(\frac{\partial \sigma_2}{\partial T}\right)_x\right] + x\left(\frac{\partial \sigma_2}{\partial x}\right)_T + xT\left[\frac{\partial}{\partial T}\left(\frac{\partial \sigma_2}{\partial x}\right)_T\right]_x + \gamma + T\left(\frac{\partial \gamma}{\partial T}\right)_x + (x-1) + \ln x\right\} \tag{16}$$

$$\left(\frac{\partial P}{\partial V}\right)_T = \frac{RT}{V_s^2 x^3}\left[x^2\left(\frac{\partial^2 \sigma_2}{\partial x^2}\right)_T - 2x\left(\frac{\partial \sigma_2}{\partial x}\right)_T + 2\sigma_2 - x + 3 - 2(\gamma + \ln x - \sigma_1)\right] \tag{17}$$

The C_p data thus obtained is entirely theoretical and calculated from the partition function. Table 3 gives the results of this calculation and compares C_p with the observed values from Giauque and Powell.[5]

TABLE 3

CALCULATED VALUES FOR α, β, C_V, AND C_p FOR LIQUID CHLORINE AND OBSERVED VALUES FOR C_p

Temp., °K	$\alpha \times 10^3$	$\beta \times 10^6$	C_V	C_p	C_P (obs.)	Error, %
180.000	1.301	47.4	10.12	16.59	16.02	3.56
190.513	1.219	50.0	10.03	15.81	15.99	−1.13
200.413	1.216	55.3	10.13	15.67	15.95	−1.76
210.000	1.241	62.1	10.11	15.56	15.89	−1.45
219.909	1.254	68.3	10.11	15.47	15.84	−2.34
229.958	1.304	82.2	10.11	15.47	15.77	−1.90
240.050	1.356	88.9	10.11	15.51	15.70	−1.21

Discussion.—In view of the assumptions made concerning degrees of freedom in writing the partition function, it seems appropriate to now consider various ways in which chlorine molecules can pack in the solid and liquid states. Once a pattern is established, theoretical molar volumes can be calculated by inscribing whatever particular-shaped volume the molecule describes in its modes of motion inside a polyhedral-shaped figure that packs without voids. These values, then, can be compared with the observed molar volumes of the solid and the liquid at various temperatures, in order to get some idea about what might be happening.

The molar value for solid chlorine, 34.34 cc, was estimated from the figures given by Sapper and Biltz,[11] who extrapolated the density obtained by Heuse[12] at liquid nitrogen temperatures to absolute zero. This datum has recently been confirmed by X-ray studies of solid chlorine by Keesom and Taconis,[13] and by Collin.[14] The latter finds solid chlorine to be orthorhombic instead of tetragonal, as reported by the former investigators. Smyth[15] concludes, from the specific heat data of Eucken and Karwat,[16] that rotation of chlorine molecules is not possible in the solid state, in agreement with calculations given below.

Using Collin's figures of 2.02 Å and 1.67 Å for the bond distance and the van der Waals radius of chlorine, respectively, a molar volume of 31.19 cc is obtained for the solid from the formula, $V = 2\sqrt{3}r^2\,lN$, assuming the structure to consist of hexagonally-packed hexagonal cylinders. Here, $r(= 1.67$ Å) is the radius of a circular cylinder contacting the inner surface of the hexagonal cylinder, l ($= 2.02 + 2 \times 1.67$) is the length of the latter, and N is the Avogadro number. Pauling's[17] figures for the bond distance (1.98 Å) and for the van der Waals radius (1.80 Å) give a value of 37.6 cc. Both agree roughly with the observed value, provided the molecules in the solid state pack as mentioned above.

For a minimum volume corresponding to free rotation for *all* the molecules, we can assume liquid chlorine to consist of face-centered, cubically close-packed spheres of 2.68 Å radius. This calls for a molar volume of $4\sqrt{2}r^3N$ ($=65.51$ cc), considerably above the volume of liquid chlorine, even at its boiling point ($V =$ 45.321 cc).

If we consider the arrangement where the molecule executes two-dimensional rotation, thus forming oblate ellipsoids rather than spheres, and if we inscribe each ellipsoid in a hexagonal title-shaped volume that packs without voids, we obtain a molar volume of $2\sqrt{3}\ r^2DN$ ($=50.2$ cc). Here $r = 2.68$ Å and D is the depth of the tile which equals twice 1.67 Å. This molar volume compares favorably with the value of 45.399 cc observed at the boiling point.

One must conclude, then, that chlorine cannot rotate appreciably in the solid state, and that only some of the molecules can rotate two-dimensionally at a given

time in the liquid state. The high entropy of fusion cannot be attributed to a general onset of rotation at the melting point, but rather would seem to indicate considerable association of the chlorine molecules with one another in the solid state. During its long, 245-degree liquid range chlorine does expand considerably and reaches a molar volume of 123.76 cc at the critical point, where rotation is definitely possible. Mellor[18] lists liquid chlorine as having the largest compressibility of all the elements at 20°C.

Summary.—A simplified partition function for liquid chlorine had been developed through the "holes-in-solid" model in accordance with the theory of significant structures. The function is made to fit only at the melting point and gives excellent agreement with observed data for vapor pressures, molar volumes, and C_p from the melting point to the boiling point, over a 67-degree range. Good agreement is also obtained for the entropies of fusion and vaporization, and calculated values of compressibility and coefficient of expansion are of the right magnitude.

The authors wish to express their appreciation to the National Science Foundation and to the summer institute of the Foundation for support of this work. We are also grateful to Mr. E. J. Fuller for his interest, valuable suggestions, and his considerable assistance with the calculations.

* This report represents one of the projects of a National Science Foundation Summer Research Program for College Chemistry Teachers, University of Utah, 1959.

† Visiting Scholar and National Science Foundation Grantee. Home address: Dept. of Chemistry, Adams State College of Colorado, Alamosa, Colorado.

[1] Hirschfelder, J., D. Stevenson, and H. Eyring, *J. Chem. Phys.*, **5**, 896(1937).

[2] Walter, J., and H. Eyring, *J. Chem. Phys.*, **9**, 393 (1941).

[3] Eyring, H., T. Ree, and N. Hirai, these PROCEEDINGS, **44**, 683(1958).

[4] Fuller, E. J., T. Ree, and H. Eyring, these PROCEEDINGS, **45**, 1594(1959); Carson, C. M., H. Eyring, and T. Ree (to be published).

[5] Giauque, W. F., and T. M. Powell, *J. Am. Chem. Soc.*, **61**, 1970(1939).

[6] Pellaton, M., *J. Chim. Phys.*, **13**, 426(1915).

[7] Johnson, F. M. G., and D. McIntosh, *J. Am. Chem. Soc.*, **31**, 1142(1909).

[8] Fuller, E. J., Ph.D. thesis, Department of Chemistry, University of Utah (in preparation).

[9] For example: "Contribution to the Thermodynamic Functions by a Planck-Einstein Oscillator in One Degree of Freedom," Office of Naval Research, Department of the Navy, Washington, D. C. (1949).

[10] Richards, T. W., and W. N. Stull, *J. Am. Chem. Soc.*, **26**, 399(1904).

[11] Sapper, A., and W. Biltz, *Z. Anorg. Allgem. Chem.*, **198**, 184(1931).

[12] Heuse, W., *Z. Phys. Chem. A*, **147**, 273(1930).

[13] Keesom, W. H., and K. W. Taconis, *Physika*, **3**, 237(1936).

[14] Collin, L., *Acta Cryst.*, **5**, 431 (1952); and *ibid.*, **9**, 537(1956).

[15] Smyth, C. P., *Chem. Rev.*, **19**, 329 (1936).

[16] Eucken, A., and E. Karwat, *Z. Physik. Chem.*, **112**, 467(1924).

[17] Pauling, L., *"The Nature of the Chemical Bond,"* 2nd ed. (New York: Cornell Univ. Press, 1948).

[18] Mellor, J. W., *A Comprehensive Treatise on Inorganic and Theoretical Chemistry*, (London: Longmans, Green and Co., Ltd., 1927), vol. 2, p. 50.

*THE GENIC CONTROL OF MATING TYPES IN PARAMECIUM BURSARIA**

By R. W. Siegel and L. L. Larison

DEPARTMENT OF ZOOLOGY, UNIVERSITY OF CALIFORNIA AT LOS ANGELES

Communicated by T. M. Sonneborn, January 13, 1960

Jennings'[1] discovery of a system of multiple mating types in *Paramecium bursaria* in 1938 followed closely Sonneborn's[2] initial description of mating types in *P. aurelia*. The detailed and brilliant experimental analyses carried out by Jennings[3] and directed toward an understanding of mating type inheritance and determination in this organism did not result in a satisfactory explanation for the various phenomena. The new investigations to be reported here, however, permit a resolution of some of the major difficulties. In particular, they demonstrate that the four complementary mating types long recognized for variety 1 are determined by specific combinations of complementary genes at two unlinked loci. Cells whose macronuclei carry dominant genes at both loci are mating type A; mating type C is brought about by the combination of homozygous recessives at both loci. The two alternative combinations of homozygous recessive alleles at one locus and at least one dominant gene at the other determine in a specific way mating types B and D.

Jennings considered a similar two-gene hypothesis untenable because it failed to account for certain of his observations; but since the new and more extensive results to be reported here support the hypothesis without ambiguity, an attempt will be made to reconcile, at least formally, the apparent exceptions originally discovered and reported by Jennings.

Since in ciliates the micro- and macronuclei of a clone are formed from mitotic products of a single initial nucleus, it can be inferred that they are isogenic. It has also been established that the micronuclei alone furnish the nuclear apparatus for new clones and that the mating type expressed by a cell is ultimately governed by its macronucleus. Within this framework, two systems of mating type control have been recognized. In *Euplotes patella*[4] and *Tetrahymena pyriformis* (variety 8),[5] (and perhaps *Paramecium caudatum*),[6] conventional genetic analyses reveal that specific mating types are determined by the genes brought together at the origin of the clone; thus, cells with a particular genotype express a predictable phenotype. On the other hand, in *P. aurelia*,[2] *P. multimicronucleatum*,[7] and *T. pyriformis* (variety 1)[8] macronuclei with presumably identical genotypes are characteristically found to govern the expression of different mating types; a single clone commonly contains cells expressing complementary types. Here a given mating type is not determined by a unique genotype *per se*, but instead the genetically pluripotent macronucleus is induced to express only one of the two (or more) possible types. The mechanism of nuclear induction or "mutation" and final mating type expression have been studied by Sonneborn[9] and Nanney.[8]

Establishment of the two-gene hypothesis for mating type determination in *P. bursaria* aligns this organism with *Euplotes* and *T. pyriformis* (variety 8); as a rule each mating type reflects a specific genic combination. However, in certain exceptional clones, Jennings reported mating type instability ("self-differentiation"),

i.e., the production, within a sexually mature clone, of cells expressing a new mating type. Moreover, qualitatively unexpected mating types appear infrequently among the progeny of various crosses. These facts suggest that "nuclear instability," similar to that in newly developed macronuclei in *P. aurelia* and *T. pyriformis* (variety 1), may occur rarely in *P. bursaria*. If so, the mechanism of mating type determination in *P. bursaria* would appear to combine elements of the two major classes of determinative systems in ciliates. A similar evaluation of the system in *T. pyriformis* (variety 8) has been set forth recently by Orias.[5]

Materials and Methods.—The taxonomic species *Paramecium bursaria* includes a large number of clones collected from nature and their sexual progeny. Jennings showed that each clone is normally self-sterile and that fertile interclonal conjugations occur only according to a recognized pattern. Interfertile clones belong to a common variety; six reproductively isolated varieties are presently known.

The strains studied by Jennings are no longer available. Four clones were isolated from Malibu Lake, California, and each was identified as representative of one of the four standard mating types known for variety 1.[10] It was important to establish at the outset that these clones conform in a general way to those previously employed. Comparisons of the two groups of clones with respect to the (1) cytology of sexual and asexual reproduction, (2) the diurnal periodicity of sexual activity in mature cells, (3) the "life cycle" stages, and (4) the deleterious effects of inbreeding as opposed to outcrossing, gave no indication of important differences.

Culture methods for *P. bursaria* have been described[3, 11] and follow closely those for *P. aurelia*.[12] Exconjugant clones were maintained in serial isolations permitting maximal fission rates, and were found to attain sexual maturity 50 to 100 fissions after their origin. Mass cultures of mature and sexually reactive cells were made available by transferring exconjugant clones to test tubes, thereafter kept at 25°C and afforded diurnal periods of light. Samples of each exconjugant clone were mixed with samples of each of the four standard mating types in order to discover the mating type of the clone. The unknown clone was classified as a particular type if it failed to mate with the standard of that type and formed pairs with the remaining three standard types. The precautions described by Jennings for avoiding abortive conjugations in selecting pairs for genetic analysis were followed throughout.

Cytogenetics.—Chen[13] has provided the cytological details of nuclear reorganization during conjugation in *P. bursaria*. The micronucleus in each animal of the mating pair undergoes two maturation (meiotic) divisions, one daughter nucleus disintegrating after each division; next, the surviving haploid nucleus divides mitotically to form migratory male and stationary female nuclei. With the exchange of the male nuclei and reciprocal fertilization, a new diploid clone is initiated from each member of the pair. The post-zygotic mitotic divisions of the syncaryon produce two macronuclei and two micronuclei; at the first cell division of the new clone, these are segregated so that the two daughter cells are supplied with the normal nuclear apparatus of the vegetative cell, a single macronucleus and a single micronucleus. The macronucleus of the previous sexual generation appears to waste away. Chen has demonstrated reciprocal fertilization in various

ways; his work leads to the conclusion that the two exconjugant clones produced from each pair mating are regularly isogenic.

The fact that at least 97 per cent of all conjugations provide a pair of exconjugant clones expressing identical mating types led Jennings to propose that mating type is genically determined. But Sonneborn[7] and Nanney[8] have suggested that cytoplasmic factors, responsible for mating type determination and reciprocally exchanged during conjugation, might bring about this result. Their argument is weakened, but not invalidated, by the observation that intracellular particles and symbiotic algae are not regularly exchanged during mating.[14]

Mating Type Determination.—The two clones ("synclones") descended as sister exconjugants from a single original pair of conjugating cells are regularly found to express a common mating type (Table 1). Since the synclones are isogenic and massive exchanges of cytoplasm are infrequent, these data provide the first evidence consistent with genic determination of mating type. The rare exceptions to synclonal uniformity are being studied and will be discussed in full in a later publication.

TABLE 1

THE FREQUENCY OF SYNCLONAL UNIFORMITY OF MATING TYPE

	Total Pairs	Pairs Which Yielded Clones Belonging to One Mating Type	Two Mating Types
Jennings' data	587	570	17
Malibu clones	135	133	2
Totals	722	703	19

The four Malibu stocks, mating types A, B, C, and D, were crossed in all six combinations of twos; conjugants were isolated from each mating and a single clone from each pair was raised to sexual maturity and tested for mating type. The results, presented in Table 2, agree with the ratios expected if it is assumed that the genotypes of the stocks are as follows: stock 8, type A, *AaBb;* 25-B, *aaBb;* 32-C, *aabb;* 3-D, *Aabb.*

TABLE 2

THE OBSERVED AND EXPECTED MATING TYPES OF THE DESCENDANTS OF PAIRS FROM INTERSTOCK CROSSES

	Mating Types of F1 Clones								
	Observed				Expected				
Cross	A	B	C	D	A	B	C	D	P
8-A × 25-B	24	21	10	4	22.5	22.5	7.5	7.5	0.5–0.3
8-A × 32-C	56	76	55	41	57	57	57	57	0.02–0.01
8-A × 3-D	44	11	19	33	40.2	13.4	13.4	40.2	0.3–0.2
25-B × 32-C	0	40	31	0	0	35	35	0	0.8–0.7
25-B × 3-D	6	8	14	10	9.5	9.5	9.5	9.5	0.3–0.2
32-C × 3-D	0	0	45	45	0	0	45	45	1

The cross 8-A (*AaBb*) × 25-B (*aaBb*) should produce mating type B F1 clones with two genotypes, *aaBb* and *aaBB;* similarly, the cross 8-A (*AaBb*) × 3-D (*Aabb*) is expected to yield both homozygous and heterozygous type D progeny (*AAbb, Aabb*). While heterozygous B and D clones crossed to type C should yield 1:1 ratios of the two parental mating types, the homozygotes when crossed to type C would be expected to produce only type B or type D progeny. These predictions are verified by the data presented in Table 3.

Further crosses of the derived homozygous type B and D clones have been carried out. The data in Table 4 are consistent with the hypothesis that F1 clones

8-B, 23-B, 98-D, and 104-D are homozygotes, for they yield only type A among their sexual progeny, and, when crossed to stock 8-A, the parental types, A and B or A and D, appear in a 1:1 ratio.

TABLE 3

MATING TYPES B AND D; HOMOZYGOUS AND HETEROZYGOUS CLONES

Parental Cross	Fl Clone	Progeny Produced in Test Cross, Fl × St. 32-C (aabb) A	B	C	D	Genotype of Fl Clone
8-A × 25-B	6-B	0	9	5	0	*aaBb*
	8-B	0	14	0	0	*aaBB*
	20-B	0	8	8	0	*aaBb*
	23-B	0	17	0	0	*aaBB*
	28-B	0	12	0	0	*aaBB*
	41-B	0	8	7	0	*aaBb*
8-A × 3-D	98-D	0	0	0	18	*AAbb*
	103-D	0	0	8	5	*Aabb*
	104-D	0	0	0	18	*AAbb*
	122-D	0	0	5	8	*Aabb*
	126-D	0	0	0	17	*AAbb*
	129-D	0	0	0	15	*AAbb*
	138-D	0	0	7	9	*Aabb*

TABLE 4

MATING TYPES OF THE DESCENDANTS FROM CROSSES INVOLVING HOMOZYGOUS B AND D CLONES

Cross	Genotypes of Clones Crossed	Progeny Observed A	B	C	D
Fl 8-B × Fl 104-D	*aaBB* × *AAbb*	13	0	0	0
Fl 23-B × Fl 98-D	*aaBB* × *AAbb*	23	0	0	0
ST. 8-A × Fl 8-B	*AaBb* × *aaBB*	11	19	0	0
ST. 8-A × Fl 23-B	*AaBb* × *aaBB*	13	13	0	0
ST. 8-A × Fl 98-D	*AaBb* × *AAbb*	34	0	0	16
ST. 8-A × Fl 104-D	*AaBb* × *AAbb*	17	0	0	15

As expected, the cross of stock 8-A × F1 8-B (*aaBB*) was found to produce some mating type A clones with the genotype *AaBb* and others with the genotype *AaBB;* the genotypes *AaBb* and *AABb* (both mating type A) were formed in the cross of stock 8-A × F1 98-D (*AAbb*). In each case, these genotypes were identified by crosses to the double recessive, stock 32-C.

Discussion.—The results of the crosses described above serve to establish the following hypothesis: mating type A is determined by the genotypes *AABb*, *AaBB*, and *AaBb;* mating type B is formed by cells genotypically *aaBB* and *aaBb;* the double recessive, *aabb*, is mating type C; finally, the combinations *AAbb* and *Aabb* determine type D. The data provide no evidence for linkage between the two loci. A curious consequence of the breeding system is that the genotype *AABB*, which should determine mating type A, cannot be formed since any mating involves a parental cell which is a recessive homozygote for at least one locus. Can these formulae account for the data presented by Jennings? One is immediately impressed by the fact that most of Jennings' crosses produced progeny predicted by the hypothesis and that genotypes can be readily assigned to the majority of his initial clones. But, as Jennings realized, the behaviour of exceptional clones must be satisfactorily explained before the two locus hypothesis is finally established. The following interpretation shows that these cases do not necessarily contradict the hypothesis.

The genotype of the macronucleus is revealed only by the phenotype expressed by a cell; on the other hand, the genotype of the micronucleus is brought to light

by the results of a breeding analysis. The results described above establish that, regularly, the genotypes of the two nuclei are found to agree; the present explanation of aberrant clones assumes that rare exceptions to this rule may occur. As an extension of ideas earlier set forth by Sonneborn and Orias, we suggest that in certain clones the two known loci concerned with mating type determination become transiently unstable in expression or dominance, and that such instability may lead to an hereditary alteration. Although these alterations are faithfully transmitted through numerous cell generations, their frequency and reversibility tend to set them apart from typical gene mutations. Representative exceptional clones will be discussed in the next paragraphs in light of this interpretation.

Jennings' clone 13 underwent self-differentiation to form mating types A and D. *Prima facie* evidence for instability of macronuclear genes is provided by the fact that the macronucleus is known to determine mating type. When these two branches of clone 13 were allowed to cross, the progeny consisted of 32 A's, 11 B's, no C's, and 17 D's. If the parental A and D subclones are both assigned micronuclei with the genotype *AaBb*, then the observed results are in good agreement with the expected 9:3:1:3 ratio; but if the D subclone is provisionally assigned the micronuclear genotype *Aabb* or *AAbb* (in agreement with its expressed or macronuclear "genotype") then the observed results do not agree with the expected ratio. Hence, this clone provides evidence for instability of expression for genes in the macronucleus.

Aberrant results from other clones analysed by Jennings are brought into line with the two locus hypothesis if instances of variable or unstable allelic expression are assumed. For example, clones 32 and 33, both originally type B, produced subclones of types D and A respectively. Crosses involving these self-differentiated D and A lines reveal that their micronuclear genotypes are *AAbb* and *AaBb*. Unfortunately, the parental type B clones were not bred further but at least the expression of macronuclear genes was altered in these clones.

Several apparent alterations in macronuclear expression have been discovered in crosses of the Malibu strains. As in Jennings' work, sublines from a given clone were found to consist of cells expressing complementary mating types. It does not seem fruitful to comment further on these and other variants so far uncovered since they are few in number and are, at present, incompletely analysed. The point to be stressed is that the appearance of exceptional clones in our material affords the opportunity to analyse in a more satisfactory way the hypothesis of hereditary alteration in gene expression.

A comparison of mating type mechanisms in the more fully studied ciliates suggests a series of variations about a central theme. The simplest and perhaps most primitive (in the evolutionary sense) situation is to be found in *Euplotes patella*, where the genotype of each clone is directly revealed by the expressed mating type and by appropriate crosses. *P. bursaria* and *T. pyriformis* (variety 8) regularly conform to this pattern, and hence genic mechanisms for mating type control have been uncovered by breeding studies; the evidence suggests further that rare variations in the expression of alleles concerned with mating type determination occur. But in other ciliates, these instances of instability are not rare, instead they have become the rule. Consequently, genetic loci concerned with the development of specific mating types cannot be defined; Sonneborn[2, 9] and Nanney[8]

postulate "mutational" changes responsible for the macronuclear differentiation of complementary mating types in *P. aurelia* and *T. pyriformis* (variety 1). Here the genotype of the micronucleus would (if it could!) permit the expression of two or more mating types, whereas the macronucleus in each cell becomes, early in its development, restricted to the expression of but a single specificity. Finally, in *P. multimicronucleatum*, unstable macronuclear expression continues throughout the history of the clone.[15]

The differential expression of alleles determining antigenic specificity has been discovered by Sonneborn *et al.*[16]; in that case, the observed phenotypic variation is brought to light only in aged clones. The dominance of serotype genes in heterozygotes of *T. pyriformis* is apparently indeterminate.[17] The question remains as to whether the basis for these hereditary transitions in gene function lies in an alteration of the primary genetic information (DNA) or only in the degree of expression of an unchanged genetic code. The difficulties in distinguishing genetic from "epigenetic" alterations have been discussed recently by others.[18]

Summary.—Multiple mating types have long been known in *Paramecium bursaria*. It has now been established that a system of complementary genes at two unlinked loci controls each of the four mating types in variety 1. Thus specific genotypes can be assigned to most, but not all, clones. The exceptions do not necessarily invalidate the two-locus hypothesis for they may represent instances of altered genic expression or dominance. If so, the mechanism of mating type determination in *P. bursaria* requires the operation of both "genetic" and "epigenetic" control systems. An evolutionary sequence originating in the genetic control of mating type, as in *Euplotes patella*, through the condition exemplified by *P. bursaria* and *Tetrahymena pyriformis* (variety 8), to epigenetic control, as in *P. aurelia*, *P. multimicronucleatum*, and *T. pyriformis* (variety 1), may be suggested.

* Supported by grants from the National Science Foundation and by Cancer Research Funds of the University of California.

[1] Jennings, H. S., these PROCEEDINGS, **24**, 112 (1938).

[2] Sonneborn, T. M., these PROCEEDINGS, **23**, 378 (1937).

[3] Jennings, H. S., *Genetics*, **24**, 202 (1939); *Proc. Am. Phil. Soc.*, **85**, 25 (1941); *Genetics*, **27**, 193 (1942).

[4] Kimball, R. F., *Genetics*, **27**, 269 (1942).

[5] Orias, E., Ph. D. Thesis, Univ. Mich. (1959).

[6] Hiwatashi, K., Science Repts. Tohoku Univ., *Biol.*, **24**, 119 (1958).

[7] Sonneborn, T. M., in A.A.A.S. symposium on *The Species Problem* (1957), p. 155.

[8] Nanney, D. L., *Am. Naturalist*, **90**, 291 (1956); Allen, S. L., and D. L. Nanney, *Am. Naturalist*, **92**, 139 (1958); Nanney, D. L., and S. L. Allen, *Physiol. Zool.*, **32**, 221 (1959).

[9] Sonneborn, T. M., *Caryologia*, **6** (suppl. 1), 307 (1954).

[10] Siegel, R. W., *Am. Naturalist*, **92**, 253 (1958).

[11] Ehret, C., *Physiol. Zool.*, **26**, 274 (1954).

[12] Sonneborn, T. M., *J. Exptl. Zool.*, **113**, 87 (1950).

[13] Chen, T. T., *J. Hered.*, **31**, 185 (1940); these PROCEEDINGS, **26**, 241 (1940); *J. Morph.*, **88**, 293 (1951).

[14] Wichterman, R., *Science*, **104**, 505 (1946); Siegel, R. W., *Exptl. Cell Res.* (in press, 1960).

[15] Sonneborn, T. M., *Anat. Rec.*, **128**, 626 (1957); Sonneborn, T. M., and Audrey Barnett, *J. Protozool.*, **5**, (*suppl.*) 18 (1958).

[16] Sonneborn, T. M., *et al.*, *J. Protozool.*, **3** (*suppl.*), 8 (1956).

[17] Nanney, D. L., *Science*, **130**, 1420 (1959).

[18] Nanney, D. L., these PROCEEDINGS, **44**, 712 (1958); Sonneborn, T. M., these PROCEEDINGS, 149–165 (1960).

*THE EVOLUTIONARY IMPLICATIONS OF THE CYTOLOGICAL POLYMORPHISM AND PHYLOGENY OF THE VIRILIS GROUP OF DROSOPHILA**

By Wilson S. Stone, William C. Guest,† and Florence D. Wilson

GENETICS FOUNDATION, DEPARTMENT OF ZOOLOGY, THE UNIVERSITY OF TEXAS

Communicated by J. T. Patterson, January 11, 1960

In 1938 Professor J. T. Patterson embarked on a very intensive collection of Drosophila species because preliminary investigations had convinced him that this fauna was very rich, comparatively unknown, and most suited for the study of the evolution of a genus. The investigations of these species fully justified his conviction (Patterson and Stone[1]). Two of the species groups he and his colleagues investigated extensively were the virilis and the repleta groups of the subgenus Drosophila. Both of these groups have added and continue to add greatly to our understanding of evolution. Flies such as Drosophila leave no fossil record, except for a few recognizable specimens in amber. Mutations are repetitive so the presence of the same allele in different species is hard to prove or to evaluate. However, Professor T. S. Painter's[2] demonstration of the characteristics of the chromosomes of the salivary gland cells of Drosophila and their unique usefulness in analyses of chromosomal abnormalities gave us a tool to analyze the direction and degree of cytological change. With this tool the chromosome phylogeny and variability can be determined and compared to the genetic changes within a species group.

Materials and Methods.—A recently described species, *Drosophila ezoana* (Takada and Okada[3]), and new strains of *Drosophila montana* were available for our study. Genetic and cytological analyses were made by crosses within and between strains of a species together with crosses between different species. The details are to be found in Guest's[4] manuscript and will be published in full later. This paper will present the critical features of the cytological evolution and diversity of this species group, and only a few crosses showing the genetic differences will be presented. The cytological differences between species and the cytological polymorphism within strains were determined in the heterozygotes or hybrids or by comparison to the standard maps of *Drosophila virilis* by Hsu[5] and the standard *Drosophila montana* by Moorhead.[6] Strains of all the species of the virilis group were used in the crosses. In some cases two strains of a species were crossed and the F_1 tested to a third species in the hope that viable offspring would be more probable from the heterotic F_1. The new members of the *montana* species were compared to the standard and giant *montana* for size.

Results.—The new strains of the *montana* from Alaska and Canada proved approximately the same size [estimated using length from head through folded wing tip (mean 4.9 mm, ♀)] as standard *montana* (mean 4.8 mm, ♀) and smaller than giant *montana* (mean 5.3 mm, ♀). Moorhead[6] showed that giant *montana* (which might have been designated a new subspecies) was larger than standard *montana* but did not otherwise differ phenotypically from the standard except for the inversion pattern. The new strains from Alaska and Canada do not differ appreciably from standard in size or other phenotypic characteristics but might be classed as a

different subspecies on inversion pattern differences. Table 1 shows tests to the closely related species of the *montana* complex, *Drosophila lacicola*, *D. borealis* and *D. flavomontana*. The Alaskan and Canadian strains were test mated to the other members of the virilis group including *Drosophila littoralis* (the F_1 female hybrids between the latter and the Smithers' strain were fertile). The variations in fertility are similar to those found by Patterson,[7, 8] by Moorhead,[6] and reported from earlier work by Patterson and Stone.[1]

Drosophila ezoana proved quite unusual in that it is by far the most effectively genetically isolated species in the group. Reciprocal crosses were made with all other members of the group (involving over 20,000 pairs of each sex, including over 6,000 with *Drosophila virilis* and 4,000 with *D. littoralis*). Only four offspring, all F_1 from *littoralis* males to *ezoana* females, survived even as far as large larvae. Table 2 shows that insemination also occurred in the reciprocal cross, and that *virilis* females were more frequently inseminated by *ezoana* males than *ezoana* females were by *littoralis* males (in this cross the alien *ezoana* sperm remained motile in the seminal receptacles of the *virilis* females ten days after the flies were placed together).

The cytological variation in the *virilis* species group including these new forms

TABLE 1

CROSSES OF STRAINS OF *Drosophila montana* FROM ALASKA AND CANADA WITH OTHER SPECIES OF THE MONTANA SUBGROUP

	U. T. No. 2501.2a Yukon				U. T. No. 2503.1 Alaska				U. T. No. 2514.1 Smithers			
	No. of Pairs	No. of Offspring ♀	No. of Offspring ♂	Fertility of F_1	No. of Pairs	No. of Offspring ♀	No. of Offspring ♂	Fertility of F_1	No. of Pairs	No. of Offspring ♀	No. of Offspring ♂	Fertility of F_1
borealis ♀	130	25	31	Fertile	120	2	1	Sterile	120	0	0	..
borealis ♂	120	0	0	..	130	0	0	..	120	2	0	Sterile
lacicola ♀	150	2	6	Fertile	120	0	0	..	120	8	8	Fertile
lacicola ♂	190	256	283	Fertile	150	108	94	Fertile	120	230	248	Fertile
flavomontana ♀	120	25	23	Sterile	110	0	0	..	120	40	43	Fertile
flavomontana ♂	120	0	0	..	120	0	0	..	120	0	0	..

All crosses were made in small mass matings of 10 pairs per vial.

proved most informative (Fig. 1 and Table 3). The *montana* complex which evolved from Primitive III, Figure 1, in North America consists of the three subspecies or forms of *Drosophila montana*, standard, giant, and the Alaskan and Canadian forms, plus three species descended from standard *montana*: *D. lacicola*, *D. flavomontana*, and *D. borealis*. Unfortunately, many of the changes in gene sequence in the X-chromosome in descendants of Primitive III have not been analyzed. We do not know the basic sequences of genes in the X-chromosomes of *ezoana*, *littoralis*, *montana*, or *lacicola*. It would seem probable that five or more inversions were present in hybrids between *ezoana* and *littoralis*, *littoralis* and *montana*, *montana* and *lacicola*, and *montana* and *virilis*. Therefore the total number of inversions analyzed, 92, plus the unanalyzed inversions in the X chromosome, would mean a total of perhaps 120 known in the evolution of members of this species group. The inversions in *Drosophila novamexicana* and the two subspecies *D. americana americana* and *D. americana texana* were worked out especially by Hsu,[5] who also studied *littoralis*, basic *montana*, *lacicola*, *flavomontana*, and *borealis*, and proposed the three primitive types, modified slightly in Figure 1, to account for the cytological phylogeny of the group. The cytological analysis of the giant *montana* strains was

made by Moorhead.[6] Since no rearrangements were found in chromosome 6, it will not be referred to further.

The chromosome phylogeny including the postulated primitive types is shown in Figure 1 and Table 3. In these illustrations we have indicated the inversions at their origin (in a primitive type, a species, or a subspecies) by capital letters. Lower case letters indicate that the inversion occurred in an ancestral form, while letters in italics indicate that the inversion is not fixed but is heterozygous in some individuals. For sample, a particular inversion, B, in the 2 chromosome would be written 2*B*, 2B, 2b, or 2*b*. We have used overlapping inversions where they occur to give direction to the phylogeny as did Sturtevant and Dobzhansky,[9] Dobzhansky and Sturtevant,[10] and Dobzhansky,[11] who reviewed the extensive work done by him and his colleagues. These are not sufficient to establish all relations and we have used the presence of added new inversions, heterozygous and especially homozygous, to establish the direction of cytological evolution. Hsu[5] and Patterson and Stone[1] have presented convincing evidence that *D. virilis* (or Primitive I) was ancestral to the group. The present paper places *D. ezoana* as an intermediate between Primitive III and *D. littoralis*, very close cytologically to the former. The arrows on Figure 1 indicate the direction or more probable

TABLE 2

INSEMINATION OF FEMALES IN CROSSES OF *Drosophila ezoana* WITH OTHER SPECIES OF THE VIRILIS GROUP

♀ ♂	Number of Females Mated*	Number of Females Dissected	Number Inseminated	Number with Motile Sperm
ezoana × *virilis*	500	100	0	0
virilis × *ezoana*	500	100	29	14
ezoana × *littoralis*	260	50	2	0
littoralis × *ezoana*	260	50	2	0
ezoana × *montana*	260	50	0	0
montana × *ezoana*	140	50	0	0

* Crosses made in small mass matings of about 20 pairs each.

direction of cytological evolution. There is no reason to think that we have found all the inversions in any species—for example, the few strains of *D. montana* from Alaska and Canada had 7 new inversions heterozygous. We know 43 inversions which are fixed in one or more species, 41 which originated in a species or the Primitive form which gave rise to it, and 2 which were only heterozygous at their origin but were fixed in a descendant form (2f and 4h). There are additional inversions fixed in X_E, X_{Li}, X_M, and X_{Lc}. Because the complexities of these inversions have so far defied analysis, we can only estimate that there are perhaps 20 to 30 additional inversions fixed in these X chromosomes. Furthermore, there are 51 new inversions heterozygous in the species in which they first occurred. as well as 8 inversions carried over from an ancestral form but still heterozygous.

All of these 92 (+ unanalyzed X inversions) are paracentric except the one pericentric in chromosome 2 which occurred in Primitive III and is present in all descendants of that form. In addition there are present in these species three centric fusions (see Patterson and Stone[1] for summary of analysis): the 3–4 fusion of *D. littoralis*, the 2–3 fusion of *D. americana americana* and *D. americana texana*, and the X-4 fusion of *americana* not found in *texana* except by gene interflow in their overlap zone. No other translocations and only a few minor shifts in

TABLE 3

CHROMOSOME VARIABILITY AND PHYLOGENY OF THE VIRILIS GROUP

Species	Chromosomes and Elements: X A	2 E	3 D	4 B	5 C	Inversions: Homozygous New/Old	Inversions: Heterozygous New/Old
virilis	..	..	..	..	..	0	0
Primitive I	..	A	..	..	..	1/0	0
Primitive II	A B	a	..	..	..	2/1	0
novamexicana	a	a	A	A	B	6/3	0
	b	B					
	C	C					
texana	a	a	..	*a*	*A*	0/3	1/4
	b			*b*	*b*		
	c						
americana	a	a	*a*	*a*	*a*	0/3	3/6
	b	*b*		*B*	*b*		
	c	*c*		*C*			
	D						
Primitive III	..	a	..	D	..	0/3	4/6
		D		E		5/1	1/0
		E		F			
		F					
ezoana	X_E	a	..	d	I	1/6	0/1
		d		e			
		e		f		(+X_E)	
		f					
littoralis	X_{Li}	a	H	d	H	5/7	2/0
		d	*I*	e	i		
		e		f	J	(+X_{Li})	
		I		M			
				N			
montana—standard	X_M	a d e f	B	d e f	C	8/7 (2f)	9/0
		G H J K	C	*H G I*	D		
		L	*D*	*L O*		(+X_M)	
				U W			
montana—giant	X_M	a d e f	b c	d e f	c d	0/7 (+8)	14/0
		g h j k	*d L*	*h g i*	*O*		
	J K L	*S T*		*l R S*		(+X_M)	
				T u			
				V w			
				X Y Z			
montana—Alaska-Canada	X_M	a d e f	b c	d e f *h*	c d	0/7 (+8)	7/0
		g h j k	*M*	*g i l*	*o P*		
	k	*U V*		*u w*		(+X_M)	
	N	*W X*		*x z*			
						8/7	30/0
lacicola	X_{Lc}	a d e f g h j k	b c	d e f *h*	c d	4/15	8/1 (4*h*)
		O P Q R	J K	P Q	*K L M N*	(+X_{Lc})	
flavomontana	X_M	a d e f g h j k	b c	d e f h	c d	6/16 (4h)	2/0
		N	E	J *K*	E	(+X_M)	
	E F G						
borealis	X_M	a d e f g h j k	b c	d e f h	c d	3/16 (4h)	4/0
		M	*F G*		F *G*		
	H I						
Homozygous	8 + X_E, X_M, X_{Li}, X_{Lc}	11	7	9	8	41 + X_E, X_M, X_{Li}, X_{Lc} new inversions + 2f and 4h old inversions	
Heterozygous	5	13	6	17	8	49 + 2*f*, 4*H* new inversions + 8 old inversions	
Total	13 + X_E, X_M, X_{Li}, X_{Lc}	24	13	26	16	92 + X_E, X_M, X_{Li}, X_{Lc}	

All forms are compared to *Drosophila virilis*, the cytological standard form. Each chromosome has a series of inversions which are given letters, following the system of Hsu.[5] New inversions are indicated by capital letters; inversions brought in from an ancestral form by lower case letters; and inversions that are not fixed in a species but occur heterozygous in part of the individuals by italicized letters. The accumulation and correlation of inversions show relations and give direction to the phylogeny.

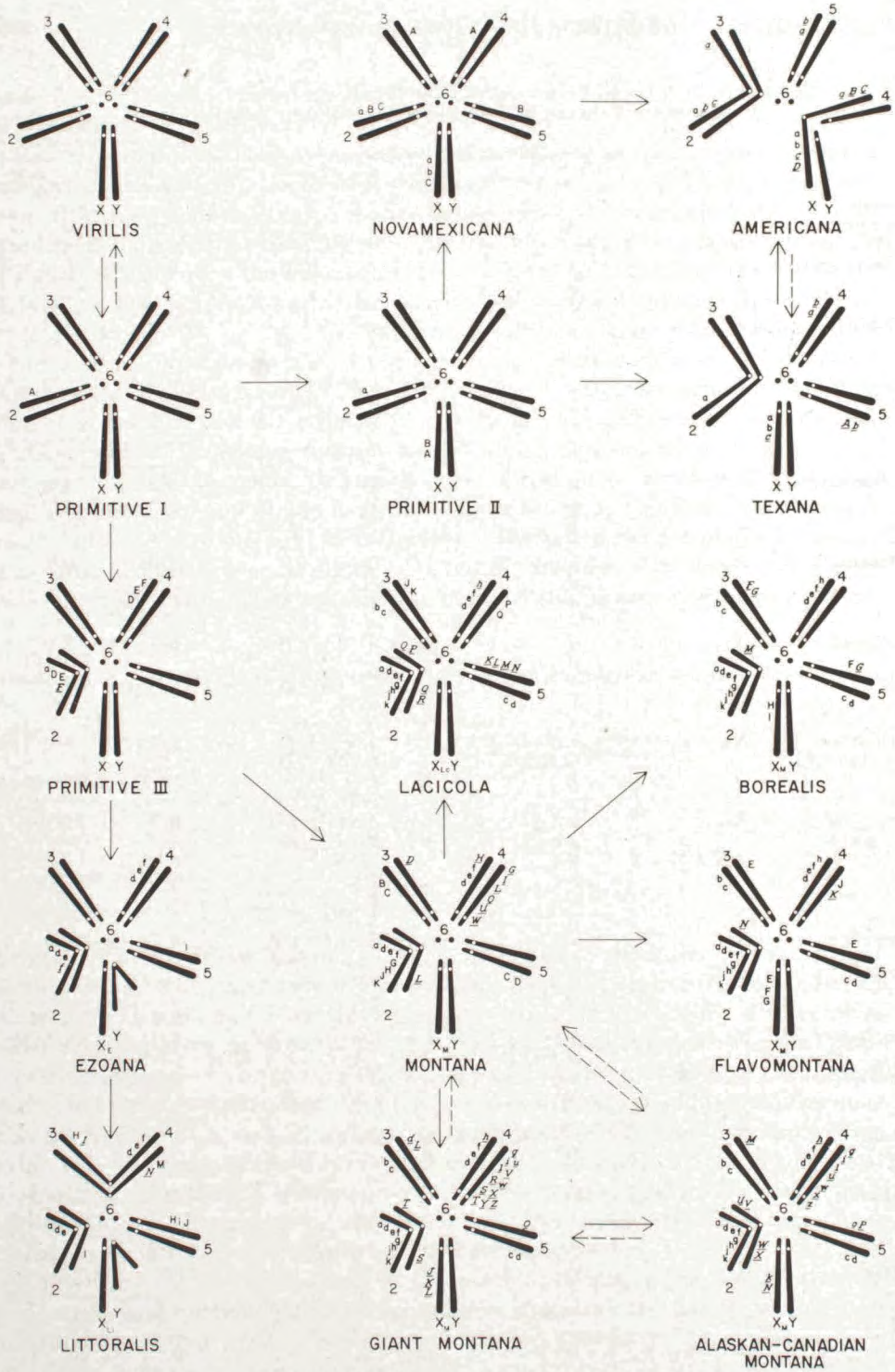


FIG. 1. The chromosome phylogeny and variability of the virilis species group.

Each inversion in a chromosome is given a separate letter. Capital letters mark the origin of an inversion in a species, subspecies, or primitive form; lower case letters indicate the inversion originated in an ancestral form; letters in italics (underscored in the figure), whether capital or lower case, show that the inversion is heterozygous, at least in some individuals. The arrows indicate the more probable evolutionary phylogeny, while arrows each way indicate gene flow between subspecies.

heterochromatin are known. It is interesting to note that the X-4 fusion without a Y and 4 fusion gives *americana* a multiple sex chromosome complex. Nevertheless this is fixed in *americana* and absent from the subspecies *texana* except for gene exchange along the band of overlap of the two subspecies, while no one of the many new paracentric inversions is fixed in one subspecies and absent in the other—Xc of *americana* approaches it most closely. Another interesting observation is that 2*F* occurred only heterozygous in Primitive III (this is the only modification we found necessary in the primitive types as first postulated by Hsu[5]), remains heterozygous in *D. ezoana*, was lost in the evolution of *D. littoralis*, but was fixed in the other line of descent of Primitive III in standard *montana* and its descendants.

Discussion.—Sturtevant and Dobzhansky[9, 10] first used a chromosome phylogeny to establish the sequence relationships in the 3 chromosome of *Drosophila pseudoobscura* and *D. persimilis*. They also indicated that the 3 chromosome of *D. miranda* was related to the other sequences through their hypothetical sequence which differs from the Standard gene sequence by one inversion. Many other inversion differences are present between these three species. Dobzhansky[12] has compared the chromosomes of *Drosophila willistoni* and three of its sibling species and Carson[13] has compared three other members of this species group. Stone[14] has reviewed the studies of chromosome polymorphism in the genus Drosophila and listed most of the extensive investigations up to that time. Despite these many investigations only two real phylogenies that represent major analyses of the chromosome evolution of large species groups exist—the virilis group as discussed here and earlier by Hsu[5] and Patterson and Stone,[1] and the repleta group investigated especially by Wasserman[15] and Wasserman and Wilson.[16] The reason for the success in these two groups and relative lack of success elsewhere is not hard to determine. The inversion changes often involve small inversions, the number of inversion differences between closely related forms is small, nearly the full series of intermediate forms is still in existence, and finally these are quite good species groups for laboratory studies including cytological analysis. For example, comparing *pseudoobscura* and *persimilis* with *miranda* is like attempting to compare *novamexicana* and *texana* with giant *montana* without the known intervening forms. By far the most remarkable chromosome phylogeny is that of the repleta group. Wasserman and Wilson[16] reported the analysis of 22 species of this group. More recently Wasserman[17] has extended the analysis so that he has the cytological phylogeny of 39 species of the more than 60 in the group. Furthermore, he has been able to show the cytological evolution of 7 other species not at present included in the group from the common cytological stem gene sequence. The ancestor(s) of the repleta group achieved some basic adaptation to desert conditions which led to a tremendous multiplication of species in the sparsely populated Southwest and especially Mexico. In these species genetic evolution was rapid, cytological evolution was not. For example, Wasserman has now recognized 100 inversions in chromosome 2, which is homologous to element E and hence to chromosome 2 of the virilis group; in the latter, consisting of nine species plus three subspecies or separate varieties, there are 24 inversions in this chromosome. The general problem of chromosome homologies in Drosophila was developed by Muller,[18] and Sturtevant and Novitski.[19] Inversion phylogenies have a unique advantage in that they

show the steps, but not the number of species in the steps, in the evolution of a group even if members and their steps are missing.

The chromosome variability in the genus has been reviewed by Stone[14] so only a few added comparisons with the data on the virilis group will be given. Most of the inversion variability in *pseudoobscura* is in chromosome 3, element C. This element is not especially variable in the virilis group. There are 50 known inversions found heterozygous in *willistoni* alone and one individual was heterozygous for 16 of them, (da Cunha, Dobzhansky, Pavlovsky, and Spassky[20]). These authors point out that there are now known the following heterozygous inversions in this species, given by chromosome arm and element: XL(A) = 11, XR(D) = 7, 2L(B) = 8, 2R(C) = 6, 3(E) = 18. The most variable species of the virilis group, *montana*, consisting of three varieties or subspecies, has the following series of heterozygous inversions, given by chromosomes and elements to facilitate comparison: X(A) = 4, 4(B) = 14, 5(C) = 2, 3(D) = 3, 2(E) = 7, total = 30. The three sibling species of *montana* are also quite variable, as are the sibling species of *willistoni*. The largest number of heterozygous inversions present in one strain (perhaps involving more than one pair as parents) of giant *montana* was 8 (Moorhead[6]) in contrast to 16 in one individual in *willistoni*. Da Cunha *et al.*[20] repeat their deduction that chromosomal polymorphism of paracentric inversions exists because of selective advantage. With this conclusion we must agree. The simplest general observation supporting it is the paucity of pericentric inversions and translocations (even the relatively innocuous centric fusions) which like paracentric inversions are two-break rearrangements and should therefore occur in as great numbers. However, the infrequent and absent types are known to have varying degrees of disadvantage when heterozygous (and they would originate heterozygous) because most of them produce aneuploid gametes at meiosis (Patterson and Stone[1]). Even paracentric inversions involving the heterochromatin which so often gives rise to position effect mutations that are often detrimental are very rare in Drosophila. The theoretical basis was developed by Fisher[21] over twenty years ago, who pointed out that slightly less than 2 per cent of unique mutational events would survive even with 1 per cent selective advantage, while no mutation without selective advantage would survive indefinitely from a single occurrence.

Da Cunha *et al.*[20] state: "The question which unavoidably presents itself, is, what causes some populations to be so much more polymorphic than others? Da Cunha, Burla, and Dobzhansky (1950)[22] advanced the working hypothesis that the chromosomal polymorphism is adaptive, and the populations which exploit a greater variety of ecological niches in the territory which they inhabit are more polymorphic than populations restricted to a narrow range of ecological opportunities."

It might be well to state the relations somewhat differently. Regions with many varied ecological niches have these filled in time by living systems, sometimes by several species and sometimes by one with great adaptive capacities which may depend on genetic polymorphism, whereas regions with serious ecological restrictions must impose similar restrictions on the variability of the genotypes. Furthermore, genotypes from a marginal restricted habitat might be able to invade an area with rich and varied ecological niches much more effectively than a genotype from a rich area could invade an area of much more restricted and intense selection, despite

population pressure which causes major migrations from densely populated centers to peripheral regions.

Carson[23] (and earlier publications) has suggested that marginal populations are homozygous because homozygosity allows maximum recombination. This is undoubtedly true but certain additional facts must be considered. For example, the restriction of crossingover in some chromosome regions by heterozygous inversions has repeatedly been demonstrated to increase recombination in others, Schultz and Redfield.[24] Furthermore, the mere effect of difference in population size must have an effect. In a very large central population the number of individuals with any chromosome or large segment of a chromosome homozygous must be very much larger than in the peripheral populations. Therefore, the number of recombinations will be much greater in the central population (although not as great a per cent), than in peripheral areas. In fact, if these new combinations are especially beneficial and dominant in their effect, they may be multiplied as inversion heterozygotes protected from immediate breakdown by crossingover until they can build up in frequency. J. F. Crow (personal communication) pointed out a second and more important reason for questioning the greater importance to survival of homozygosity of peripheral populations. The importance of a sexual system and of recombination over an asexual system increases with population number. Further consideration stresses the importance of the role of selection against the ill-adapted migrants from the population centers in establishing the genotypes of the peripheral populations. The evidence that necessarily peripheral populations connected to parent populations give rise to new forms and species does not seem sufficient. As Carson pointed out, *Drosophila robusta* does not have such budded-off species. Rather it seems that isolation plus restricted population size are both necessary. This has been discussed and the genetic effects elaborated and illustrated in bird evolution by Mayr[25] and for insects and invertebrates in general by White.[26] Both of these seem to be necessary factors in the evolution and elaboration of the repleta species group in Drosophila in addition to the desert adaptation of the ancestral form. Probably most of the more than 60 species in the repleta group evolved in the desert and semidesert conditions of Mexico and the Southwest, an environment where both isolation and initial restriction in size would occur frequently.

There are some interesting conclusions to be drawn from comparisons of the cytological evolution and polymorphism of different species groups with very different population distributions and densities. Wharton[27] made the first extensive analysis of the role of fusions, pericentric inversions and changes in heterochromatin in the genus. Further adequate discussions are to be found in Patterson and Stone[1] and Stone.[14] We shall deal with the role of paracentric inversions, both fixed and heterozygous, in the evolution of the species group. Wasserman[15–17] has investigated the repleta group, particularly in the southwest United States, Mexico, and Central and South America and the Antilles around the Caribbean Sea. These are usually small populations, particularly in the desert areas, where most of them occur. The 39 analyzed members of the group are characterized by relatively few inversion differences between species. Even so, there are decidedly more inversion differences fixed between species than occur as heterozygotes within species. The virilis group includes species with very small populations (e.g.,

novamexicana), those which are small, and *virilis* which in Asia seems to have large populations. This last species and the most restricted species, *novamexicana*, seem to be cytologically homozygous, whereas the others are variable. Spieth[28] demonstrated that *lacicola* and *borealis*, which are sympatric in northern Minnesota, live in a restricted high humidity belt around lakes. Other members of the group found in North America are also restricted to banks of streams and lakes. Along desert streams of the southwest the collections of *novamexicana* have been few so we must defer final decision—so far it is homozygous for gene arrangements although the three populations investigated for heterotic properties by Stone, Alexander, and Clayton[29] prove to have some very interesting genetic differences.

Drosophila pseudoobscura and *persimilis* have more inversions heterozygous in their populations than the number of fixed inversion differences. However, the restricted species with comparatively small populations, *Drosophila miranda*, differs from these two by many more fixed inversions than the total of variable inversions in the three species. Unfortunately for an analysis, the species of the willistoni group are too diverse cytologically to determine the number of inversion differences fixed between them. The species *willistoni* has one of the larger if not the largest population distribution in the genus, perhaps being the largest species in numbers and large population distribution of any amenable to genetic analysis.

Perhaps the most significant finding is that there is no direct correlation between number of individuals in a species and number of heterozygous (unfixed) inversions in a species. *Drosophila pseudoobscura*, with a widespread distribution and large populations in western North America, has somewhat fewer inversions heterozygous than *montana*, although the latter species is at present characterized by small linear populations spread over a considerable area. A guess, which certainly overestimates the relative number of *montana*, would estimate their ratios as *montana: pseudoobscura: willistoni* = $1:10^4:10^8$. Nevertheless there are known only 50 heterozygous inversions in the latter species but 30 in *montana*, even though *willistoni* has been sampled much more extensively. Perhaps this is good evidence that the difficulties discussed by Haldane,[30, 31] in terms of the conditions for coadaptation in polymorphism for inversions together with the cost of natural selection, limit the number of cumulatively heterotic gene combinations associated with inversions that may be expected in a population. Dobzhansky and Pavlovsky[32] claim that the inversions in certain populations of *pseudaobscura* are heterotic because of genes with *specific combining ability*, and that different populations differ in this respect so that the same inversions are not necessarily successfully interchangeable between populations. This can hardly be the case in the tremendous populations of *willistoni* with a number of inversions heterozygous in each chromosome for da Cunha *et al.*[20] point out that individuals with the same set of inversions are rare. In *willistoni* inversions must be retained by heterotic genes which have *general* and *cumulative combining ability*. This seems to be the case also in *montana*. Several inversions may be heterozygous in a strain but we do not find consistent heterozygotes between certain gene sequences in a population, so far as our more limited sampling allows us to determine.

The effective uniqueness of each inversion and its loss if it lacks selective advantage (Fisher[21]) allows us to make some interesting calculations about the number of inversions which has been utilized in the evolution of the genus and also

the number which occurred but was lost. Stone[14] estimated the number of inversions fixed in the evolution of the genus using the number fixed per species in the virilis and repleta groups compared to the number heterozygous in those and other groups. The number of variable (heterozygous) inversions then numbered 592 in the 42 species which had been studied. The virilis and repleta groups differ in ratio of fixed to heterozygous inversions from 1.2:1 for the former to 2:1 for the latter, as now determined by Wasserman.[17] The number of species in the genus was earlier estimated at 650 but M. R. Wheeler now estimates that there are two to three times that number. On the basis of the 650 species, the number of inversions fixed in the evolution of the genus was estimated at between 6,100 and 36,500. This was a very conservative estimate as no additional allowance was made for greater cytological differences between than within species groups or subgenera. With the larger number of species now proposed for the genus, the number of paracentric inversion differences fixed in its evolution is probably between 22,000 to 56,000, while perhaps 18,000 to 28,000 are now heterozygous in the many populations around the world. If we assume that the selective advantage of the inversions in their initial struggle to be established was one per cent, this would mean that from 1.1 to 2.8 million inversions with this much selective advantage occurred, but the remainder were eliminated. This leaves the vast majority of inversions, conservatively ten or one hundred times as many, which did not have selective advantage, or were disadvantageous, that also were eliminated. When we remember that inversions are relatively unique events whereas mutations occur and recur time and again, we get some further idea of the tremendous numbers of trials of rearrangements and mutations in different combinations and sequences which have gone into the evolution of even this small genus. These repeated and varied trials with natural selection and time enough to absorb the cost (Haldane[31]) make evolution inevitable, as Fisher[21] pointed out. Wright[33] has reviewed his concepts of the necessity of a balanced array of forces (mutation, selection, population structures, etc.) and of the importance of complex balanced genotypes and their shifts to higher selective peaks. We have presented some evidence on the results of variations in population structure and the tremendous array of variability available through time to make possible the changes necessary to reach more highly adapted genotypes.

Summary.—The virilis group of the genus Drosophila has been revised and extended. Strains of *Drosophila ezoana* from Hokkaido and new strains of *Drosophila montana* from Alaska and Canada have been tested and compared to earlier tests with members of the group. *D. ezoana* is isolated genetically more than any other member of the group. Cytologically it is very close to the postulated Primitive III in gene arrangement and in part validates this postulated ancestral form. The strains of *montana* from Canada extend the known range and cytological variability of this species. The several strains proved to be genetically diverse as had other strains of *montana*. The virilis group consists of nine species. The chromosome phylogeny has been worked out so that we know the lines of evolution and the necessary primitive forms (cytologically) to fill out the phylogeny, Figure 1. *Drosophila virilis* has been demonstrated to be both genetically and cytologically nearest the primitive ancestor of the group. In addition to the normal *virilis* arrangement of genes in the X and the four major autosomes, there are 92 known and

analyzed heterozygous or homozygous inversions in this group (plus 20 to 30 more which are fixed, i.e., homozygous, in the X chromosomes of *Drosophila ezoana, montana, lacicola, and litioralis*). There are 43 analyzed plus these added X chromosome inversions which have been fixed in the evolution of one or another member of this species group. There are now known 49 inversions which are present sometimes in some species but not fixed (plus 2f and 4h which are variable in some species but fixed in others). The amount of cytological variability cannot be predicted from the present population of a species since more unfixed, sometimes heterozygous, inversions occur in *montana* than in *pseudoobscura* but less than in *willistoni*. *Drosophila montana* is much less frequent than the other two species and, like other members of the virilis group, is restricted to the high humidity belt along streams or lakes.

There exist now two extensive chromosome phylogenies in the genus Drosophila where the direction and extent of cytological variation in the evolution of the species has been thoroughly established. These are the virilis group discussed here, consisting of 9 species plus 3 subspecies or varieties (Figure 1) and in addition, there is the remarkable repleta group and its relatives which has been analyzed, particularly by Wasserman. He will soon publish a revised phylogeny which includes now 39 species in the repleta group plus 7 species in closely related groups. The extensive genetic evolution but very conservative cytological evolution has made this possible.

It is most remarkable that only 100 years after Darwin published *The Origin of Species* we have established so many of the genetic mechanisms involved in evolution. Perhaps it is even more remarkable that we have been able to establish the direction and extent of cytological changes in the well-established cytological phylogeny of 9 species in one species group and 46 species in a complex involving several other species groups.

We wish to thank Dr. Eizi Momma who brought us the strains of *Drosophila ezoana* from Hokkaido; Dr. D. D. Miller and Mr. Chris Dahlie, who collected the strains of *Drosophilia montana* in Canada and Alaska; Dr. Marvin Wasserman, who allowed us to include some of his unpublished data on the repleta group; Dr. M. R. Wheeler, who discussed these general problems and checked the manuscript; and Dr. J. F. Crow, who read the manuscript and made several suggestions. Professor J. T. Patterson began the work on the virilis group with us and continues to contribute inspiration and interest in these problems.

* This work was supported by grants from the Rockefeller Foundation, the U.S. Public Health Service, and a contract with the Atomic Energy Commission.

† Present address: Department of Biology, University of Alabama, University, Alabama.

[1] Patterson, J. T., and W. S. Stone, *Evolution in the Genus Drosophila* (New York: The Macmillan Co., 1952).

[2] Painter, T. S., *J. Hered.*, **25**, 465 (1934).

[3] Takada, Haruo, and Toyoki Okada, *Jap. J. Zoo.*, **12**, 133 (1958).

[4] Guest, William C., Unpublished Ph.D. dissertation (1959).

[5] Hsu, T. C., Univ. Texas Pub., No. 5204 (1952), p. 35.

[6] Moorhead, Paul S., Univ. Texas Pub., No. 5422 (1954), p. 106.

[7] Patterson, J. T., Univ. Texas Pub., No. 5204 (1952), p. 7.

[8] *Ibid.*, p. 20.

[9] Sturtevant, A. H., and Th. Dobzhansky, these PROCEEDINGS, **22**, 448 (1936).

[10] Dobzhansky, Th., and A. H. Sturtevant, *Genetics*, **23**, 28 (1938).
[11] Dobzhansky, Th., *Genetics and the Origin of Species* (New York: Columbia University Press, 1951, Third revised edition).
[12] Dobzhansky, Th., *J. Hered.*, **41**, 156 (1950).
[13] Carson, Hampton L., *Evolution*, **8**, 148 (1954).
[14] Stone, W. S., *Cold Spring Harbor Symposia on Quant. Biol.*, **20**, 256 (1955).
[15] Wasserman, Marvin, Univ. Texas Pub. No. 5422 (1954), p. 130.
[16] Wasserman, Marvin, and Florence D. Wilson, Univ. Texas Pub. No. 5721 (1957), p. 132.
[17] Wasserman, Marvin, Unpublished data (1959).
[18] Muller, H. J., in *New Systematics*, ed. Julian Huxley (Oxford, Clarendon Press, 1940), p. 185.
[19] Sturtevant, A. H., and E. Novitski, *Genetics*, **26**, 517 (1941).
[20] Da Cunha, A. Brito, Th. Dobzhansky, O. Pavlovsky, and B. Spassky, *Evolution*, **13**, 389 (1959).
[21] Fisher, Ronald A., *The General Theory of Natural Selection* (New York: Dover Publication, Inc., 1958, 2nd revised edition).
[22] Da Cunha, A. Brito, H. Burla, and Th. Dobzhansky, *Evolution*, **4**, 212 (1950).
[23] Carson, Hampton L., *Cold Spring Harbor Symposia on Quant. Biol.*, **23**, 291 (1958).
[24] Schultz, Jack, and Helen Redfield, *Cold Spring Harbor Symposia on Quant. Biol.*, **16**, 175 (1951).
[25] Mayr, Ernst, in *Evolution as a Process*, ed. Julian Huxley (London: Allen and Unwin, 1954), p. 157.
[26] White, M. J. D., *Australian J. Sci.*, **22**, 32 (1959).
[27] Wharton, Linda T., Univ. Texas Pub. No. 4313 (1943), p. 282.
[28] Spieth, Herman T., *Science*, **113**, 232 (1951).
[29] Stone, Wilson S., Mary L. Alexander, and Frances E. Clayton, Univ. Texas Pub. No. 5422 (1954), p. 272.
[30] Haldane, J. B. S., *J. Gen.*, **55**, 218 (1957).
[31] *Ibid.*, **55**, 511 (1957).
[32] Dobzhansky, Th., and Olga Pavlovsky, *Evolution*, **7**, 198 (1953).
[33] Wright, Sewall, *Cold Spring Harbor Symposia on Quant. Biol.*, **20**, 16 (1955).

---

*SOME HOLOMORPHIC SEMI-GROUPS**

R. P. LANGLANDS

DEPARTMENT OF MATHEMATICS, YALE UNIVERSITY

Communicated by Einar Hille, January 25, 1960

In this note we state some basic spectral properties of a class of operators associated with a representation of a Lie group. We merely indicate the proofs since we intend to give details in another context.

Let $T(.)$ be a strongly continuous representation of the Lie group $\mathfrak{G}$ in the Banach space $\mathfrak{X}$. For a in $\mathfrak{A}$, the Lie algebra of $\mathfrak{G}$, let $A(a)$ be the infinitesimal generator of the one-parameter group, $T(exp(ta))$, $-\infty < t < \infty$, and let $A^*(a)$ be the adjoint of $A(a)$. It is known that

$$\mathfrak{W}_k = \{x \epsilon \mathfrak{X} \,|\, x \epsilon \text{Domain}(A(a_1) \ldots A(a_k)) \text{ for all } a_1, \ldots, a_k \epsilon \mathfrak{A}\}$$

is dense in X and that

$$\mathfrak{W}_k{}^* = \{x^* \epsilon \mathfrak{X}^* \,|\, x^* \epsilon \text{ Domain } (A^*(a_1) \ldots A^*(a_k)) \text{ for all } a_1, \ldots, a_k \epsilon \mathfrak{A}\}$$

is dense in $\mathfrak{X}^*$ in the weak* topology. Let $\{e_1, \ldots, e_n\}$ be a basis for $\mathfrak{A}$ and set $A_i =$

$A(e_i)$, $A_i^* = A^*(e_i)$. If $\alpha = (\alpha_1, \ldots, \alpha_k)$, $1 \leq \alpha_i \leq n$, is a sequence of integers we denote a product such as $A_{\alpha_1} \ldots A_{\alpha_k}$ by A_α; $|\alpha| = k$ is the length of α. The operator $B^\circ = \Sigma_{|\alpha| \leq m} a_\alpha A_\alpha$ (the coefficients are complex numbers) is defined on $\mathfrak{W}_m$ and, denoting α in reversed order by α^*, the operator $\tilde{B}^\circ = \Sigma_{|\alpha| \leq m} a_\alpha A^*_{\alpha^*}$ is defined on $\mathfrak{W}_m{}^*$. The closure B of B° and the weak* closure $\tilde{B}$ of $\tilde{B}^\circ$ are well-defined operators. If for any real n-vector, $\xi = (\xi_1, \ldots, \xi_n)$, $|\Sigma_{|\alpha| \leq m} a_\alpha \xi_\alpha| \geq \rho \|\xi\|^m$ ($\rho > 0$ is fixed and $\|\xi\|$ is the ordinary Euclidean norm) then

THEOREM 1. *The adjoint B^* of B is $\tilde{B}$.*

To prove this we observe that if $B^* x_1^* = x_2^*$ then,[1] for x in $\mathfrak{X}$, $x_1^*(T(g)x)$ is a weak solution of the equation

$$\Sigma_{|\alpha| \leq m} a_\alpha R_{\alpha^*}\{x_1^*(T(g)x)\} = x_2^*(T(g)x);$$

R_i is the infinitesimal transformation

$$R_i f(g) = \lim_{t \to 0} t^{-1} \{f(\exp(te_i)g) - f(g)\}.$$

We use the properties of weak solutions of elliptic equations to show that x_1^* is in $\mathfrak{W}_{m-1}{}^*$ and then apply an adaptation[2] of the mollifier technique.

If the stronger condition

$$(-1)^{j-1} \mathrm{Re}\{\Sigma_{|\alpha| \leq m} a_\alpha \xi_\alpha\} \geq \rho \|\xi\|^m,$$

with $2j = m$, is fulfilled then

THEOREM 2. *The operator* B *is the infinitesimal generator of a semi-group,* S(t), *of class $H(\phi_1, \phi_2)$, for some ϕ_1 and ϕ_2.*[3]

The theorem is equivalent to an inequality $\|R(\lambda, B)\| \leq M/[\rho(\lambda, S)]$ for the norm of the resolvent of B; M is a constant and $\rho(\lambda, S)$ is the distance of λ from a sector

$$S = \{\zeta \,|\, \psi_2 \leq \arg(\zeta - \zeta_0) \leq \psi_1\}, \quad \frac{\pi}{2} < \psi_2 \leq \pi \leq \psi_1 < 3\pi/2.$$

To obtain the inequality we observe that

$$x^*(T(g)(B - \lambda)x) = \Sigma_{|\alpha| \leq m} a_\alpha L_\alpha x^*(T(g)x) - \lambda x^*(T(g)x),$$

with

$$L_i f(g) = \lim_{t \to 0} t^{-1}\{f(g \exp(te_i)) - f(g)\};$$

partially invert this equation in a neighborhood of the identity using a parametrix; and then establish appropriate estimates[4] for the parametrix. It is of interest to note that if a_α is real when $|\alpha| = m$, $S(t)$ is holomorphic in a half-plane.

The semi-groups, $S(t)$, have a canonical representation. Let μ be a left-invariant Haar measure on $\mathfrak{G}$, then

THEOREM 3. *There is a unique function* h(t, g) (*defined for* t *in an open sector containing* $(0, \infty)$) *in* $L_1(\mu)$ *for each* t *and such that for all representations* T(.) *of* $\mathfrak{G}$

$$S(t)x = \int_{\mathfrak{G}} h(t, g) T(g) x \mu(dg).$$

The integral is a Bochner integral and $h(t, g)$ is analytic in t and g. We remark finally that, when t is in the interior of the domain of $S(.)$ and x is in X, $S(t)x$ is an analytic vector.

The above results generalize theorems of Nelson[5] and Nelson and Stinespring.[1]

* Research supported by the Office of Ordnance Research under contract SAR-DA-19-020-ORD-5074. The author thanks C. T. Ionescu Tulcea for his advice during the preparation of this paper.

[1] Nelson, E., and W. F. Stinespring, *Amer. J. Math.*, **81**, 547–560 (1959).

[2] Langlands, R. P., *On Lie Semi-Groups* (submitted to *Canad. J. Math.*).

[3] For terminology see Hille, E., and R. S. Phillips, *Functional Analysis and Semi-Groups*.

[4] These are essentially estimates for the resolvents of strongly elliptic differential operators with constant coefficients and are obtained from estimates for the fundamental solution of the associated parabolic equation similar to those of Silov G. E., (*Usp. Mat. Nauk.*, **10**, 89–100 (1955)).

[5] *Ann. Math.*, **70**, 572–615 (1959).

---

*THE EXTENT OF ASYMPTOTIC STABILITY**

By J. P. LaSalle

RIAS, BALTIMORE

Communicated by S. Lefschetz, January 8, 1960

In studying the stability of a system it is never completely satisfactory to know only that an equilibrium state is asymptotically stable or for that matter to know only that it is unstable. In a mathematical sense it may be asymptotically stable but from a practical point of view be unstable, and, conversely, it may be mathematically unstable but practically stable. Both stability and instability are local concepts. An equilibrium state of a system may be unstable, and yet it may be true that the system always tends to return, perhaps not to the equilibrium state itself, but sufficiently near the equilibrium state. An equilibrium state can be asymptotically stable and yet perturbations which would be considered small compared to the perturbations to be expected may cause the system to drift away from the equilibrium never to return. As a practical matter, it is necessary to have some idea of the size of the region of asymptotic stability. It is never possible to do this by examining only the linear approximation to the system. The effect of nonlinearities must be taken into account, and Liapunov's stability method[1] provides a means of doing this. The purpose of this paper is to report some mathematical theorems that underlie methods for estimating regions of asymptotic stability. These methods, with examples illustrating them, are to be discussed elsewhere in greater detail.[2]

The system whose stability is being investigated is described by the vector differential equation

$$\dot{x} = X(x). \tag{1}$$

The state of the system at time t is an n-vector $x(t) = (x_1(t),. . .,x_n(t))$. The phase velocity $dx/dt = \dot{x}$ is defined by the vector field $X(x) = (X_1(x),. . .,X_n(x))$. For each initial state x° we assume there is a unique solution $x(t)$ of (1) satisfying $x(0) = x^\circ$, and that this solution depends continuously on the initial state x°. The equilibrium state being investigated is at the origin: $X(0) = 0$. The Liapunov method depends upon the construction of a suitable domain Ω and a suitable

Liapunov function $V(x)$, which is a kind of generalized energy function. We assume throughout that $V(x)$ has continuous first partials in Ω. With reference to the system (1), we define

$$\dot{V}(x) = \frac{\partial V}{\partial x_1} X_1 + \ldots + \frac{\partial V}{\partial x_n} X_n = (\text{grad } V) \cdot X.$$

If $x(t)$ is a solution of (1), then

$$\frac{d}{dt} V(x(t)) = \dot{V}(x(t)).$$

No knowledge of the solutions of (1) is required to compute $\dot{V}(x)$. It is computed directly from a knowledge of the differential equations which describe how the system changes. The difficulty lies in constructing $V(x)$. This requires experience and technique—a technique in which Russian mathematicians and engineers excel. The theorems stated below describe what are suitable Liapunov functions for determining the extent of asymptotic stability. The basic result is

THEOREM 1. *Let Ω be a bounded closed set with the property that every solution of (1) starting in Ω remains for all future time in Ω. Suppose there is a scalar function $V(x)$ with the property that $\dot{V}(x) \leqq 0$ in Ω. Let E be the set of all points in Ω where $\dot{V}(x) = 0$. Let M be the largest invariant set in E. Then every solution starting in Ω approaches M as $t \to \infty$.*

In some instances the construction of a Liapunov function $V(x)$ will itself guarantee the existence of a set Ω. For instance,

THEOREM 2. *Let Ω denote the closed region defined by $V(x) \leqq l$. If, in addition Ω is bounded and $\dot{V}(x) \leqq 0$ in Ω, then every solution starting in Ω approaches M as $t \to \infty$. (M is set defined in Theorem 1.)*

Note with regard to Theorem 2 that if $V(x) \to \infty$ as $||x|| \to \infty$, then the set Ω defined by $V(x) \leqq l$ is bounded for all values of l. If $\liminf_{\|x\| \to \infty} V(x) = l_0$, then Ω is bounded for all $l < l_0$.

Thus, under suitable circumstances, the set Ω is an estimate of the region of asymptotic stability. According to Theorem 1 the procedure is to find a region Ω and a suitable function $V(x)$. If $\dot{V}$ does not vanish identically along any solution starting in Ω except the origin, then every solution in Ω approaches the origin at $t \to \infty$. It seems in some examples to be easier to separate the problems of finding Ω and constructing a Liapunov function $V(x)$ although as Theorem 2 points out the Liapunov function itself may determine Ω.

If the origin is stable and every solution approaches the origin as $t \to \infty$, then the system is said to be *completely stable* (asymptotically stable in the large). The region of asymptotic stability is the whole space. The basic theorem leading to methods for establishing complete stability is

THEOREM 3. *Let $V(x)$ be a scalar function with continuous first partials for all x. Assume that*

i. $V(x) > 0$ *for all* $x \neq 0$
ii. $\dot{V}(x) \leqq 0$ *for all* x.

Let E be the set of all points where $\dot{V}(x) = 0$ and let M be the largest invariant set contained in E. Then every solution bounded for $t > 0$ approaches M as $t \to \infty$.

To establish the complete stability of a system one needs (i) to establish that all solutions are bounded for $t \geqq 0$ and (ii) to construct a function $V(x)$ satisfying the conditions of Theorem 3 and such that M is the origin. Here again one may be able to conclude from the Liapunov function $V(x)$ itself that all solutions are bounded for $t \geqq 0$. This is true, for instance, if $V(x) \to \infty$ as $||x|| \to \infty$, although it often is easier to consider (i) and (ii) as separate problems. Boundedness is a type of stability and can itself be investigated by Liapunov methods.[3]

* This research was partially supported by the United States Air Force through the Air Force Office of Scientific Research of the Air Research and Development Command, under Contract Number AF 49(638)-382. Reproduction in whole or in part is permitted for any purpose of the United States Government.

[1] Among the available references on Liapunov's method may be mentioned, (*a*) Hahn, W., *Theorie und Anwendung der Direckten Methode von Ljapunov* (Berlin: Springer-Verlag, 1959). (*b*) Antosiewicz, H. A., "A survey of Liapunoc's second method," in *Contributions to the Theory of Nonlinear Oscillations IV*, Annals of Math. Studies No. 41 (Princeton University Press, 1958). (*c*) Cesari, L., *Asymptotic Behavior and Stability Problems in Ordinary Differential Equations* (Berlin: Springer-Verlag, 1959). (*d*) Malkin, I. G., *Theory of Stability of Motion*, AEC Translation Series, AEC-t-3352 (translated from a publication of the State Publishing House of Technical-Theoretical Literature, Moscow-Leningrad, 1952).

[2] In a paper by the author to appear in the latter part of 1960 in a Special Nonlinear Issue of the *Proc. of the IRE*.

[3] This has been studied extensively by Taro Yoshizawa. See his paper on "Liapunov's Function and Boundedness of Solutions," *Funkcialaj Ekvacioj* **2**, 95–142 (1959).

---

*VIRUS-CELL INTERACTION WITH A TUMOR-PRODUCING VIRUS**

BY MARGUERITE VOGT AND RENATO DULBECCO

DIVISION OF BIOLOGY, CALIFORNIA INSTITUTE OF TECHNOLOGY

Communicated by George W. Beadle, January 18, 1960

The polyoma(PY) virus or parotid tumor agent[1, 2]—a DNA-containing virus[3, 4]—is characterized by a duality of action: it produces neoplasias of various types in different species of rodents,[5] and causes cell degeneration in mouse embryo tissue cultures.[6] In the experiments to be reported here, it was possible to obtain in cellular cultures *in vitro* the oncogenic effect of the virus; this afforded the possibility of studying the relationship between the oncogenic and cytocidal effect of the virus. The results so far obtained reveal a situation novel in animal viruses and suggest the existence of a host-virus interaction with characteristics reminiscent of temperate bacteriophage.

Material and Methods.—The PY virus was obtained from Dr. Rowe of the National Institutes of Health. A stock was prepared from a single plaque and serial passages of this stock in mouse embryo tissue cultures were used for the experiments. In these passages, the virus maintained both the cytocidal activity in mouse embryo tissue cultures and the property of eliciting heart, liver, and kidney sarcomas within a few weeks after injection into newborn Golden hamsters. The virus was assayed by plaque formation on mouse embryo monolayer cultures by means of the technique previously described.[7]

Cultures from trypsinized whole embryos of either Swiss mice or Golden hamsters were prepared as previously described.[7] All experimental cultures were secondary cultures at the time of the first exposure to the virus. Plaque assays were done on monolayer cultures of mouse embryo cells which had been serially transferred two to five times. The growth medium for the cells consisted of reinforced Eagle's medium[8] supplemented with 20 per cent calf serum. Experimental cultures were grown in Eagle's medium supplemented with 10 per cent calf, horse, or fetal bovine serum, as indicated later.

Results.—The multiplication of the virus: Confluent monolayer cultures of either mouse or hamster cells were infected with virus at a multiplicity of about 10 mouse plaque-forming units per cell. After an adsorption period of forty minutes, the layers were washed to remove most of the non-adsorbed virus, and were covered

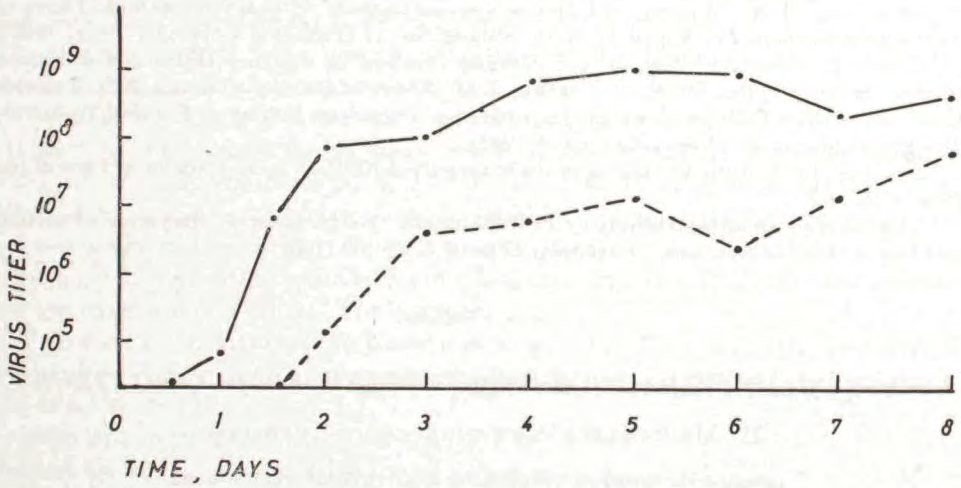


FIG. 1.—Extra-plus intracellular virus per culture at various times after infection.——Mouse embryo culture. – – – Hamster embryo culture. Fluid changes were done on the third and sixth day after infection. The growth medium was Eagle's medium supplemented with 10 per cent horse serum.

with Eagle's medium supplemented with 10 per cent of either calf, horse, or fetal bovine serum. The cultures were subsequently incubated at 37°C and the virus in the supernatants and in the cells (after disruption by three cycles of freeze-thawing) determined at various time intervals.

The growth curves obtained are reported in Figure 1, where the titer of intra-plus extracellular virus per culture is given. The curves show a long latent period, as found for another tumor-producing virus, the Rous virus.[9] The virus production was initially much greater in the mouse cultures; after about a week the difference decreased. At that time, however, the hamster cultures, which had continued to grow, contained many more cells than the mouse cultures, so that the average production of virus per cell was always much smaller in the hamster cultures.

Early behavior of the infected cultures (first week): The mouse cultures appeared unchanged for the first day after infection. Infected cultures containing a number of cells sufficiently low to allow the counting of the cells *in situ* showed after 24 hours a threefold increase in cell number, equal to that of uninfected cultures. The

cell number stopped increasing on the second day after infection. Degenerative changes became visible in the majority of the cells during the third and fourth day, simultaneously with the increase in virus titer. A proportion (about 20%) of the cells, however, remained unaltered as already observed by using fluorescent antibodies.[10] These unaltered cells multiplied in the subsequent days—in fact, frequent mitoses were observed—while more cells underwent degeneration: a balance of these two processes maintained the culture in a steady state.

The hamster cultures, in contrast, continued to increase in cell number during the whole week after infection. Cell counts on parallel cultures with lower cell concentrations showed no difference in the division rate of infected and control cultures for six days of observation. Neither did the infected hamster cultures show obvious signs of degeneration. Since, by plating the cells several hours after infection, most cells proved to be virus-yielders, it must be concluded that they released virus in small quantities without degeneration.

Late behavior of the infected cultures: The mouse cultures remained in the steady state for about four weeks. During this period the virus titer in the supernatants remained constant at a level of about 10^8 PFU per culture, in spite of the fluid changes. This prolonged existence of the steady state in the cultures is by itself of special interest and is being investigated in greater detail. The observations can, at present, be interpreted as follows: It is unlikely that the multiplying cells belonged to a virus-resistant type which was originally present in the culture, since such cells would have replaced the sensitive cells in a few days. It is also unlikely that the multiplying cells represented either partly resistant cells—like those occurring in several virus-carrying cultures of poliovirus[11] and Newcastle disease virus[12]—or a non-infected fraction of sensitive cells. In both cases, in fact, they would have been infected after a few days by the progeny virus accumulating in the medium in large amounts. It is therefore concluded that the surviving cells are infected cells which do not undergo degeneration. The conclusion that the surviving cells are altered cells is also indicated by the finding that all cells of a mouse embryo culture infected with PY virus become resistant to vesicular stomatitis virus.[10] It seems, furthermore, that the cells carry the virus in a state in which the fate of the virus-cell complex is undetermined (see below). Cells containing the virus in this "uncommitted" state can divide but have a considerable chance of being killed by a shift of the virus to the state of extensive, cytocidal multiplication.

A gradual change was observed in the mouse cultures after four weeks. The proportion of degenerating cells decreased significantly together with the titer of intra- and extracellular virus of the cultures. The cell number increased and weekly transfers became possible. The outgrowing cells were of a new type, more elongated than the original cells and with a tendency to form interwoven net-like structures when the cultures became more crowded. Ten weeks after infection, the cultures appeared to be made up entirely of the new cell type. They could be transferred twice weekly, contained no more degenerating cells than normal ones, and produced little virus.

The hamster cultures, at the end of the first week after infection, were made up of a single dense layer of cells indistinguishable from the controls. During the second week a striking difference between the infected and control cultures became apparent. Whereas the number of cells in the control cultures appeared to increase

only slightly during this time, the infected cultures continued to increase in cell number to a value approximately three times that of the control cultures. This led to strong acidification of the medium of the infected cultures. The new cells were more elongated than the control cells and had a tendency to grow in interwoven netlike structures similar to those described above for the infected mouse cells. Whorls of heavy cell strands became noticeable above the continuous cell layer in the infected cultures, but not in the control cultures.

After fourteen days, the cultures were dispersed with trypsin for injection into animals (see below), or for further transfers. No difference between the growth rate of control and infected cultures was observed during the first week after the transfer. In the second week after the transfer, however, whorls of heavy cell strands again appeared in the infected cultures but not in the control cultures; at the same time the medium became strongly acidified. The virus titer decreased drastically in the transformed cultures. Frequently no extra- or intracellular virus could be detected; in other cases titer of 10^3 PFU or less per 10^6 cells were obtained.

This proliferative response in hamster embryo cells to PY virus was first observed in experiments carried out in collaboration with Dr. G. Freeman. It has since been observed and followed in four independent experimental series, occurring in calf or fetal bovine serum medium but not in horse serum medium. The proliferative response failed to appear in two other experimental series. The observations tend to show that the occurrence of a proliferative response depends on the physiological state of the cells at the moment of infection, a point which is under further investigation.

Nature of the transformed cells: As to the nature of the new cells which became established both in infected mouse and hamster cultures, it is unlikely that they were originally present; in fact, no selective conditions favoring multiplication of such cells were present in the hamster cultures in which no cell destruction took place. It is more likely that these new cells were cells of the original type transformed or converted by the virus. Since the transformed cells of the mouse cultures became established in the presence of high virus concentrations, it can furthermore be assumed that these cells are resistant to superinfection with PY virus. This conclusion is also supported by the fact that superinfection of transformed hamster cells with PY virus failed to give evidence of virus production during the first week after infection.

The ability of the transformed cells to grow under conditions unfavorable to the growth of the control cells suggested that they were of neoplastic nature. To test this possibility, 10^6 to 4×10^6 cells of six independently transformed hamster embryo cultures were inoculated under the skin of 18–20 day old hamsters. All six cultures gave rise to tumors at the site of inoculation; five tumors were palpable six days, one tumor two weeks, after the inoculation. All six tumors grew progressively without any signs of regression. In three cases, the animals were killed when the neoplasias had reached a diameter of about 3 cm. The neoplasias were well localized; no metastases or tumors at other locations were found. Histologically, the neoplasias were constituted by fusiform cells. Fragments of the tumors were trypsinized, and tissue cultures were prepared from the cell suspensions. The outgrowing tumor cells formed whorls similar to those of the original cultures whenever the cell layers became crowded. Frequently no virus or only very small

amounts (100 PFU per 10^6 cells) of virus could be demonstrated in these cultures.

As controls, more than sixty hamsters of the same age were inoculated with 10^6 to 10^7 cells of uninfected hamster embryo cultures from the same culture batches in which the transformed cultures had been contained. In none of the hamsters were nodules formed. Four infected cultures in which no *in vitro* transformation had been observed likewise failed to induce tumor formation in the animal. Neither did ten hamsters inoculated with 5×10^7 to 10^8 PFU of PY virus form any tumors at the site of inoculation. The hamsters are still alive and it is therefore unknown whether they formed tumors of the organs normally affected by PY virus.

Conclusions.—In these experiments, the PY virus gave rise to two types of virus-cell interaction: a cytocidal interaction, leading to extensive virus synthesis and cell degeneration, and a moderate interaction leading to the transformation of the cells into neoplastic cells, usually unable to produce detectable virus and resistant to superinfection with the same virus. The cytocidal interaction is most frequent in the mouse cultures, the moderate interaction in the hamster cultures. The different reactions of the mouse and hamster cultures reproduce and clarify the events occurring in the animal: it is in fact known that in the newborn mouse the virus produces extensive cell degeneration and only later—after several months—tumors; whereas in the newborn hamster the virus produces few degenerative phenomena but within a few weeks leads to formation of tumors. The results obtained extend those of Dawe and Law[13] in showing that differences in virus-cell interaction explain the various effects of the virus in the animal, including the disappearance of the virus from hamster tumors.[14, 15, 16]

The following hypothesis is put forward to explain the results of our experiments: upon entering a cell, the virus assumes an "uncommitted" state in both hamster and mouse cells, during which it may undergo a limited multiplication without appreciably affecting the normal properties of the cell. From this "uncommitted" state, the virus has the choice of entering either the state of cytocidal multiplication or the integrated state. The late transformation of the mouse cultures would be due to the selection of a few transformed cells. In the hamster cultures, on the other hand, the choice would be almost exclusively toward the integrated state, both in the animal and in the tissue culture.

The state of the virus in the transformed cells is unknown. Two properties of cultures of these cells, i.e., the absence or low level of virus production and the resistance to superinfection, are similar to the properties of lysogenic bacterial cultures and suggest that the integrated virus exists as provirus. Other hypotheses are, however, not excluded: the virus could ultimately be lost from the transformed cells and resistance to superinfection could be a secondary consequence of the transformation.

The transformed, neoplastic cells are able to grow above the monolayer to which the normal cells are usually confined. This suggests that *in vitro* the normal cells are still subjected to growth-regulating mechanisms from which the transformed cells can escape. This property of PY-transformed cells, which is also characteristic of cells transformed by the Rous virus, may be general for neoplastic cells *in vitro;* if so, it may open a wider approach to the study of neoplasia-producing viruses.

These experiments will be reported in detail elsewhere.

* Aided by grants from the National Foundation and from the American Cancer Society, Inc.

[1] Gross, L., *Proc. Soc. Exp. Biol. Med.*, **83**, 414–421 (1953).

[2] Stewart, S. E., *Anat. Rec.*, **117**, 532 (1953).

[3] DiMayorca, G. A., B. E. Eddy, S. E. Stewart, W. S. Hunter, C. Friend, and A. Bendich, these PROCEEDINGS, **45**, 1805–1808 (1959).

[4] Smith, J., M. Vogt, G. Freeman, and R. Dulbecco (to be published).

[5] Stewart, S. E., B. E. Eddy, and M. F. Stanton, *Proc. Can. Canc., Conf.*, **3**, 287–305 (1959).

[6] Eddy, B. E., S. E. Stewart, and W. H. Berkeley, *Proc. Soc. Exp. Biol. Med.*, **98**, 848–851 (1958).

[7] Dulbecco, R., and G. Freeman, *Virology*, **8**, 396–397 (1959).

[8] Fourfold concentration of amino acids and vitamins.

[9] Temin, H. M., and H. Rubin, *Virology*, **8**, 209–222 (1959).

[10] Henle, G., F. Deinhardt, and J. Rodriguez, *Virology*, **8**, 388–391 (1959).

[11] Vogt, M., and R. Dulbecco, *Virology*, **5**, 425–434 (1958).

[12] Puck, Th.T., and S. J. Cieciura, *Symp. Latency and Masking in Viral and Rickettsial Infection* (Burgess, 1957).

[13] Dawe, C. J., and L. W. Law, *J. Nat. Canc. Inst.*, **23**, 1157–1177 (1959).

[14] Habel, K., and P. Atanasiu, *Proc. Soc. Exp. Biol. Med.*, **102**, 99–102 (1959).

[15] Negroni, G., R. Dourmaskin, and F. C. Chesterman, *Brit. Med. J.* 1359–1360 (1959).

[16] Sachs, L., and E. Winocour, *Nature*, **184**, 1702–1704 (1959).

THE STABILITY OF NON-DISSIPATIVE COUETTE FLOW IN THE PRESENCE OF AN AXIAL MAGNETIC FIELD

BY W. H. REID

BROWN UNIVERSITY

Communicated by S. Chandrasekhar, January 18, 1960

1. The effect of an axial magnetic field on the stability characteristics of Couette flow in the limiting case of zero viscosity and infinite conductivity has been examined recently by Chandrasekhar.[1] He showed that an adverse gradient of angular velocity can always be stabilized by a sufficiently strong magnetic field and that the required field strength can be derived from the solutions of the related nonmagnetic problem. Within the framework of the "small gap" approximation, the nonmagnetic problem has recently been solved exactly,[2] and in this paper, therefore, we present a determination of the magnetic field strength required to completely stabilize the flow.

2. In the small gap approximation it is assumed that the gap, $d = R_2 - R_1$, is small compared to the mean radius, $R_0 = {}^1/_2 (R_2 + R_1)$. The angular velocity distribution can then be approximated by the linear profile

$$\Omega = \Omega_1 [1 - (1 - \mu)\zeta], \tag{1}$$

where

$$\mu = \Omega_2/\Omega_1 \quad \text{and} \quad \zeta = (r - R_1)/d. \tag{2}$$

In the absence of a magnetic field, Rayleigh's criterion shows that the angular velocity distribution (1) is unstable for $\mu < 1$ and we wish to determine, therefore, the magnetic field strength required to stabilize the flow under these conditions.

3. By considering an axisymmetric perturbation of the velocity distribution (1) whose t- and z-dependence is of the form

$$\exp [i(pt + kz)], \tag{3}$$

we find that the linearized equation for v, the radial component of the perturbed velocity, can be reduced to the form

$$\left(p^2 - \frac{H^2}{4\pi\rho} k^2\right)(D^2 - a^2)\, v = 2\,\Omega_1^2\,(1 - \mu)\,\frac{R_0}{d}\,a^2[1 - (1 - \mu)\zeta]v, \tag{4}$$

where

$$a = kd \qquad \text{and} \qquad D = d/d\zeta. \tag{5}$$

In equation (4), the magnetic permeability has been set equal to 1 to avoid confusion with the present use of μ to denote the ratio of angular velocities of the cylinders. The boundary conditions are

$$v = 0 \text{ at } \zeta = 0 \text{ and } 1. \tag{6}$$

For the related nonmagnetic problem, we have the equation

$$(D^2 - a^2)\, v = -a^2\lambda[1 - (1 - \mu)\zeta]v \tag{7}$$

with

$$\lambda = -2\,\Omega_1^2(1 - \mu)\,R_0/d. \tag{8}$$

Thus, if the characteristic values $\lambda(a;\ \mu)$ of equation (7) are known, then the solution of equation (4) can be written in the form

$$p^2 = k^2\left[\frac{H^2}{4\pi\rho} - \frac{2\Omega_1^2(1 - \mu)R_0 d}{a^2\lambda(a;\ \mu)}\right]. \tag{9}$$

From the solution of equation (7), which can be expressed quite easily in terms of Airy functions, it is found that for all positive characteristic values of λ, $a^2\lambda$ is a monotonic increasing function of a. Accordingly, if we let

$$\Lambda(\mu) = (1 - \mu)\lim_{a\to 0}\frac{1}{a^2\lambda(a;\ \mu)}, \tag{10}$$

then the minimum field strength, H_{min}, required to stabilize the flow is given by

$$\frac{H_{min}^2}{4\pi\rho} = 2\,\Omega_1^2 R_0\, d\,\Lambda(\mu). \tag{11}$$

4. For small values of $1 - \mu$, $\Lambda(\mu)$ has the linear behavior

$$\frac{\Lambda(\mu)}{\frac{1}{2}(1 + \mu)} = \frac{1 - \mu}{n^2\pi^2}\,[1 + O(\epsilon^2)], \tag{12}$$

where

$$\epsilon = \frac{1 - \mu}{\frac{1}{2}(1 + \mu)} \tag{13}$$

and $n = 1, 2, \ldots$ denotes the mode. For large values of $1 - \mu$, it has the asymptotic behavior

$$\Lambda(\mu) \sim \frac{1}{(-x_n)^3 (1 - \mu)}, \tag{14}$$

where x_n are the zeros of the Airy function $\mathrm{Ai}(x)$ in Miller's notation[3] and $n = 1, 2, \ldots$ again denotes the mode. For values of $1 - \mu$ intermediate between these two extremes, one must employ the detailed solution of equation (6).

5. For the lowest mode of instability ($n = 1$), an evaluation of $\Lambda(\mu)$ from the exact solution of equation (7) leads to the results shown in Figure 1. These results would not appear to be unreasonable when we recall that for $1 - \mu < 0$ the flow

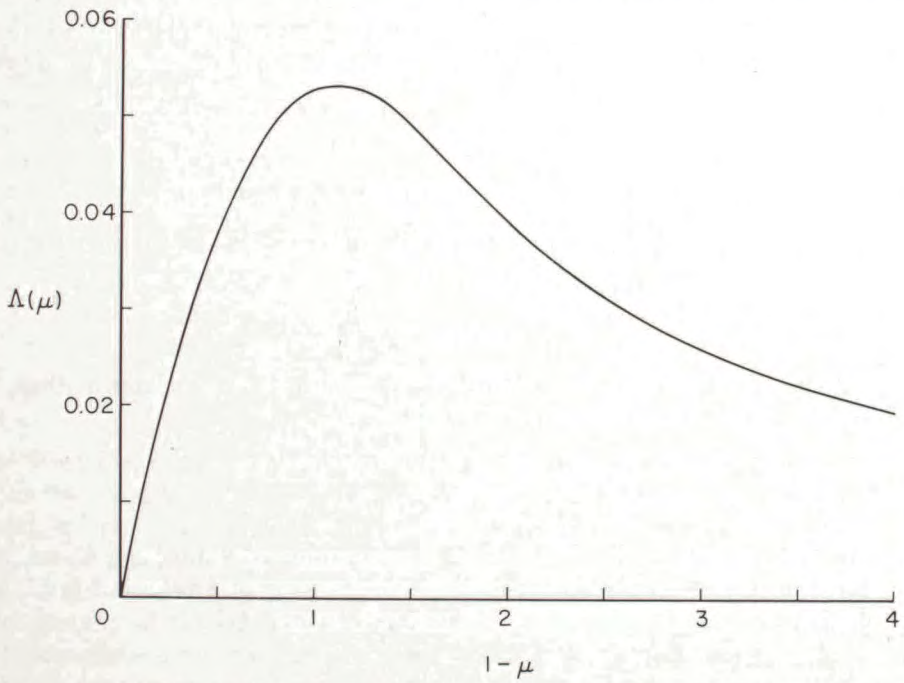


FIG. 1.—The behavior of $\Lambda(\mu) = (H_{\min.}^2/4\pi\rho)/(2\Omega_1^2 R_0 d)$ for the first mode of instability ($n = 1$).

is already stable in the absence of a magnetic field and that for large values of $1 - \mu$ the region of instability is confined to a narrow region adjacent to the inner cylinder. Thus, for both small and large values of $1 - \mu$, the magnetic field strength required to stabilize the flow becomes vanishingly small.

From Figure 1 it is seen that there exists a critical value of the magnetic field strength which is just sufficient to stabilize the flow for arbitrary rates of rotation. This critical value of the field strength is

$$\frac{H_{cr}^2}{4\pi\rho} = 0.1063\ \Omega_1^2\ R_0\ d \tag{15}$$

and occurs for

$$1 - \mu_{cr} = +\ 1.1275. \tag{16}$$

The ratio of $H^2/4\pi\rho$ to $\Omega_1^2 R_0 d$ is a measure of the relative importance of magnetic and inertia forces. The result (14) shows, therefore, that if this ratio exceeds the critical value of 0.1063, then the flow will always be stable.

I am indebted to Professor S. Chandrasekhar for some helpful comments. This work was supported by the Office of Naval Research.

[1] Chandrasekhar, S., "The Stability of Non-Dissipative Couette Flow in Hydromagnetics," these PROCEEDINGS, **46**, 253–257 (1960); see also Velikhov, E. P., "Stability of an ideally conducting liquid flowing between cylinders rotating in a magnetic field," *Soviet Phys.—JETP*, **36**, 995–998 (1959).

[2] Reid, W. H., "Inviscid modes of instability in Couette flow," *J. Math. Anal. and Applications* (to appear).

[3] Miller, J. C. P., *The Airy integral, giving tables of the solutions of the differential equation* $y'' = xy$, *British Association Mathematical Tables*, Part B (Cambridge: The University Press, 1946).

---

*EXCESSIVE GROWTH OF THE SYMPATHETIC GANGLIA EVOKED BY A PROTEIN ISOLATED FROM MOUSE SALIVARY GLANDS**

BY RITA LEVI-MONTALCINI AND BARBARA BOOKER

DEPARTMENT OF ZOÖLOGY, WASHINGTON UNIVERSITY, ST. LOUIS

Communicated by Viktor Hamburger, January 4, 1960

The discovery that mouse sarcomas produce a diffusible agent which selectively promotes the growth of the sensory and sympathetic ganglia in the chick embryo,[1, 2] confronted us with three major problems: (*a*) the characterization of the growth agent, (*b*) the analysis of its mode of action on the embryonic nerve cells which were increased in number and in size under the impact of the agent to an extent unmatched by any previous experimental device, and (*c*) the question of the significance and distribution of nerve-growth agents in tumors and other tissues.

These problems were investigated using the method of explanting embryonic ganglia *in vitro* together with the tumor or other tissues to be tested. The finding that fragments of tumor explanted in proximity to the ganglia elicited exuberant nerve fiber outgrowth, and that this effect is apparent within 5–6 hours, greatly speeded up and simplified the bio-assaying procedures, thus making possible the biochemical approach to our problem.[3] The isolation of a nerve-growth promoting protein fraction from the neoplastic tissue was the first step in this direction.[4] In experiments aimed at the further characterization of the nature of the agent, Cohen made use of snake venom as a source of proteolytic enzymes. This led to the discovery that the snake venom also contains a nerve-growth promoting factor which replicates in all respects the effects of mouse sarcomas on the sensory and sympathetic ganglia of the chick embryo *in vitro* and *in vivo*.[5, 6] Since the snake venom is produced in a modified salivary gland, the mouse salivary glands were tested as another possible source of the nerve-growth promoting factor. The extract of the mouse submaxillary glands proved to contain a nerve-growth promoting agent even more potent than the two mentioned above.[7, 8] It was found that this agent likewise promotes the growth of the sensory and sympathetic embryonic ganglia of the chick

embryo, leaving other systems unaffected. The similarity extends also to other facets of the phenomenon such as the massive neurotization of the viscera of the chick embryo. The potency of this factor, its ready availability, its presence in various tissues of different vertebrates, suggested an investigation of its effects on a wider scale. In all previous experiments the chick embryo was the test object. We have now investigated the effects of the nerve-growth factor in mammals. The results of *in vitro* experiments on mouse and rat sensory and sympathetic ganglia were reported.[7, 8] We will report in this paper the results of *in vitro* effects on human fetal ganglia and of *in vivo* experiments on the sympathetic ganglia of newborn, young, and adult mice. We will also report on experiments designed to establish the relationship between salivary glands and nerve-growth agents. In a second paper, we will present evidence of the near-total disintegration of the sympathetic ganglia in mammals as a result of daily injections of the antiserum to the nerve-growth factor. The agents used in all these experiments were prepared by Dr. S. Cohen and they are described by him in another paper in this issue.

In vitro Effects on Sensory and Sympathetic Ganglia of Human Fetuses.—Four human fetuses, three about two-and-a-half months old and one about three-and-a-half months old, were obtained from the Medical School of Washington University. They resulted from hysterotomy for therapeutic abortion and were made available as soon as delivered.† The sensory and sympathetic ganglia of these fetuses were explanted in tissue culture: the same hanging drop technique was used as in all previous experiments.[3, 5, 7] The medium consisted of one part of chicken plasma, one part of synthetic medium, and one part of the purified salivary fraction. Control cultures were prepared using one drop of physiological solution instead of the salivary fraction. A total of forty experimental and forty control cultures were prepared; in each culture a large number of ganglia were explanted. The effects of the salivary extract on ganglia of the two-and-a-half month fetuses were similar in all respects to the effects elicited by mouse sarcomas, snake venom, and the mouse salivary extract on ganglia of chick embryos (Fig. 3), mouse, and rat embryos. A dense halo of nerve fibers surrounded the ganglia in the experimental cultures; it was already apparent 12 hours after the beginning of the experiment and increased in density and in size at the end of the first day (Fig. 5). A comparable, but somewhat slower, reaction was observed in ganglia explanted from the older fetus. A considerable degree of liquefaction of the cultural medium took place on the second and third day of culture; the experiments were then discontinued. Control ganglia showed few or no nerve fibers in the area surrounding the explant 24 hours after the preparation of the culture (Fig. 2).

In vivo Effects on the Sympathetic Ganglia of Newborn and Adult Mice.—(*a*)*Material and methods:* The effect of the salivary extract was tested on newborn and adult mice. Solutions of the active extract at different concentrations and different degree of purification were at first assayed in three groups of newborn mice and then on adult mice.

Group 1: Ten newborn mice were injected daily with the salivary extract referred to in Cohen's paper as fraction CM-1 (these PROCEEDINGS, this issue). This solution was injected subcutaneously in the amount of 0.05 ml per gm of body weight at a concentration of 1,500 units of biological activity per ml. One unit of biological activity is defined as that amount per ml required to elicit a 3+ response

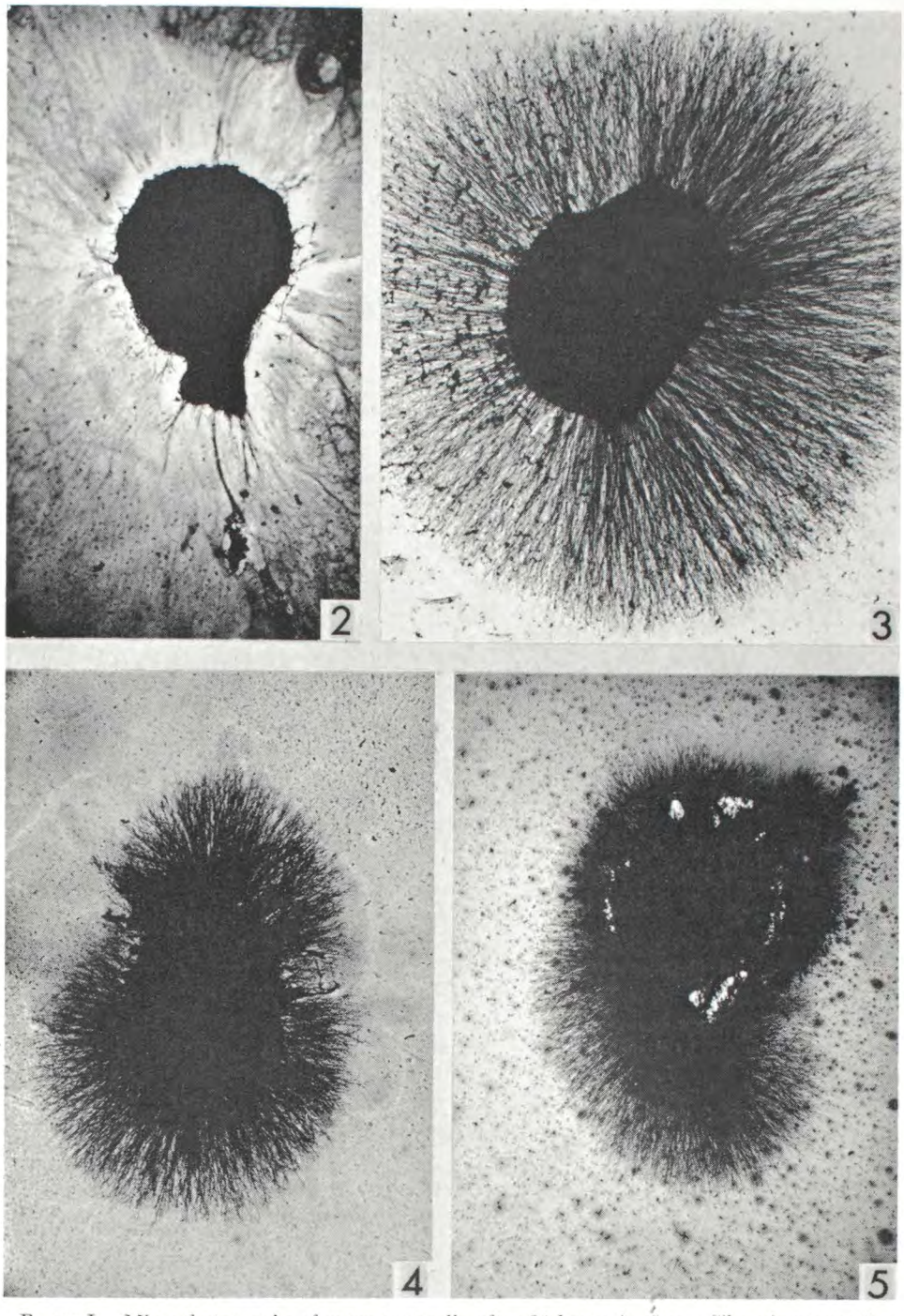


PLATE I.—Microphotographs of sensory ganglia after 24 hours *in vitro*. Silver impregnation. FIG. 2.—Ganglion of a $2^1/_2$ months human fetus in the standard control medium. FIGS. 3, 5.—Ganglia of a 7-day chick embryo (Fig. 3) and of a $2^1/_2$-month human fetus (Fig. 5) in a medium containing the purified salivary protein at a concentration of 1:18,000. FIG. 4.—Ganglion of a 7-day chick embryo in a medium containing mouse serum at a concentration of 1:30. Short and dense halo in Figs. 4 and 5 characteristic of strong and slightly inhibitory effects of the growth agent at high concentration.

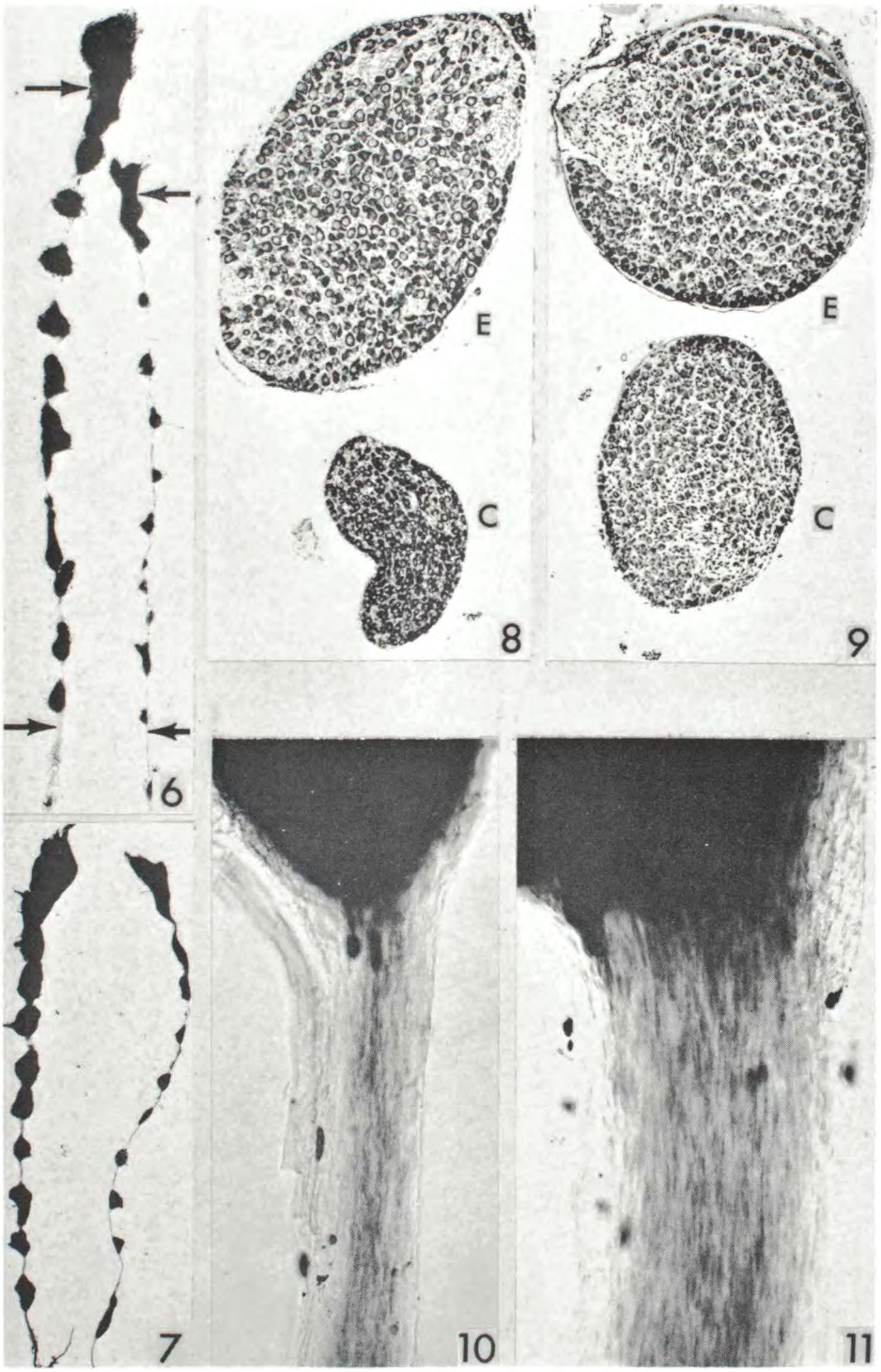


PLATE II.

FIGS 6, 7.—Whole mounts of the sympathetic thoracic chain ganglia of experimental (E) and control (C) mice 19 and 12-day old respectively. Experimental mice injected with the CM-3 salivary fraction since birth. FIG. 8.—Transverse section of stellate ganglia in experimental (E) and control (C) ganglia of Fig. 6. Sections through levels indicated by upper arrows in both chains of Fig. 6. FIG. 9.—Transverse section of superior cervical ganglia of two adult mice. E, mouse injected for 1 week with the CM-1 salivary fraction. C, control ganglion. FIGS. 10, 11.—Sympathetic nerve trunk of control and experimental chain ganglia of Fig. 6e at higher magnification. Low arrows in Fig. 6 indicate areas enlaged in Figs 10, 11.

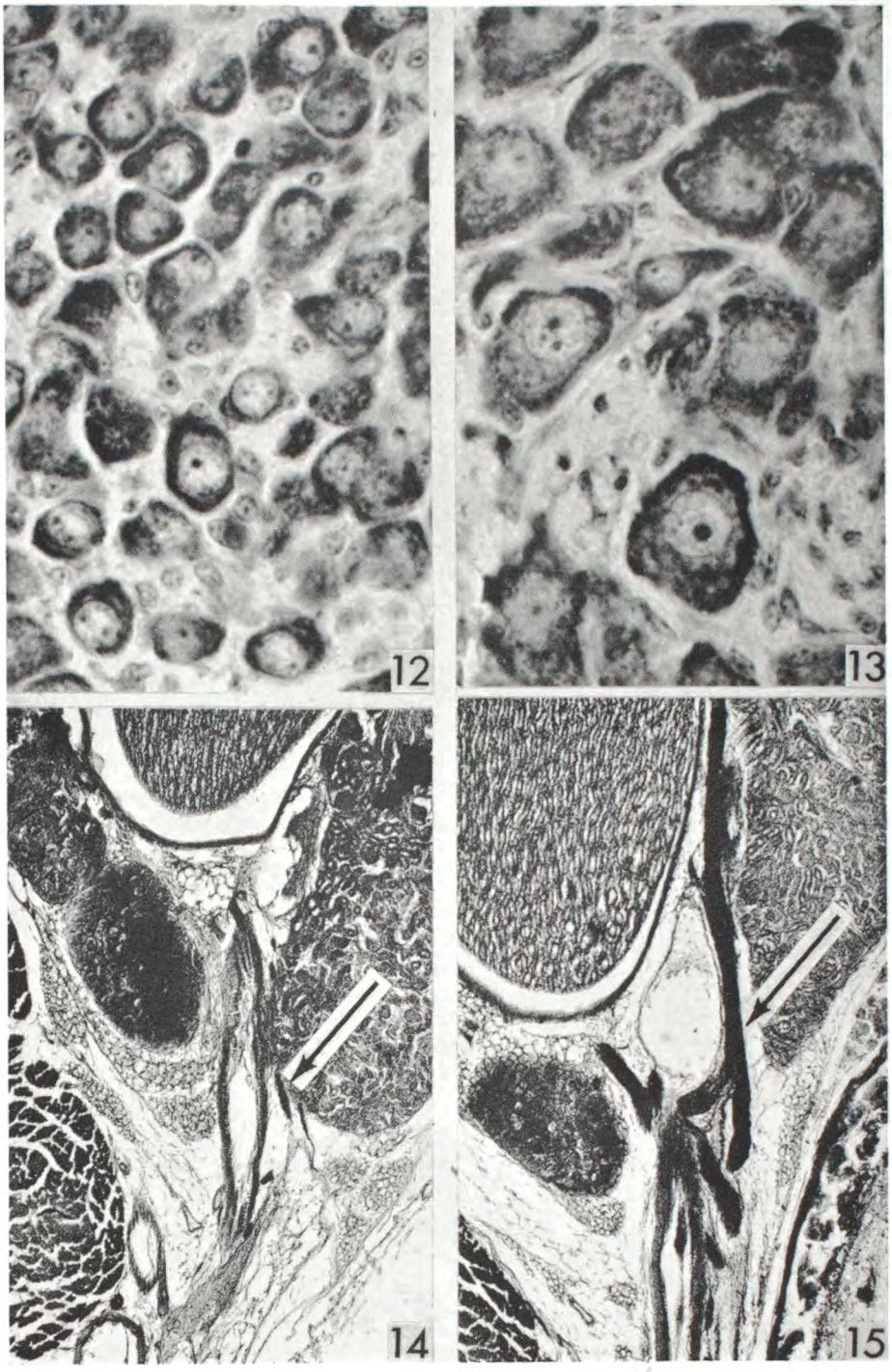


PLATE III.

FIGS. 12, 13.—Comparison of cell size in control and experimental stellate ganglia represented in Figs. 6, 8. Toluidin blue stain. FIGS. 14, 15.—Comparison of size of sympathetic nerve along the renal artery in control (Fig. 14) and experimental 19-day old mouse (Fig. 15) injected daily with the CM-3 salivary fraction since birth Arrows point to nerve in both figures. Cajal De Castro silver impregnation.

in tissue culture. The injected and control mice of the same litters were sacrificed between the 7th and the 14th day and examined for effects on the nervous system and other systems. When it was found that such treatment had consistently elicited a significant increase in the sympathetic ganglia, a second series of experiments was performed with a more concentrated solution.

Group 2: Thirty newborn mice were injected with the CM-1 fraction at a concentration of 6,000 units per ml. The solution was injected daily, in the same amount as used in previous experiments. The injected and untreated mice of the same litters were sacrificed every day or every other day between the second and the thirtieth day.

Group 3: Ten newborn mice were injected daily, from birth, with a more highly purified fraction referred to as CM-3 fraction in the paper by S. Cohen. The solution was injected in the same amount and in the same concentration as in the experiments of Group 2. The injected and control mice were sacrificed between 1 and 9 days and at 12 and 19 days respectively.

Group 4: Fifty adult mice were injected with the CM-1 fraction at the same concentration and in proportional doses per body weight as in groups 2 and 3. The injected and control mice were sacrificed in groups of 3 to 4 between the end of the first week and the fourth week and compared with controls.

The injected and control mice of all 4 groups were dissected and used for investigation of the sympathetic ganglia; other components of the nervous system were also examined. The sympathetic ganglia were either dissected out and stained with hematoxylin and toluidin blue for counts of mitotic figures and of nerve cells, or they were left *in situ* and studied after silver impregnation and sectioning of the whole organism. This material was used for the study of the neurofibrillar differentiation of nerve cells and of the peripheral distribution of sympathetic nerve fibers in injected and control animals.

Counts of mitotic figures were made in sympathetic ganglia of mice of the third group between 12 hours and 9 days. The mitoses were counted in each section of the superior or stellate ganglia in control and treated mice.

Area measurements were made in ganglia dissected from mice 5 to 27 day old, of groups 2 and 3. Each section was projected with the help of the camera lucida and the contour of the section was drawn on cardboard. The total number of sections was then weighed and the weight compared with that of the same control ganglion. Since the weight is proportional to the volume, the figures indicate a similar ratio between the volume of experimental and control ganglia. A total of 18 control and 18 experimental ganglia were measured and compared. The same technique was used on a small number of ganglia of the fourth group.

Cell counts were performed in sympathetic ganglia of groups 3 and 4, by inserting a micrometer disk in the ocular and counting all nerve cells in every other section of the experimental and control ganglia.

Two additional series of experiments were performed. In the first series we tested the serum of adult and weanling mice for the presence of the nerve-growth factor. A total of 150 adult mice of both sexes and of 30 weanling mice were tested. The blood was either collected from the blood vessels immediately after decapitation of mice in light chloroform anesthesia, or it was drained directly from the aorta and the heart in mice anesthetized with nembutal. The blood was

allowed to clot at room temperature and then stored for half an hour in the refrigerator. The serum was then collected in separated vials and each specimen tested on sensory ganglia of 8-day chick embryos explanted *in vitro* with the usual hanging drop technique. All sera were also tested at dilutions of 0.1, 0.01, and 0.001.

In the second series of experiments we extirpated the submaxillary and sublingual salivary glands in 25 adult and 5 weanling mice, and we inspected the sympathetic ganglia of the operated and control mice between 2 weeks and 6 months after the operations.‡

(*b*) *Effects of the purified salivary extract on newborn mice:* The newborn mice injected with the CM-1 fraction in the weak and even more in the strong concentration, exhibited side effects which will be mentioned but not described in detail. From the third day on, the growth rate dropped sharply and at the end of the first month, the mice were barely larger than at the end of the first week. The hair growth was severely impaired, the lids opened 6 to 7 days earlier than in controls and the cutting of the inferior and superior incisors and their calcification took place 5 days earlier than in controls. The animals recovered if the injections were discontinued at the end of the first month; dwarf mice resumed growth and three months later they did not differ from untreated controls at a macroscopical inspection. The effects mentioned above did not affect the vitality of the mice in the doses used. None of the forth injected mice died as a result of the treatment. No side effects were observed in newborn mice injected with the more purified fraction CM-3. They were healthy and vigorous as controls. Obviously, we are dealing with 2 factors, one of which was removed in the process of purification.

Both fractions CM-1 and CM-3 evoked a marked overgrowth of the sympathetic ganglia (Figs. 6, 7, 8, 9). In the following we will consider only the results of the injections of fractions CM-1 and CM-3 in the concentration of 6,000 units per ml (groups 2 and 3).

The average *volume increase* of the superior cervical ganglia in group 2, as determined by comparison of 13 experimental and 13 control ganglia was 3 : 1. The corresponding figures for the same ganglia of mice injected with fraction CM-3 and controls (group 3) were higher: measurements of 3 experimental and 3 control ganglia at 12 days gave a ratio of 4.1 : 1 and on 2 experimental and 2 control ganglia at 19 days gave 6.4 : 1. More long range experiments are planned to establish the ceiling of this effect.

The results of *cell counts* in 12 control and 12 experimental ganglia of mice injected since birth with the CM-3 fraction are given in Table 1. The increase in cell number in the injected mice over the controls averages 2.5 and 2.18 respectively in one 12- and one 19-day old mouse. The results of cell counts in adult mice, as given in the same Table for 5 controls and 2 experimental ganglia, show no increase in cell number in the injected adult mice over the controls. It is of interest to note that the total cell population in the normal stellate ganglia is 13,000 whereas the same ganglion in an experimental mouse has a population of over 30,000. The mechanism of this cell increase will be dealt with below.

The concomitant *increase in cell size* in injected animals is shown in Figures 8 and 9 for the stellate ganglia of the 19-day old mice and adult mice respectively. No size measurements were made. Since the volume increase in the ganglia was 4 to 6

times (see above) whereas the increase in cell number in the same ganglia was about twofold, we conclude that cellular hypertrophy has a greater share in the end effect than the increase in cell number.

Cytological examination showed that the hypertrophic neurons differ from controls also in the more intense basophilia and in the size of the nucleoi which are much larger than in controls (Figs. 12, 13). A parallel increase in neurofibrillar material in the hypertrophic nerve cells is apparent in the silver-stained ganglia. Observations of ganglia dissected from three-day old mice injected with the CM-1 or CM-3 fractions since birth, indicate that the size increase is already evident at that time.

It was of interest to decide whether the increase in cell number in the injected mice is due to an increase in *mitotic activity* or to other mechanisms such as the production of a larger number of sympathetic nerve cells at the expense of germinal or pluripotential cells present in the ganglia. The presence in the ganglia of a fairly

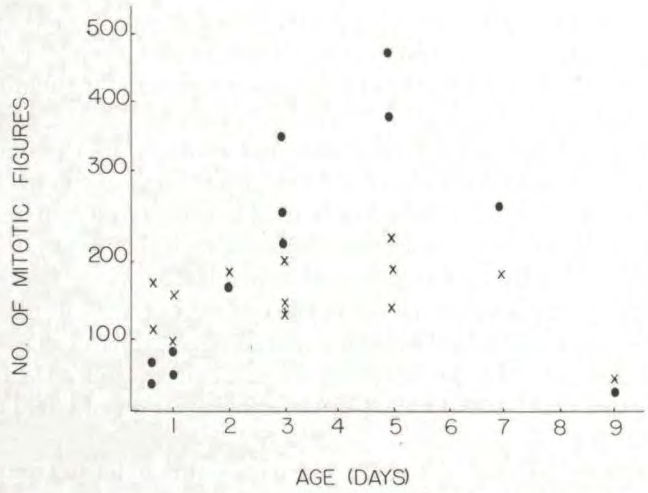


FIG. 1.—Effect of the nerve-growth factor on mitotic activity. Crosses and dots indicate number or mitoses per ganglion (superior cervical ganglion) in control and experimental mice respectively.

large number of small-sized cells, beside the satellite cells, could suggest this possibility. On the other hand, since the mitotic activity is still high at birth and comes to an end at 9 days, the injection of the nerve-growth factor in newborn mice could also affect this process. Counts of mitotic figures in control and experimental ganglia between 1 and 9 days showed a sharp increase in the mitotic activity of the experimental ganglia between 3 and 7 days with a peak at 5 days. These results, presented in Figure 1, favor the hypothesis that the increase in nerve cells in the injected mice is due to an increase in mitotic activity. Although there is no way of deciding how many of the dividing cells are neuroblasts, the results correlate well with the finding of an increase in cell number in later stages; they are also in agreement with observations on the effects of nerve-growth agents on mitotic activity in the spinal ganglia of the chick embryo.[9]

(*c*) *Peripheral distribution of sympathetic nerve fibers:* One would expect that the increase in cell number and cell size in sympathetic ganglia of the injected mice

would result in a parallel increase in the size of nerves emerging from the enlarged ganglia. This increase was in fact observed and it is documented in Figures 10 and 11. A comparison of the cephalic, thoraic, and abdominal regions of experimental and control mice shows an increased density and thickness of the nerve plexuses around the blood vessels of the injected animals. In the kidney, sympathetic nerve bundles were traced along the intrarenal blood vessels and also among the renal tubules, in much larger number in the experimental than in control animals. Figures 14 and 15 show the increase in thickness of the sympathetic nerve along the renal artery in a 19-day injected mouse compared to a control of the same age.

These effects, the increase in number and size of sympathetic nerve cells and the hyperneurotization of the viscera, are very similar to the effects called forth by mouse sarcomas, snake venom, and the salivary extract in the chick embryo.[1, 2, 5, 7] The two sets of experiments differ in two respects: (1) While in chick embryos, the sympathetic nerve fibers produced in excess follow in many instances anomalous routes and even force their way into the lumen of blood vessels, no such deviations were observed in mice injected with the salivary gland fractions. Thus the quantitative rather than the qualitative aspect of the distribution of sympathetic nerves seems to be affected in mammals in post-natal periods. (2) Whereas these agents evoke in the chick embryo a striking response also in the sensory ganglia,[2, 9] this effect is barely noticeable in newborn mice. Measurements of a number of sensory ganglia showed only a slight increase in the experimental material.

TABLE 1

TOTAL NERVE CELL NUMBERS IN SYMPATHETIC GANGLIA OF MICE INJECTED WITH SALIVARY GLAND FRACTIONS

Fraction	Age	Ganglia	Control	Experimental	Ratio Exp./Cont.
CM-3	12	Thoracic N. 6	1,365	3,212	...
		Thoracic N. 7	1,165	2,731	...
		Thoracic N. 8	1,155	4,422	...
		Thoracic N. 9	1,026	2,849	...
		Thoracic N. 10	1,465	2,567	...
		Total	6,176	Total 15,781	2.5
CM-3	19	Stellate			
		Thoracic N. 2	14,400	30,800	...
		Thoracic N. 3	1,644	3,684	...
		Thoracic N. 4	1,770	2,133	...
		Thoracic N. 5	1,094	3,144	...
		Thoracic N. 6	820	2,328	...
		Thoracic N. 7	1,362	2,758	...
		Thoracic N. 8	1,392	4,162	...
		Total	22,482	Total 49,009	2.18
CM-1	Adult	Stellate	14,000	13,689	...
		Stellate	12,000	...	...
		Average	13,000	13,689	1.05
	Adult	Sup. Cerv.	13,300	15,770	...
		Sup. Cerv.	16,415	...	...
		Sup. Cerv.	15,652	...	...
		Average	15,122	15,770	1.03

(*d*) *Effects of fraction CM-1 on adult mice:* The daily injection of 0.05 ml per body weight of fraction CM-1 (6,000 units per ml) was well tolerated and the injected

mice did not show any adverse effects. The sympathetic ganglia were considerably larger than in controls: the difference was evident at a macroscopic inspection of the 50 injected and 50 control mice. Area measurements of the ganglia in a few of cases gave a twofold enlargement, compared with controls. The size increase was due to cellular hypertrophy of the individual neurons (Fig. 9). The cell number was apparently not increased (see Table 1).

Nerve-Growth Effects of Blood Serum of Adult and Young Mice.—Previous experiments *in vitro* gave evidence of a mild nerve-growth effect elicited by embryonic mouse heart on sensory and sympathetic ganglia of chick embryo.[3] Traces of the same activity were then found in homogenates of striated muscle of adult mice. Bueker[10] detected activity in partially purified preparations of thymus, kidney, and muscle. We found in some instances evidence of activity in the urine of adult mice. The same activity was detected in mouse saliva. We then proceeded to test the serum of adult and weanling mice.

Observations to be reported in detail elsewhere disclosed a considerable sexual dimorphism in the sympathetic nerve cells of adult mice. In male mice, the sympathetic neurons are considereably and consistently larger and more intensely stained with basic dyes than in female mice of the same size. These results suggested tests of the blood serum of mice of the two sexes separately. The results are summarized in Table 2. A maximal effect was obtained from the serum of 15 male

TABLE 2

NERVE-GROWTH EFFECTS OF MOUSE SERUM *in vitro*

Age	Concentration	Response*			
		++++	++	+	±
Adult males	1/10	15			
	1	10	30	20	25
Adult females	1	1	7	10	32
Weanling	1		4		26

* ++++ to ± give degrees of effects from maximal to barely detectable.

mice and one female mouse. In 15 cases with a 4+ effect at a dilution of 1 : 10 (Fig. 4) an effect was still detectable at a dilution of 1 : 1000. The nerve-growth effect of the serum collected from adult females or from weanling mice of both sexes was consistently milder than that of the serum of adult males. These sex and age differences have a parallelism in the finding of Cohen (these PROCEEDINGS, this issue) of a higher specific activity in the submaxillary salivary gland of male than of female mice and of much lower activity in the same gland of weanling mice. These results indicate that the nerve-growth factor is present in higher concentration in the blood of adult male than female mice and that it is in even lower concentration in the blood of weanling mice. They also show a considerable variation among mice of the same group. Experiments in progress are expected to answer the question of whether such variations are correlated with physiological differences in the tested animals and if the stress resulting from the administration of the anesthetic may account for such variations.

Effects of the Extirpation of the Submaxillary and Sublingual Glands in Adult and Weanling Mice.—The operated mice were sacrificed between two weeks and six months after the operations and were compared with controls of the same size.

When mice in the weanling stage were operated, the controls were selected from the same litters.

In the first days after the operation, the animals showed signs of discomfort and the fur became ruffled. In the following days, the mice recovered, but in most instances the fur remained deranged. The operated adult males differed from controls also in another respect. They became much more tame than controls and easier to handle. The correlation between submaxillary salivary glands and other endocrine glands, in particular sex glands, have been investigated by many authors[11, 12] and will not be discussed here. They are mentioned, however, since they may have a bearing on the present results.

In all the experimental and control mice, the sympathetic chain ganglia were dissected out, stained with toluidin blue, and sectioned at 10 microns. Since the superior cervical ganglion might have been indirectly affected by the extirpation of part of its peripheral field of innervation, the salivary complex, we used instead the stellate ganglion which does not contribute to the innervation of the salivary glands.

Results.—Twenty operated adult males and twenty controls were examined between three weeks and two months after the operation. In five mice deprived of the salivary glands a slight decrease in size of the sympathetic nerve cells was detected. The nerve cells also stained less intensely than controls with toluidin blue and appeared similar to sympathetic nerve cells of female mice. No differences were noticeable in the other 15 operated mice. Five adult female mice were operated and compared with controls three weeks after the operation. No size differences were detected between these and control nerve cells. Equally negative were the results in 5 mice operated during the weanling stage. One of these was compared with a control of the same litter, six months after the operation, the other mice one month after the operation. In all instances, the sympathetic chain ganglia appeared of the same size as the controls and the histological examination of the stellate ganglia revealed no changes in cell size.

The serum of mice deprived of the salivary glands was also tested for the nerve-growth factor. In one mouse deprived of the glands two months earlier the serum evoked a 4+ effect *in vitro* as the serum of control mice. In the other specimen the effect varied from a 2+ to a barely detectable effect. These results indicate that the nerve-growth agent is present, even in the absence of the salivary glands.

Summary.—Previous work has provided evidence for the presence of nerve-growth promoting agents in a variety of biological materials: mouse sarcomas, snake venoms, and mouse submaxillary salivary glands. In the present investigation the effect of the active fraction isolated from the mouse salivary glands was tested *in vitro* on ganglia of human fetuses; it was found that it elicits the same effects as on ganglia of other species. The active fraction was then injected in newborn and in adult mice. In all instances the injection resulted in a marked increase of the sympathetic ganglia; the response varied with the age of the animal, the amount, and the purity of the fraction injected. In some instances a sixfold increase in size was observed. Slight nerve-growth promoting effects of different mouse tissues had been observed *in vitro* in previous experiments. We have now found evidence for the presence of the nerve-growth factor in the serum of adult and weanling mice. Maximal effects were obtained from the serum of adult male mice; the serum of female mice is less effective. This sex difference is paralleled by a sex difference in the size of adult sympathetic nerve cells.

* This work has been supported by a grant from the National Science Foundation and by a contribution from an Institutional grant of the American Cancer Society to Washington University.

† We wish to express our appreciation to Dr. Willard Allen of the Department of Gynecology and Obstetrics of the Washington School of Medicine who made this material available to us.

‡ The microphotographs in this and in the following paper were made by Mr. Cramer Lewis of the Department of Illustration of the Washington University School of Medicine.

[1] Levi-Montalcini, R., *Ann. N. Y. Acad. Sci.*, 330–343 (1952).

[2] Levi-Montalcini, R., and V. Hamburger, *J. Exptl. Socl.*, **123**, 233–288 (1953).

[3] Levi-Montalcini, R., H. Meyer, and V. Hamburger, *Cancer Research*, **14**, 49–57 (1954).

[4] Cohen, S., R. Levi-Montalcini, and V. Hamburger, these PROCEEDINGS, **40**, 1014 (1954).

[5] Levi-Montalcini, R., and S. Cohen, these PROCEEDINGS, **42**, 571–574 (1956)

[6] Cohen, S , and R. Levi-Montalcini, these PROCEEDINGS, **42**, 695–699 (1956).

[7] Levi-Montalcini, R., in *The Chemical Basis of Development*, (Baltimore: The John Hopkins Press, 1958), pp. 645–664.

[8] Cohen, S., in *The Chemical Basis of Development*, (Baltimore: The John Hopkins Press, 1958), pp. 665–676.

[9] Levi-Montalcini, R., and V. Hamburger, *J. Expl. Zool.*, **116**, 321–362 (1951).

[10] Bueker, E. D., I. Schenklein, and J. Bane, *Anat. Record*, **133**, 256 (1959).

[11] Lacassagne, A., *Compt. Rend. Soc. Biol.*, **133**, 280–281 (1940).

[12] Junqueira, L. C. U., A. Faier, M. Rabinovitch, and L. Frankenthal, *J. Cell. and Comp. Physiol.*, **34**, 129–158 (1949).

---

*DESTRUCTION OF THE SYMPATHETIC GANGLIA IN MAMMALS BY AN ANTISERUM TO A NERVE-GROWTH PROTEIN**

BY RITA LEVI-MONTALCINI AND BARBARA BOOKER

DEPARTMENT OF ZOÖLOGY, WASHINGTON UNIVERSITY, ST. LOUIS

Communicated by Viktor Hamburger, January 4, 1960

The observation by S. Cohen that a rabbit antiserum against a protein fraction of the salivary gland inactivates the *in vitro* nerve-growth effects of this protein (pp. 302–311, these PROCEEDINGS) suggested to him to test the effects of the antiserum on newborn mice. The finding of a remarkable decrease in size of the sympathetic ganglia of the injected mice prompted an extensive investigation of the effects of the antiserum on the sympathetic ganglia of mice and other mammals. The results of this study are reported in the following pages.

Materials and Methods.—Newborn mice were injected daily with 0.05 ml of the rabbit antiserum per 1.5 gm of body weight.† Controls of the same litters were either injected with serum of a normal rabbit, or they were not treated at all. Twenty experimental and twenty control mice were sacrificed between the 12th hour after the first injection and the 25th day. Two groups of newborn mice, injected for 8 and 20 days respectively after birth, were sacrificed three and four months after the termination of the treatment. An equal number of untreated mice of the same litters were available for control. The same techniques as used in the previous experiments (pages 373–384) were used for area measurements, cell and mitotic counts, and for histological examination.

The effect of the rabbit antiserum was then tested on newborn rats, rabbits, and one pair of kittens. The amount injected was in the same proportion to the body

weight as in the experiments with newborn mice. A limited number of experiments were also performed on adult mice and on one pair of young adult squirrel monkeys.

Effects of the Antiserum on Newborn Mice.—The injection of the rabbit antiserum in newborn mice did not affect their development in any way. Mice injected daily for a period of 25 days did not differ from mice injected with normal rabbit antiserum or from untreated controls. Since mice injected with the normal serum were identical in all respects with untreated controls, including the development of the sympathetic ganglia, only untreated animals were used for comparison in most experiments.

The effects of the antiserum on the development and growth of the sympathetic ganglia were dramatic in their sudden outburst, in their severity, and in the end effects. An inspection of sympathetic ganglia at different trunk and head regions in the same animals showed that all ganglia were affected in the same way; therefore, the data presented here on the superior cervical ganglia can be considered as representative of the degree of reduction which took place in all sympathetic ganglia.

A decrease in mitotic figures is already noticeable 12 hours after the first injection; the decrease becomes more pronounced at the end of the first day. Between the second and the third day, the mitotic activity is sharply reduced and the number of degenerating cells is greatly increased. The neuroblasts which are present are considerably smaller than the control cells. As a result, the volume of the ganglia is reduced to approximately $^1/_6$ of the controls on the fourth day. No cell counts were performed at this stage since most of the neuroblasts are still small and not easily distinguishable from satellite cells.

Between the fourth and the ninth day, the process of cell atrophy and death continues at a somewhat slower pace; the disintegrative processes of preceding stages have in fact so much reduced the population of nerve cells as to set limits to the process itself.

The effects of the daily injections of antiserum in a 9-day mouse are illustrated in Figure 5. The products of disintegrating cells which in earlier stages encumbered the ganglia have now disappeared. A few nerve cells, smaller than controls but otherwise in apparently normal condition, are scattered among a uniform population of satellite cells. The latter do not seem to be affected by the antiserum at this stage. A reduction in their number takes place in more advanced stages when only a few satellites are still present in each section of the diminutive ganglia (Fig. 8).

At 20 days, counts of nerve cells in the superior cervical ganglia of experimental and control mice show that the sympathetic nerve cells are reduced in one instance to less than 1 per cent of the control (Fig. 1, Table 1). The reduction of volume of the same ganglion was to 4.3 per cent of the control. The process seems to have reached its peak. Counts of cells in another pair of experimental and control ganglia of a 25-day-old mouse give slightly higher figures: 1.7 per cent of the cell population of the control are present in the experimental ganglion. Such differences may well be accounted for as individual variations. It should be noted that a considerable variation in the cell population was also observed in ganglia of untreated mice (see Table 1). The results, seem, however, to indicate that the process has not

further advanced, and that the few cells which escaped death in earlier stages may now be able to survive.

It was of interest, in this connection, to examine the injected mice some months after the termination of the treatment. Seven newborn mice of two litters were injected daily with the antiserum until the eighth and the twentieth day respectively. Experimental and untreated mice of the same litters were examined three to four months later. The treated mice did not differ from controls in their general appearance. The lack of adverse effects on the visceral functions of the injected mice was illustrated by the fact that one of these mice delivered a normal litter.

Two experimental and two control mice of each group were sacrificed at the end of the third month and the sympathetic chain ganglia were dissected out and compared. Two more pairs of mice injected for 8 days were sacrificed at the end of the fourth month (Figs. 2, 8). The results are given in Table 1. The reduction in cell number in the superior cervical ganglia fluctuates between 2.56 per cent and 0.84

TABLE 1

EFFECT OF ANTISERUM INJECTIONS ON THE VOLUME AND CELL NUMBER OF THE SYMPATHETIC GANGLIA IN MAMMALS*

Mammal	Age, Days	No. of Inject.†	Ganglion	Volume Ratio, Exp./Cont.	Number of Cells Cont.	Number of Cells Exp.	Cell Ratio, Exp./Cont.
Mouse	2	2	Sup. Cerv.	0.37:1			
Mouse	4	4	Sup. Cerv.	0.16:1			
Mouse	9	9	Stellate	0.13:1			
Mouse	20	20	Sup. Cerv.	0.04:1	13,300	91	0.70:100
Mouse	25	25	Sup. Cerv.	..	16,415	279	1.70:100
Mouse	90	8	Sup. Cerv.	..	16,447	421	2.56:100
Mouse	120	8	Sup. Cerv.	..	14,800	140	0.94:100
Mouse	120	20	Sup. Cerv.	..	13,000	110	0.84:100
Mouse	Adult	20	Sup. Cerv.	..	15,652	5,328	34.00:100
Rat	4	4	Sup. Cerv.	6.64			
Rat	7	7	Sup. Cerv.	10.54	32,000	2,310	7.00:100
Rabbit	3½	3	Sup. Cerv.		66,300	6,200	9.00:100
Rabbit	5	5	Sup. Cerv.		67,000	9,300	14.00:100
Rabbit	7	7	Sup. Cerv.		68,000	11,050	16,00:100
Cat	7	7	Sup. Cerv.		114,000	8,600	7.70:100
Monkey	7	7	Sup. Cerv.	1.65			

* Details of experiments in text.
† Beginning at birth, except for adult mice.

per cent of the corresponding control ganglia. In all instances, the residual cells were much smaller and did not stain with basic dyes as deeply as the controls. The function of the surviving cells will be tested in other mice of the same litters which are still alive. The 20-day treatment, as well as the 8-day treatment, is therefore sufficient to destroy 97 per cent to 99 per cent of the sympathetic nerve cells. Since the mice were examined some months after the end of the treatment, it is proved that the damage inflicted to nerve cells is irreversible. Experiments with higher amounts of antiserum and possibly an even more potent antiserum will show whether it may be possible to attain a total extermination of the sympathetic nerve cells.

Effects of the Antiserum in Other Newborn Mammals.—The few experiments performed up to now on newborn rats, rabbits, and kittens are not sufficient to give more than a very incomplete idea of the effects of the antiserum in these species.

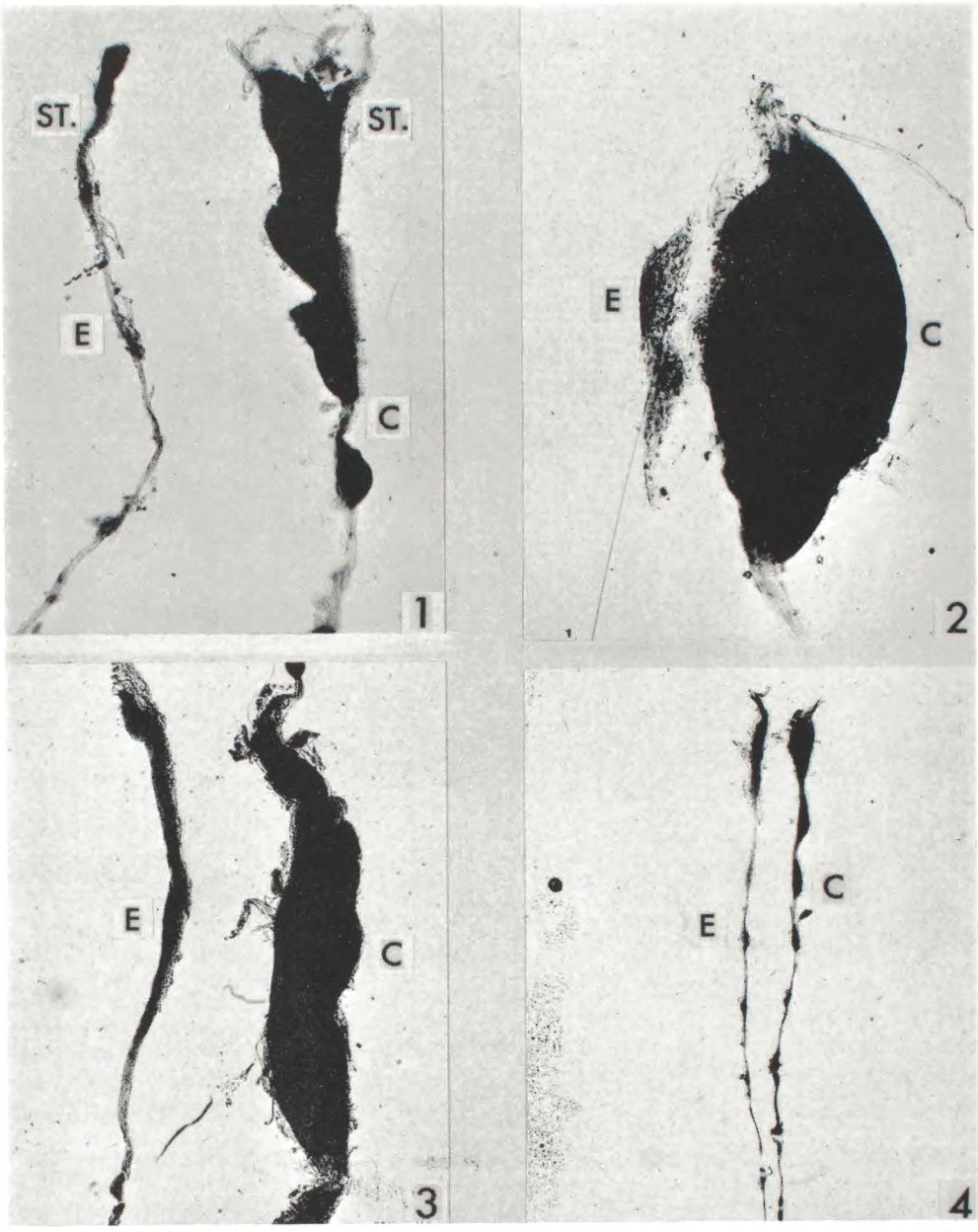


PLATE I.—Effects of rabbit antiserum against the purified protein of mouse salivary gland.

FIG. 1.—Stellate (St.) and first ganglia of sympathetic thoracic chains in control (C) and experimental (E) 20-day old mice. Experimental mouse injected daily since birth with the antiserum to the mouse salivary protein. 30×. FIG. 2.—Superior cervical ganglia in control (C) and experimental (E) 4-month old mice. Experimental mouse injected daily from birth to the 8th day with the antiserum to the salivary protein. 33×. FIG. 3, 4.—Effects of the antiserum in a 7-day old rat (FIG. 3) and in a $3\frac{1}{2}$-day old rabbit (FIG. 4); both injected daily since birth. FIG. 3, stellate ganglia in control (C) and experimental rat (E). 30×. FIG. 4, stellate and sympathetic thoracic chains in control (C) and experimental (E) rabbit. 4×.

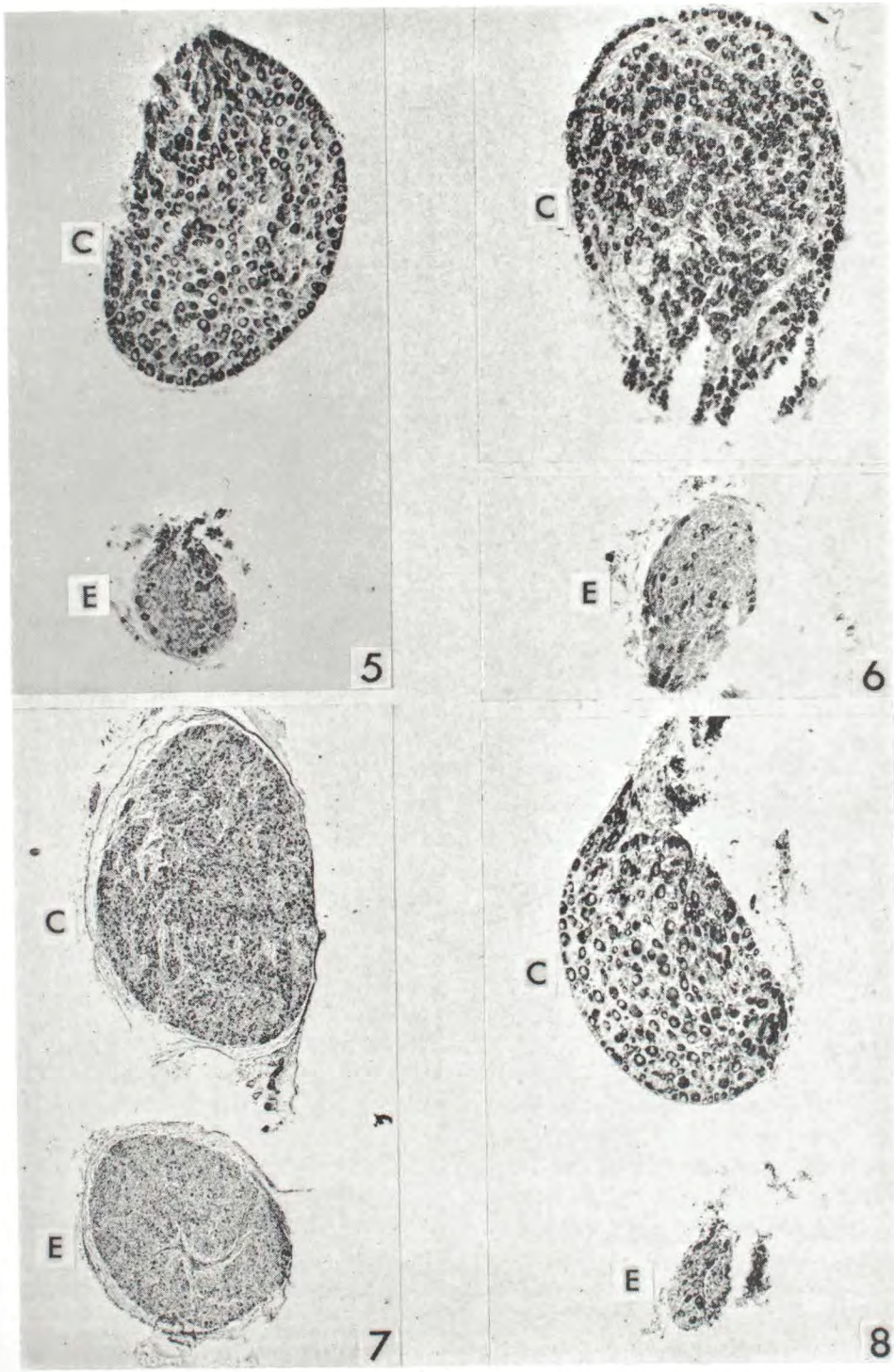


PLATE II.—Transverse sections of superior cervical ganglia in control (C) and experimental (E) animals, injected with rabbit antiserum to the salivary protein.

FIG. 5.—9-day old mice; E, injected daily since birth. 90 ×. FIG. 6.—7-day old rats; E, injected daily since birth. 90×. FIG. 7.—7-day old kittens; E, injected daily since birth; the ganglion consists of satellite cells and few nerve cells. 30 ×. FIG. 8.—4-month old mice; E, injected from birth to the 8th day. 60×.

The results obtained are, however, so impressive as to justify the contention that the antiserum affects the sympathetic ganglia of these mammals in a similar way as described above for newborn mice (Figs. 3, 4, 6, 7).

Two newborn rats were injected with the antiserum (0.05 ml per 1.5 gm of body weight). The experimental and control animals were sacrificed respectively at 5 and 7 days. The results observed are so similar to the ones described in mice at the same developmental stages as to make a description unnecessary. The number of cells in the superior cervical ganglion of one injected rat at 7 days was reduced to 7 per cent of the control (Table 1). The surviving cells are reduced in size when compared to controls but otherwise apparently in good condition (Figs. 3, 6).

Three newborn rabbits were injected with the rabbit antiserum and sacrificed at $3^1/_2$, 5, and 7 days. Since the ganglia are rather large in this species and the nerve cells easily distinguishable from satellites even in earlier stages, cell counts were feasible in three-and-a-half day old ganglia. A high reduction in the number of nerve cells was observed: only 9 per cent of the control population is present in the injected rabbit at this stage (Fig. 4). The two rabbits of the same litter, injected and sacrificed two and four days later respectively, showed a somewhat less severe atrophy of 14 per cent and 16 per cent respectively. Furthermore, the surviving cells were not reduced in size as in the younger animal. Investigation of animals injected for a longer period will answer the question whether rabbits develop a resistance to the antiserum which could account for such results.

The effects of the antiserum in one adult mouse, one young squirrel monkey, and a newborn kitten are shown in Table 1.

Discussion.—The results reported in this and in the previous paper bring to light the remarkable capacity of sympathetic nerve cells of newly born mammals to increase in size and number when injected with a mouse salivary gland protein, as well as their vulnerability to an antiserum to this protein.

The possibility that the sympathetic ganglia in man may be likewise affected by the nerve-growth factor is suggested by the *in vitro* experiments reported in the preceding paper.

The salient aspects of these phenomena are: their universality, their target specificity, and the unsuspected growth potentialities of young and adult nerve cells which materialize under the impact of nerve-growth promoting agents.

Of particular significance is the new finding that the antiserum against the salivary gland protein not only inactivates this protein, but, if injected alone into a newborn mammal, destroys its sympathetic cells almost totally in a remarkably short time. No other organs and tissues appear to be affected. On the other hand, normal serum leaves the sympathetic system as well as all other systems intact.

The question arises whether the near-total destruction of the sympathetic nerve cells is a direct or an indirect effect of the antiserum. It is conceivable that in the normal animal a factor circulates which is necessary for growth and maintenance of the sympathetic system and that the antiserum inactivates this factor. This hypothesis is supported by the detection of the nerve-growth agent in the blood of young and adult mice. Alternatively, the antiserum may exert a cytotoxic affect by combining with the antigen in or on the surface of the nerve cells. The same questions are raised in other investigations of the cytotoxic effects of the antisera.[1] Immuno-

chemical techniques, such as the detection of antibodies labeled with a radioactive isotope or with a fluorescent dye, may show if there is localization of the antiserum on the sympathetic nerve cells and if so, provide evidence in favor of the second alternative. These experiments will be performed in the near future.

The results reported in these and in previous papers[2–5] give evidence for the existence of closely related nerve-growth promoting proteins in two seemingly unrelated sources: mouse sarcomas and salivary glands. One may wonder whether both structures produce these proteins. We have positive evidence that the mouse sarcomas manufacture the nerve-growth agent even when they grow in the chick embryo.[6,7] Corresponding experiments in which the salivary glands were transplanted in the chick embryo were negative so far. Furthermore the nerve-growth agent was detected in serum of adult mice which had been deprived of their salivary glands two months earlier. The sympathetic ganglia of these mice did not show appreciable differences from control mice. Since the salivary glands and their homologue, the snake venom glands, contain the agent in high concentration, the only alternative would be that these glands store, but do not produce, the growth agent. If this suggestion would prove to be correct, we would still be faced with the problem of identifying the source of the nerve-growth agent in the organism. The possibility ought to be considered that the nerve-growth agent is not manufactured in any particular organ or organs, but in the mesenchymal tissue. The only evidence in favor of this hypothesis comes from the *in vivo* and *in vitro* experiments with mouse sarcomas and from *in vitro* experiments with explants of embryonic mouse heart.[8] Epithelial structures like carcinomas proved to be completely deprived of the property of stimulating nerve growth *in vivo*[9] as well as *in vitro*.[8] Research in progress is now aimed at the investigation of this problem.

Finally, we should like to call attention to other aspects of these experiments. They gave evidence of the high tolerance of the organism for such deviations from normality as a sixfold increase in volume of the sympathetic ganglia, or their near-total extinction. The injected animals apparently did not differ from controls when raised and observed in the sheltered conditions of the laboratory. Physiological tests are expected to reveal these differences and will therefore be applied to the treated and control animals.

Summary.—We have reported the effects of an antiserum to the nerve-growth factor which selectively destroys most of the sympathetic nerve cells in a variety of newborn mammals. Daily injections for a period of 8 days resulted in the disappearance of up to 99 per cent of the sympathetic nerve cells. This process is irreversible. It is suggested that the salivary glands do not produce the nerve-growth agent but merely accumulate and store it. The mode of action of the antiserum and the possible role of the nerve-growth agent as a maintenance factor for sympathetic neurons are under investigation.

* This work has been supported by a grant from the National Science Foundation and by a contribution from an institutional grant of the American Cancer Society to Washington University.

† For preparation of the antiserum see paper by Cohen, S., 302–311, these PROCEEDINGS.

[1] Edds, M. V. (Ed.), *Conference on Immunology and Development* (Chicago: The University of Chicago Press, 1956).

[2] Cohen, S., and R. Levi-Montalcini, these PROCEEDINGS, **42**, 695–699 (1956).

[3] Levi-Montalcini, R., and S. Cohen, these PROCEEDINGS, 571–574 (1956).

[4] Levi-Montalcini, R., in *The Chemical Basis of Development* (Baltimore: The John Hopkins Press, 1958), pp. 645–664.

[5] Cohen, S., in *The Chemical Basis of Development* (Baltimore: The John Jopkins Press, 1948) pp. 665–676.

[6] Levi-Montalcini, R., *Ann. N. Y. Acad. Sci.*, 330–343 (1952).

[7] Levi-Montalcini R., and V. Hamburger, *J. Exptl. Zool.*, **123**, 233–288 (1953).

[8] Levi-Montalcini, R., H. Meyer, and V. Hamburger, *Cancer Research*, **14**, 49–57 (1954).

[9] Bueker, E. D., *Cancer Research*, **17**, 190–199 (1957).

INFORMATION TO CONTRIBUTORS

THE PROCEEDINGS is the official organ of the NATIONAL ACADEMY OF SCIENCES and of the NATIONAL RESEARCH COUNCIL for the publication of brief accounts of important current researches of members of the ACADEMY and of the COUNCIL and of other American investigators. The PROCEEDINGS will aim especially to secure prompt publication of original announcements of discoveries and wide circulation of the results of American research among investigators in other countries and in all branches of science.

ARTICLES should be brief. The viewpoint should be comprehensive in giving the relation of the paper to previous publications of the author or of others and in exhibiting, where practicable, the significance of the work for other branches of science. Elaborate technical details of the work and long tables of data should be avoided, but authors should be precise in making clear the new results and should give some record of the methods and data upon which they are based.

MANUSCRIPTS should be prepared with a current number of the PROCEEDINGS as a model in matters of form, and should be typewritten in duplicate with double spacing, the author retaining one copy. Illustrations should be confined to text figures of simple character, though more elaborate illustration may be allowed in special instances to authors willing to pay for their preparation and insertion. Particular attention should be given to arranging tabular matter in a simple and concise manner.

MANUSCRIPTS will be accepted only from members of the Academy who will assume responsibility for the propriety and scientific standards of the paper and for any printing costs in excess of those allowed them by the Academy. Manuscripts should be addressed to THE PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES, 2101 Constitution Ave., Washington 25, D. C.

GALLEY PROOF will be sent, with the understanding that charges for author's corrections shall be billed to him. Authors should therefore make final revisions on the typewritten manuscripts. Original artwork or figures will be returned if requested when the manuscript is submitted. Because of time limitations, page proofs will not be sent.

REPRINTS should be ordered when proof is returned, on the reprint order form which will be enclosed with the proof. They will be furnished at cost, approximately as follows:

SCHEDULE OF REPRINT RATES (POSTAGE NOT INCLUDED)

Quantity	*up to 4 pp.*	*up to 8 pp,*	*up to 12 pp.*	*Standard Covers*
50	$ 7.85	$15.10	$22.30	$6.90
100	8.95	17.30	25.60	8.40
150	10.10	19.50	28.95	9.95
add'l 100's	2.20	4.40	6.60	3.05

CONTENTS

file: to be read 64

TO THE MEMBERS OF
THE NATIONAL ACADEMY OF SCIENCES

This report, *Federal Support of Basic Research in Institutions of Higher Learning,* was prepared by the Academy's Committee on Science and Public Policy in accordance with action taken at the annual meeting of the Academy in April 1963. It will be released on March 19, 1964, after which it will be available to the public at two dollars a copy. Please consider it a privileged document until that date.

Frederick Seitz
President

FEDERAL SUPPORT OF BASIC RESEARCH IN INSTITUTIONS OF HIGHER LEARNING

NATIONAL ACADEMY OF SCIENCES

FEDERAL SUPPORT OF BASIC RESEARCH IN INSTITUTIONS OF HIGHER LEARNING

FEDERAL SUPPORT OF BASIC RESEARCH IN INSTITUTIONS OF HIGHER LEARNING

Committee on Science and Public Policy
National Academy of Sciences

National Academy of Sciences—National Research Council
Washington, D.C.
1964

Publication Number 1185

Library of Congress Card Catalog Number 64-60021

The present report, which is addressed to a very basic issue involving the relationship between science and our society, was undertaken by the National Academy of Sciences on the request of its membership at the annual meeting of the Academy in April of 1963. There was an overwhelming opinion among the members not only that the issue was an exceedingly urgent one to study, but also that the Academy's Committee on Science and Public Policy was a most appropriate body to explore the views of the scientific community and to formulate responsible conclusions.

On behalf of the membership of the Academy, I would like to thank the study group, including its consultants, for the high level of dedication it brought to the task.

Frederick Seitz, President
National Academy of Sciences

Washington, D. C.
March 19, 1964

The Committee wishes to acknowledge its great indebtedness to Professor Dupree and Dean Price for their valuable contributions as active participants in its deliberations and in the preparation of this report. It acknowledges also its appreciation of the financial support of this study by the Ford Foundation.

Preface

This report had its origin in a resolution, passed by the American Society of Biological Chemists in April 1963, urgently requesting the National Academy of Sciences "to enunciate the principles and philosophy which could serve as a basic policy in the future conduct and administration of federal programs in support of fundamental research." The resolution described the situation that impelled the request in the following terms:

> *"The condition of mutual dependence between the federal government and institutions of higher learning and research is one of the most profound and significant developments of our time. It is abundantly clear that the fate of this nation is now inextricably interwoven with the vigor and vitality of these institutions. In turn, the fate of these institutions is dependent upon the wisdom and enlightenment with which federal funds are made available in support of their activities. It is imperative, therefore, that the conditions governing this mutual interdependence be subject to continuing appraisal and that the policy underlying administration of federal programs in support of research assures that this relationship will continue to be mutually beneficial."*

Several other scientific societies passed similar resolutions calling for consideration by the National Academy of Sciences of federal support of basic research in institutions of higher learning.

The Academy voted at its annual meeting of 1963 to undertake an appraisal of the subject as defined in the resolution. In June, the Council of the Academy asked the Academy's Committee on Science and Public Policy to prepare a report. Almost the entire membership of the Committee has participated actively in its preparation. Moreover, in response to announcements in several scientific periodicals and to personal letters soliciting the views of the membership of the National Academy of Sciences, many comments and constructive suggestions were submitted to the Committee. It is against the background of the thoughtful expression of many individual investigators, therefore, that the Committee has prepared this report, taking account of a broad spectrum of opinion among scientists. The Committee accepts full and sole responsibility, however, for its conclusions.

The resolution that called for this report was prompted by an increasing concern, both in the Congress and in the scientific community, about the principles that guide the federal government's system of science support in the universities. The sheer size of the government's financial stake in research and development might alone have triggered this stock-taking. The figure of $14.9 billion, so often heard, is not fiscal year 1964 government investment in *basic* research, but rather in its *total* research and development effort, encompassing many military and space development programs. Nevertheless, a figure of nearly $1.5 billion (this year) for basic research in the United States, of which almost half goes to institutions of higher learning, is sufficient cause for thought and discussion.

More immediately, reports of the Intergovernmental Relations Subcommittee of the House Committee on Government Operations, dealing with grant policy and administrative practices of the National Institutes of Health, have marked the beginning of a period in which government agencies have been revising their policies. Much of the discussion within the scientific community has been closely focused on administrative changes of direct consequence to the individual investigator. Even the original resolution of the American Society of Biological Chemists, however, envisaged not a narrow examination of specific issues but a study covering the general policies of all the government agencies supporting basic research in the universities. The action of the National Academy of Sciences confirmed this concern with principles rather than specific cases. The swift-moving events of the last half of 1963—the period of the deliberations relating to this report—have amply justified the wisdom of emphasizing the fundamental relationships of the government and institutions of higher learning, rather than specific incidents.

Three main elements have entered into the Committee's consideration—the federal government, the institutions of higher

learning, and the community of professional scientists in these institutions, most of whom are also members of teaching faculties. These are the same three elements dealt with in the statement of the President's Science Advisory Committee entitled, *Scientific Progress, the Universities, and the Federal Government,* issued in November 1960. That report set forth a rationale for federal support of basic research in institutions of higher learning and reasons why the support of basic research and the support of graduate education must be merged. The present report is a sequel, in that it accepts the major assertions of the report of the President's Committee and moves on to consider how the donors and recipients of government support should manage their interrelationship.

One principle dominates all others in the present report: The government and the universities must work within two noble traditions characteristic of all free societies—the political freedom of a democratic people and the freedom of scientific inquiry. The scientific community, the Congress, and the Executive have long since agreed both that a strong and free development of science is a national necessity and that accountability for the use of government funds is a fundamental part of the exchange by which a people in a democracy entrusts power to its leaders, who are in fact and theory public servants. Can freedom of scientific inquiry and accountability be reconciled? We believe that they can be and must be. We ask in this report: What are the policies by which accountable support can effectively advance scientific inquiry in the common interest? How can inaccurate conceptions of both *the necessary freedom for scientific research* and *the accountability of funds* be prevented from stifling the fruits of research—a potent resource of our society not only for today but for the future?

Many important matters cannot receive full consideration here. Development and applied research claim and will continue to claim a large share of money and talent in both government and industry. In many instances, the scientific community has found the surroundings it needs for outstanding work within the walls of both governmental and industrial laboratories as well as in the universities. Moreover, the universities have essential purposes that transcend basic research, graduate education, and science itself. Nevertheless, we shall give but little attention to these considerations, and will limit our report for the most part to consideration of federal support of basic research in institutions of higher learning. It is at this point, where the universities, the government, and the scientific community come together, that the issue of reconciling scientific freedom with fiscal responsibility appears most clearly and is in greatest need of wise formulation of policy and mutually satisfactory means of implementation.

Contents

CONCLUSIONS

The commitment of large public funds for the support of basic research in universities has led not only to spectacular growth of the scope of scientific effort but also to advances in quality: American science has reached a position of world leadership. We attribute this in no small measure to enlightened policies of several federal agencies committed to furtherance of basic research; specifically to the current emphasis on support by research project grants and by fixed-price research contracts (not too unlike grants), coupled with an extensive use of advisory scientific bodies, such as panels or study sections, to select scientifically meritorious projects for support. We believe that research project grants and contracts should remain the backbone of federal policy in support of basic research in science in universities. The emphasis on large programmatic ventures and laboratories which has been manifest in recent times must not lead to a loss of emphasis on individual scientists: the individual investigator has been and will remain the source of strength in American science.

Concerning Federal Agencies

1. The criterion of selection for grant or contract support of basic research has been primarily the scientific quality of the work proposed. The selection of projects on this basis has come about in various ways, but particularly as a result of the judgment of scientists well versed in the areas concerned. We believe this merit judgment should be retained as a prime basis for federal support. The methods of obtaining this merit judgment at present vary; the following meas-

ures will strengthen and bring greater effectiveness to the judging process.

(a) Federal agencies not presently using study sections or advisory panels for the merit rating of research proposals would improve the quality of their research programs by the adoption of these or similar devices.

(b) Membership in the panels and sections should be on a relatively short-term rotating basis, and wide circles (in terms of scientific disciplines, geography, and function) of the scientific community should be tapped for this service. This is necessary because conscientious service on such panels is very costly in time to consulting scientific personnel. Moreover, we are convinced that infusion of new blood into the sections and panels is conducive to the maintenance of high scientific standards and helps to induce the selection of the most original and promising research proposals.

(c) When panel, section, or consultant activity has resulted in ordering of proposals by scientific merit, the order suggested should be seriously considered by the federal agency staffs and modified only in special circumstances which are explained to the panel or section members.

(d) Panels and sections should not be involved in detailed evaluation of proposed budgets, although panel judgments on the general reasonableness of proposed budgets should be seriously considered by agency staffs. Detailed budget considerations should be the responsibility of agency staffs alone. However, panel or section judgments as to the proper duration of grants or contracts should be given considerable weight by the agency staffs. While panels and sections must supply the primary judgments regarding scientific merit, questions of administrative responsibility and agency policy must be dealt with by full-time staff members, and the agency itself must assume responsibility for the final decisions with regard to awards of grants and contracts. For this reason, we strongly endorse the efforts of the government to improve the quality of the career service, by providing compensation at levels comparable with private salaries, and by encouraging staff members to continue their scientific and professional advancement.

(e) Consultation with scientific referees by mail is less satisfactory than the panel-section procedures. Where this procedure is used, however, it is essential to keep the referees informed as to the effect of their advice in each case. Failure to do so is bound to lead to less responsible attitudes among referees and in the end to purely administrative choices of projects. We do not believe that personnel whose main functions are administrative can for long retain keen judgment as to what is most promising in science. We believe, therefore, that purely administrative mechanisms for selec-

tion of worthy research proposals would lead to inferior programs and thus to a waste of public funds.

2. The advantages of grants generally outweigh those of fixed-price contracts for basic research. However, research contracts have been developed into legal instruments that place few restrictions on the principal investigator beyond those imposed by grant arrangements under present regulations. Unfortunately, there is a current trend toward introducing into grant and contract negotiations and regulations administrative restrictions that are inimical to effective basic research. We believe that this trend should be reversed, with the universities taking increasing responsibility for proper administration of grants and contracts.

3. We recognize and endorse the fundamental legal principle that public funds may be spent by contractors and grantees only for stated purposes, and thus that diversion of funds to other purposes cannot be tolerated. We welcome in principle the issuance of guidelines concerning the expenditure of grant and contract funds. But we discern a recent trend toward unnecessary restriction of scientific freedom and increases in the bookkeeping chores of scientists in both grants and contracts; we believe that this trend will result in lower returns on the investment of public funds in science.

4. The project proposal by an applicant states the purpose of the requested grant. The implications of this are not always understood by applicants. We believe that many difficulties could be avoided if the federal agencies, in their printed instructions for the preparation of research proposals, explained clearly the relation between the contents of a proposal and the purpose of the grant. Scientists should bear in mind in making application for grants that the preambles of their proposals define the purposes for which granted public funds may be spent. We believe that a project proposal should include:

(a) Broad objectives of the proposed research in terms of areas of scientific knowledge to be advanced.

(b) Specific early research objectives stated as illustrative of the broader aims.

(c) Scientific tactics (experimental methods) to be employed.

We also hold that the grant or contract instrument should explicitly recognize the broad objectives (a) as its legal purpose. Only a deviation from the broad objectives of a project proposal, thus stated, should be considered as constituting a change in the purpose of the grant, thus calling for special approval from the federal agency.

5. Current regulations concerning the expenditure of grant moneys restrict the transfer of funds from one budgetary item to

another. We believe that these regulations are quite proper insofar as they deal with the compensation of senior personnel, with travel (especially travel abroad), and with improvements in the facilities of the grantee institution. On the other hand, we believe that the principal investigator should be given maximum latitude in spending other grant moneys for the stated purpose of the grant as he sees fit. Ordinarily, so much time passes between the preparation of a proposal and the expenditure of grant funds that preferred tactics change, new equipment becomes available, and so forth. We believe that the principal investigator should be free to shift funds between budget items of equipment and expendable supplies, and that a provision that the principal investigator explain the reasons for substantial shifts, in his application for renewal or continuation of the grant, would provide an adequate safeguard against misuse of grant funds. At the very least we urge that the present limit (usually $500) on purchase of initially unspecified equipment be increased in some proportion to the total value of the grant. Thus principal investigators will be spared a great deal of wasteful paper work to obtain, necessarily, either perfunctory approvals or arbitrary refusals from remote agency staffs.

6. The accounting for part-time service of principal investigators and other academic personnel in projects supported by research grants or contracts, whether or not such service is paid for with grant funds, must be realistically related to the input of professional effort on the project. We believe that accounting for research effort in terms of time input, i.e., in terms of days or hours, is unrealistic and can lead to fiscal policies that fail to make allowances for the nature of scientific research. We recommend that accounting for effort of professional personnel on a grant or contract be expressed in terms of some fraction of the total effort applied by the individual to his university duties.

The full fiscal year of a grant, or the full academic year, is recommended as the minimum period of time for which accounting of service should be made by a university. However, the time periods in which individual scientists have no university duties, such as summer vacations, may be accounted for separately.

7. We are not competent to enter into a detailed discussion of the problem of appropriate overhead costs. We believe, however, that inadequate provision for such costs is harmful to the universities as communities of scholars dedicated to the balanced education of American youth. We urge that overhead payments be provided for, on grants as well as on contracts, based on application of essentially the same formula in both instruments.

8. While we strongly endorse the project grant/contract system of research support, we believe that three auxiliary types of

support are also necessary for the healthy growth of American science.

(a) The first of these are institutional or general research grants related to existing totals of project grants, now being made on too modest a scale by the National Institutes of Health and the National Science Foundation. These should be strengthened and broadened in purpose to overcome serious imbalances created in the universities by the growth of existing project research support and to meet the need for initial support of new projects.

(b) The second type is necessary to meet the problem of junior faculty members who have difficulties obtaining support for independent research. We believe that a system of *small research grants*—on a modest scale—should be introduced. These would be awarded to junior scientists for individual research on the basis of a very general outline of their research interests, supported by letters of endorsement from senior scientists personally acquainted with the work of applicants. Aside from an agreed sum as reimbursement to the grantee institution for work of the applicant, the budget should provide only for supplies and smaller items of equipment, but should not be broken down into component parts. The grantee investigator should, within the purpose of the grant, be allowed to pursue such researches as appear most fruitful to him in the broad area defined in the application. Some truly original ideas and discoveries have come from young scientists, and we cannot afford to tie them down to narrowly defined research objectives.

(c) The nation faces the problem, in addition to that of rapidly growing population, of an even faster-growing need for highly educated personnel. This, we believe, makes the efforts to increase the number of strong educational institutions a matter of first importance. Therefore, we urge a third type of auxiliary support: a distinct and selective program of research grants to be made available to some weaker institutions on the basis of demonstrated will to utilize new funds to raise the level of research and graduate education. The number of strong institutions must grow. We recognize that the framing of criteria by which such grants can be awarded is not an easy task, and invite careful study of the problem by a competent task force.

9. We subscribe to the conviction, expressed in the President's Science Advisory Committee 1960 report, *Scientific Progress, the Universities, and the Federal Government,* that research and the graduate education of young scientists are intimately related. Considerable progress has been made in modifying federal agency policies to adapt them to this principle since the issuance of that report. We urge continuing review of such policies in the same direction; only thus can the nation be prepared for the future.

10. In surveying the practices and regulations of the several federal agencies engaged in support of basic research, we find an extraordinary diversity. At the same time we find a growing tendency to provide the same principal investigator with multiple grants and contracts, often from different agencies, to support closely related facets of his work.

We recognize the advantages of some variation in the practices of the several agencies, and of multiple sources of support where a principal investigator is engaged in research toward several objectives. We believe, however, that the present situation forces investigators to devote too much time to detailed accounting and other non-productive administrative matters. We urge that vigorous efforts be undertaken (a) to simplify and align the requirements of the several agencies regarding preparation of research proposals, accounting, progress reporting, and similar matters, and (b) to reduce the need for multiple support by more inter-agency agreements designating a single agency to provide total support of an investigator's work in a given scientific area.

Concerning the Universities

11. A clearer recognition by university administrations of the purpose of federal project grants and contracts for basic research is an essential requirement.

12. In dealing with federal agencies, university administrations should assert more clearly and emphatically the central purpose of American universities: the advanced education of American youth integrated with the scholarly activities of teachers; in the natural sciences these activities take primarily the form of scientific research. This purpose is not inconsistent with the purpose of the federal government in providing grants and contracts for basic research. It should be stated and restated lest both the government's purpose and the purpose of the universities be obscured by the administrative practices of the agencies.

13. University administrations, certainly no less than federal agencies, can defeat the basic purpose of federal grants or contracts for project research by their policies; for instance, by imposition of unnecessary bureaucratic controls and red tape on principal investigators, or by neglect of the investigator's problems in dealing with federal agencies. We urge a more consistent policy of positive cooperation between university administrations and the faculties engaged in research under federal sponsorship. The specific organizational forms such a policy calls for depend upon local circumstances. One form, which we believe could be widely useful, is a joint committee or board, made up of representatives of the administration, the faculty engaged in research, and supporting staff.

Some of the responsibilities that should be assumed, or acted upon more consistently, by university administrations are as follows:

(a) There should be a clear definition of the mutual responsibilities and authority of university administrations and principal investigators under grants and contracts.

(b) There should be a review of research proposals by faculty personnel to ensure only that they are not inconsistent with the concept of the university as a community of scholars engaged in both education of youth and the advancement of knowledge.

(c) There should be assistance to faculty personnel in the preparation of research proposals, to ensure that the wording of the proposals will not place undue restrictions on the scientific freedom of principal investigators.

(d) Principal investigators should be educated in the responsibilities that they assume when using federal funds in support of research.

(e) There should be an explanation to faculty personnel, primarily principal investigators, of the purposes for which overhead funds and institutional grants are being spent. Understanding of this will reduce rather widespread misunderstandings among faculties and assist in developing more harmonious relations between faculties and university administrations.

(f) Principal investigators should be relieved of as much budgetary work as possible, kept informed of the status of and commitments under grants and contracts, alerted to the possibility of disallowance of certain expenditures, and in other ways apprised of essential fiscal requirements.

Concerning the Scientific Community

14. We believe that understanding of the purpose of the federal support of basic research by the project grant/contract system is not sufficiently widespread in the scientific community. Grants and contracts are given as trusts to institutions for a purpose, which is substantially as described by the principal investigator in his proposal. The investigator assumes a major responsibility in accepting federal funds and has an obligation to account for their proper use. Acceptance of a grant commits him to a conscientious effort to achieve its stated purpose; he acquires no other rights to the granted or contracted funds.

15. To make the project grant/contract system consistent with essential freedoms of scientific research, the substance of project proposals must be properly formulated. We have described (conclusion 4) the general form of proposals that should be acceptable to federal agencies and that should minimize the problem of overly restrictive interpretation of the purpose of a grant. We urge the

scientific community to present proposals in accordance with the recommendations contained in conclusion number 4.

16. The quality and effectiveness of the project grant/contract system can be no better than the scientific community makes it, by conscientious and enlightened service on panels, study sections, and other advisory bodies and as consultants in the selection of the best research proposals. We urge the scientific community to see such service in this light and to give time willingly to it.

17. In concluding our findings, we want to remind that part of the total scientific community to which we address ourselves that they, being part of the university community, are part of a society of scholars; that they have an obligation to their society: to share in the education of youth as well as in advancing scientific knowledge.

The federal government, the universities, and the scientific community have entered into an enlightened partnership whose common purpose is the advancement of scientific knowledge and the upbringing of younger cadres to continue this task. This report is but a reminder of this central fact and an attempt to set out a few simple guidelines that should reduce some mutual irritations and help the partnership in its grand purpose of advancing the welfare of our nation and of all mankind.

INTRODUCTION

The Role of Basic Research and of the Scientist in Mid-Twentieth Century America

Characteristics of Basic Research

The objective of basic research is to increase our understanding of nature. The objective of development and of applied research is to apply such understanding to human uses. Because a use for some result of basic research is not immediately apparent, it need not remain useless forever; on the other hand, it is not to be taken as inevitable that it will become useful. Centuries of experience demonstrate the likelihood that some results of basic research will prove useful and that it is often impossible to foresee before the research is carried out which results will be useful and which not. The total cost of all basic research in progress in a given period may be more than repaid by the long-lasting benefits from the uses of even a small part of the result.

By definition, the objectives of basic research, in contrast with the objectives of developmental research, are *exploration of the unknown or little known.* Frequently it becomes apparent in the course of research efforts that a different approach must be taken in order to realize anticipated objectives. It is then folly to insist on proceeding according to the original plan, and so to fail or to delay progress toward meaningful results. An investigator, necessarily being unable to describe in advance the discoveries that will be made in the course of his research, should not be expected to adhere to a course mapped out in advance. Progress is the measure of his success, and progress is initially oriented by a particular question or set of questions, by tentative experimental plans, by tentative indication of usable techniques and methods. As the investigator proceeds from such a starting point, subsequent developments may indicate that the initial plans, experiments, or methods are less promising than anticipated or even that they will not lead to significant results. Responsibility as well as wisdom then dictates that they should be

replaced by other questions, experiments, or methods. Retaining the original approach runs the risk of forcing a change in the direction of the research, while a new formulation may actually be required for satisfactory progress of the kind originally anticipated.

The Scientific Community

The community of scientists is not a formal organization limited by any membership list or even by national boundaries. No single leader anywhere has an authorized right to speak for the whole of it. Membership is based on scientific accomplishment. It has been in existence at least since the seventeenth century, and over the years it has gradually developed the means of publication and continuous internal criticism by which the results of research and interpretations of them are checked and winnowed. The various fields of science are "disciplines" in the literal sense of the word, for the scientific community has developed the apparatus by which the results of its activity are continuously subject to scrutiny and criticism of the most searching sort. The great and evolving strength of this disciplinary system stems from the continuous exercise of objective judgment by the scientific community concerning the validity and significance of scientific findings. The expressions "freedom of science" and "freedom of scientific inquiry" refer to the intellectual freedom of the scientist to conduct his research and reach his conclusions in his own way, and then to test them against the judgment of his peers. These often-misunderstood expressions do not refer to special political or economic freedoms but to the reasonable contention that experienced scholars and investigators have the best prepared minds in their own fields for devising pathways to new knowledge and for interpreting what they find as they progress.

World Leadership in Basic Research Has Shifted to the United States

Though no longer a colony of Great Britain, the United States remained colonial in its research institutions long after 1776. Indeed many scientists living today grew up in an atmosphere of awe toward the great European centers of learning. When James B. Conant looked out over the assembled delegates at the Harvard Tercentenary in 1936, he could feel that his university, for all its resources, still had only a modest place among the ancient and illustrious centers of research and education in the western world. At the commencement in 1947, when he and Secretary of State George C. Marshall looked out on the assemblage and contemplated the wreck of western Europe, they both saw that the United States had a new and unique responsibility. It was on this occasion that the Secretary of State made the speech that led to the Marshall Plan. Just as the

American people responded to the call of Marshall for the rehabilitation of Europe, the American university and the American segment of the scientific community had to respond to the clear demand of history that they assume the responsibilities of world leadership.

This fundamental change of position coincides with the rise of federal support for scientific research. World leadership could not possibly have come to the United States if the government had not possessed both the enlightenment and the mechanisms to allow American scientists to take up the challenge. Yet the new leadership was not entirely a matter for self-congratulation, since it was born of the misfortunes of civilization as well as of American action. American leadership in basic research had its roots in the blood shed along the Somme and the Marne and at Verdun. The destruction of the freedom of the German university system by the Nazis played its part. Twice-sacked Louvain served as a symbol for the destruction of institutions of higher learning. One of the more inspiring features of this gloomy scene is the fact that many victims of war and totalitarianism found opportunities in the United States for the brilliant research of which they were capable.

Statistical measures give only a pale indication of the extent of the American assumption of world leadership in basic research. The percentage of Americans among the foreign memberships of the great academies of Europe went up very steeply after 1945. The award of Nobel prizes is another measure of quality in certain fields of science. In the years 1900 to 1930, Americans received only 4 of 92 awards. In the decade 1931 to 1940, the United States was still represented by only 9 of 34 awards. Yet, in the decade 1941 to 1950, the number rose to 15 of 36 awards, and, in the decade 1951 to 1960, to 27 of 52 awards, or about half. In 1933 in key British and German scientific journals, references to American work were a small fraction of all references to foreign sources. In 1963, references to American journals exceed considerably in number those to all other foreign journals. The use of such means of measurement is not necessary, however. Common observation affords massive and persuasive proof that the United States has assumed a large role in basic research since 1945.

Has Federal Support Been a Boon to Science?

The United States has achieved scientific leadership by being willing to invest heavily in science. American leadership and federal support have joined to make the mid-twentieth century a brilliant period in the history of science. The period since 1945 has been amazingly productive of scientific advances.

Physics has moved into one of the great ages of its history as experimentation with ever higher energies has made it possible

to get at the particles that make up the nucleus of the atom. Without large accelerators, which cost many millions of dollars provided by federal support, physicists would be shut out from many lines of investigation. Yet these great accomplishments of experimental nuclear physics have been only part of the story. Progress in solid-state physics has been spectacular. Many groups have developed skills in theoretical physics unknown in the United States 30 or 40 years ago. Out of the basic research has come a flood of applications. The fission of uranium and thermonuclear reactions have, of course, been used in the bombs. But nuclear reactors are also used for peaceful purposes, such as the production of electric power. The theory and experiments of solid-state physics lie behind the development of the transistor. Masers and lasers, undreamed of and unnamed a few years ago, now attract both scientific and public attention. The general picture in American physics is one of vigorous activity and significant progress, with no slowing down in sight.

In chemical science, a new and deeper understanding of molecular structure and behavior has come into being, due in large part to American initiative. Skillful use of totally new and costly techniques, such as nuclear magnetic resonance, electron spin resonance, and microwave spectra, for example, has played an important role in this progress. The new understanding is the foundation beneath many of the developments of new materials for agriculture, textiles, structural materials for almost all of modern industry, power production, communications, and biological manipulation of all sorts, particularly chemotherapy. Chemistry has also been stimulated in the post-war period because its lines of research have tended to converge with those of physics and biology. On the one hand, the discovery of the transuranium elements is closely akin to nuclear physics; on the other hand, the discovery of the biological activity of nucleic acids has brought chemistry into central problems of genetics by making possible the study of the gene at the molecular level. All this work requires electron microscopes, ultracentrifuges, mass spectrometers, and similar equipment to proceed at all. No university can hope to acquire much of such equipment without assistance. It also requires many investigators trained to new standards of excellence in chemistry and, at the same time, much more aware than their predecessors of developments in other fields.

Biology has moved into a spectacular new biochemical and biophysical era marked by fruitful concentrated attacks on its simplest and most fundamental phenomena. The genetic material was shown to be nucleic acid. The structure of DNA was discovered, and this led quickly to understanding in molecular terms the reproduction, mutation, and action of the gene, and later to deciphering the genetic code. These are among the greatest scientific advances

of all time. They shed a brilliant new light on age-old questions of the origin and nature of life. They have led to new insights into the nature and action of viruses, major agents of disease. Extension of all these revolutionary findings to man is initiating what will surely prove to be a period of great progress in understanding human genetics, physiology, and pathology. Side by side with these biochemical achievements, which include many other things such as deeper and fuller understanding of photosynthesis, upon which our supply of food and energy ultimately depends, have also come biophysical achievements such as those in radiation biology and electron microscopy. The latter, by opening up a new order of visibility, has revealed previously unsuspected similarities of cellular structure in all living creatures and is leading to corresponding advances in understanding cellular functioning.

The shift to biochemical and biophysical molecular biology has not, however, rendered classical fields less fertile. Ecology, animal behavior, and many other older areas have become major objects of investigation in new and promising ways. Genetics has put new life in biological research that many gossips thought moribund—taxonomy, for instance. The new style of work in biology is heavily dependent upon modern physical instruments—such as electron microscopes, ultra-centrifuges, spectrometers, scintillation counters, amino acid analyzers, computers, and the like. Skilled technical assistance is needed in their use. Again, no university is able, unaided, to keep pace with the demands.

Mathematics in the United States has moved from colonial status to a position of pre-eminence. The solution of a famous unsolved problem by George D. Birkhoff in 1913 was an American scientific landmark. Such events have been rare. Since 1959, however, young American mathematicians have contributed to the solutions of at least five problems of comparable importance. In every case, some of the work involved in these solutions was supported by a government agency. Mathematics has also moved into an important auxiliary position in almost every line of research.

The role of science in modern society has recently been described by the President of the National Academy of Sciences, Dr. Frederick Seitz, in the following terms:

"It is important to note that the first support of science in European society was provided by the enlightened aristocracy in a desire to increase that enlightenment. Everyone hoped that the work of the scientists would prove useful, but did not demand it. In this period, well before the Industrial Revolution, it was considered sufficient to get more understanding of the laws of nature relating to matter and energy, to understand more about such things as the shape and size of the earth, the distances to the moon,

the planets and the sun, and to classify the various forms of life which are found on the earth.

"Events proved that the systematic knowledge and general concepts which came out of science were exceedingly valuable in helping man to live more nearly in harmony with nature in countless ways. They lightened his burdens and made him more free. The useful aspects of science were greatly magnified once the Industrial Revolution got under way in the seventeenth and eighteenth centuries. At first, the engineer, who was responsible for the Industrial Revolution, found that only portions of science were useful, and even then, only in a limited way.

"In our century, the discoveries of science have become so complex that the scientist has had to work hand in hand with the engineer in exploiting them for practical purposes. This cooperation between the scientist and the engineer is now so close that the person who is not a professional scientist or engineer is quite apt to think of science almost exclusively in terms of applications. I wish to emphasize, however, that the uses of science for human welfare in areas such as energy conversion, communications, and medicine are always accompanied by contributions to human enlightenment which lift our minds farther and farther from the primitive origins of the past."

We believe that the scene in basic research would be far different if the federal government had not played a positive role. The federal government, the universities, and the scientific community have worked together to make this present age of science possible. Indeed, one of the outstanding accomplishments of the democratic system of government in the United States over the last 25 years had been the forging of a durable and flexible alliance between government and science. In its totality, the system of support of research in the universities by federal funds is a fine example of responsible government in action. The system has been made of different pieces at different times, and only a complicated statistical analysis can define the extent of the relation. However, from the very breadth and complexity of the system stems a lack of public understanding, even among people who have had experience with parts of it.

Clearly the system was not created in secret, as some conclude, without the consultation and support of the people's representatives—the Congress, on the one hand, and the spokesmen for the scientific community on the other. Some of the best legislative talent of a generation laboriously shaped its components, and the procedures have been thoroughly tested at every level of the government. The story of the fashioning of the system is worth the telling in brief form simply because, so well known in its discrete parts, it is so seldom put together for consideration as a whole.

BACKGROUND OF THE ALLIANCE BETWEEN THE FEDERAL GOVERNMENT AND INSTITUTIONS OF HIGHER LEARNING

I

The Heritage Available in 1939

Congress and Science

The Congress has had continuous and fruitful relations with science ever since the early days of the republic. Long before the end of the nineteenth century, it had learned some obvious lessons about the administration of science. For instance, the attempt by the Joint Library Committee to arrange for the publication of the scientific results of the Wilkes Expedition (the first major national effort in the professional use of scientists in exploration, 1838-1842) had demonstrated the inappropriateness of any attempt by Congress to oversee directly a scientific enterprise in every technical detail. Congress had played its part in the creative resolution of the problem of overlapping scientific jurisdictions when the United States Geological Survey was established in 1879. If larger appropriations for the scientific work of the government were not always forthcoming, they were not withheld after 1865 because of any theoretical doubts about the propriety of federal support.[1] The Allison Commission amply aired the whole subject between 1884 and 1886.

One characteristic of the governmental posture toward science in the nineteenth century is worthy of special note: the Congress at no time took a stand against the government's participation in basic research. Through the continuous spectrum of scientific activities, from the pursuit of knowledge for its own sake to the intensive application of the fruits of research, the government was

---

[1] A. Hunter Dupree, *Science in the Federal Government: A History of Policies and Activities in 1940* (Cambridge, Massachusetts, 1957), 73, 195-214, 380. Professor Dupree's study was supported by a grant from the National Science Foundation.

naturally at all times concerned with the applications that would further its missions. Yet the rule to which nineteenth-century lawmakers gave allegiance was that the federal government should do "such work as is within neither the province nor the capacity of the individual or of the universities, or of associations and scientific societies." [2] When the ability of private colleges to conduct research was low, the federal government considered it part of its responsibility to help science as such. As Thomas Jefferson said, "a public institution can alone supply those sciences which though rarely called for are yet necessary to complete the circle, all the parts of which contribute to the improvement of the country, and some of them to its preservation."[3] The Smithsonian Institution is the major example of the federal government's commitment to basic research in the nineteenth century, but it is not the only one. In an age particularly conscious of the sphere of action of local institutions, both public and private, Congress saw the need for basic research and attempted to meet it.

The Federal Scientific Establishment before 1939

Congress opened the twentieth century with an increasing awareness of the government's need for research institutions to carry out many of its functions. For instance, in 1901 it met the constitutional demand for standards of weights and measures by changing a modest and administratively orphaned program into the National Bureau of Standards. The charter was broad and flexible enough to give the new institution a place among the national physical laboratories of the world and to enable it to cope successfully with rapidly changing scientific and technological developments.

By 1916 an impressive federal scientific establishment with its own laboratories and highly educated personnel had taken clear shape. It was responsive to the government's need for research in its own operations, such as the Army and Navy, at the same time that it served some large interests of the country that could not provide their own research. American agriculture had at its disposal a unique and flexible research service that had few parallels and was already beginning to affect the welfare of the nation in a broad way. Even so recent a development as the airplane called forth a governmental response in the creation of the National Advisory Committee for Aeronautics in 1915.

---

[2] [Alexander Agassiz], "The National Government and Science," *Nation,* Vol. 41 (1885), 526.

[3] Thomas Jefferson, in J. D. Richardson, com., *Compilation of the Messages and Papers of the Presidents, 1789-1897* (Nashville, 1905), I, 409.

The Constitutionality of Federal Activity in Science

Congressional enactment of legislation, creating the federal research establishment over a long period of time and in response to many different needs, provides important background for the constitutional position of science within the government. Each piece of legislation stands the test of constitutionality in terms of solving a problem of the government, rather than in terms of specific authorization in the Constitution. Science is specifically mentioned in the Constitution only in connection with patents, but among the founding fathers the advancement of science was generally considered to be closely related to the advance of political freedom and representative government. Patents, weights and measures, and the census were all matters that suggested in 1787 the interest of the federal government in activities that were to grow in range and depth with the increasing development of science and technology. By the twentieth century the growth of the government's scientific establishment was clear evidence that the power to tax for the general welfare, to regulate commerce, to establish post offices and post roads, to raise and support armies, to provide and maintain a navy, involved the power to conduct research in furtherance of government missions.

Public health provides an example of the constitutional basis for government support of research. Not mentioned specifically in the Constitution at all, public health became an object of concern to the federal government as early as 1798, when it undertook the specific task of providing hospitals for merchant seamen. Yet health is a common concern that transcends community, state, and national boundaries. Federal responsibility for public health has followed disease and the conditions that produce disease into areas where no local authority is capable of acting effectively. The commerce clause, the taxing power, the appropriation power, the postal power, the treaty-making power, and the national war power have all contributed to the development of the public health function of the federal government. In 1912, the act creating the Public Health Service stated that the "Public Health Service may study and investigate the diseases of man and conditions influencing the propagation and spread thereof. . . ." This grant of power was recognized even in the 1930's as "broad enough to cover virtually any activity in the field of public health. . . ."[4] Thus Congress has built up through its legislation a many-rooted statutory structure which upholds the government's research operations.

[4] National Resources Committee, *Research—A National Resource* (Washington, 1938), I, 96-97.

Professional Scientists and the Necessary Conditions for Research in Government Service

In a continuous conversation with Congress over a century and a half, the scientific community also has taken a solicitous interest in the building of the federal research establishment. Those scientists who have undertaken the responsibility of carrying out research for the government and of administering the scientific bureaus have not been backward in stating the special requirements that science demands of its partner—the government. Though varying in intensity as times and issues change, these requirements are so stable that Ferdinand Rudolph Hassler, the first director of the United States Coast Survey, formulated most of them before 1842 in almost their modern form. The major requirements that one generation of scientists after another has urged upon the government may be summarized in the following propositions.

(1) *The need for long-term support.* The scientist cannot fit his experiments or the staffing and equipping of a laboratory into short periods arbitrarily laid down by a budget tied to a calendar.

(2) *The need for flexibility in objectives.* Research, as an exploration of the unknown, by definition precludes rigid projection of the shape of scientific thought and experimentation very far into the future.

(3) *Freedom to publish.* The discovery of knowledge without its communication leaves the process of research incomplete. American scientists have insisted on this point early and late, and they have suffered when it has been breached, as when the brilliant explorations of Lewis and Clark failed to have their full effect because of the lack of machinery for publication of the results.

(4) *Access to the international scientific community.* Government research, like all other research in the United States, grew up under the shadow of European accomplishments. To break communication with Europe meant not only cutting off a source of knowledge of great value but also blocking the avenue for American science to add to its stature by making contributions of its own.

(5) *The need to improve the position of the professional scientist in American society.* The people who represented science in discussions with the government were aware that pay and conditions of work were a reflection of the value that Americans placed on science, and they worked incessantly to raise that value because of their sense of what science could contribute to the national life.

Congressional Friends of Science

As the spokesmen for science urged these five themes before Congress through the years, they had to contend with many dif-

ficulties. Scientists could not attract attention by their numbers, and in the earlier periods they had trouble establishing an obvious connection between their research and the practical interests of the common man. The lament of Senator Simon Cameron, as he slashed at a $6,000 appropriation for the Smithsonian Institution in 1861, echoes down through the years. "I am tired of this thing called science here." Yet the Senate voted the $6,000 by twenty-eight to six.[5] Joseph Henry, the secretary of the Smithsonian, had friends in Congress, and scientists have in every generation had effective help from members of both Houses. The two groups—scientists and politicians —built the research establishment together.

The friends of science in Congress may or may not have constituted a majority. They have usually not had a scientific education, and their interest in science has not stemmed from any professional connection with it. Sometimes their attention has been called to the subject by people and institutions within their home districts, but usually they have discovered science as an area of public policy through their specialized work on committees in Congress. The friends of science have usually joined the scientists who appear before them in considering science "non-political" in any narrow sense of the term. As a corollary, they have come from all political parties and have often divided among themselves on other issues. It has been their constant work over the years to hold the hearings, to study the issues, to draft the organic acts, and to defend the appropriations that have made the federal scientific establishment possible.

The Status of the Various Sectors of Science Support

Great as had been the accomplishments of the government in institution-building and precedent-building for science, the years between the onset of the Great Depression and the second World War brought into sharp relief the shortcomings of the American research structure and the need for more and better research. Each of the major sectors of science support had its own tradition and internal coherence, but their greatest limitation was a lack of clear relation, even in some cases a lack of communication, between them. The four major sectors of American society that provided the support of science were: the government; the universities; industry; and the private foundations.

a. *The government:* The government's research establishment had lost some of the lustre of its position relative to other sec-

---

[5] W. J. Rhees, ed. *The Smithsonian Institution: Documents Relative to its Origin and History, 1835-1899* (Smithsonian Institution, *Miscellaneous Collections,* XLII-XLIII, Washington, 1901), I, 611.

tors of science support by the 1930's. The depression had meant severely cut budgets that did not rebound quickly. The bureaus had trouble holding good scientists and in securing adequate laboratories and equipment. The Department of Agriculture, with its network of experiment stations and land-grant colleges, weathered the storm better than many other agencies. The military departments were able to carry on research only at a very modest level through most of the 1930's. In terms of financial support, national security ranked well below agriculture and only a little above natural resources in the functional categories of government research and development.

b. *The universities:* In contrast, the American university had clearly emerged by the 1930's as the home of basic research. It had also, thanks to federal grant programs to the states beginning with the Morrill Land-Grant Act of 1862, developed a distinctive capability for conducting research in certain broad fields of applied science such as agriculture. Yet the American university was a strikingly recent phenomenon in the nation's experience. It had scarcely begun to take form in 1880, and much of the development of its strong and specialized departments, its laboratories, and its great research libraries came after 1900. The best creative brains of American science found a haven as professors at a small number of universities, where they taught graduate students and performed research supported in part by university funds derived from state or private sources. In part also, university research was supported by the professors themselves, in the sense that they did not render accounting to anyone for their time or for many minor expenditures. They simply did what research their other duties and their own pocketbooks allowed them to do.

c. *Industry:* Industrial research as a distinct sector had crystallized even later than the universities. The spread of the industrial research laboratory among the corporations of the United States had been one of the most striking developments of the years after World War I. And the laboratories had found for themselves an increasingly well-defined and effective place in corporate structure. More and more businesses were finding science not only a useful handmaiden in testing and production but also an organized source of innovation and diversification. In some industries, notably electrical manufacturing and chemicals, research had moved to the center of the stage. In these industries, increasing emphasis on creative thinking and basic research could be noted. By and large, industrial research was tied to corporate organization, and research as an independent business or as the function of industry associations was a minor theme. In only a few instances, where the number of economic units was large, as in the case of the Bureau of Mines, did the fed-

eral government play the direct role in industrial research to which it was quite accustomed in agriculture. The morale was high in the industrial sector in the late 1930's, and an air of confidence and self-sufficiency was evident.

d. *Private foundations:* The remaining sector, which held a position almost as a peer of the three already described, was the private foundations. Since early in the twentieth century, when the fortunes of Rockefeller and Carnegie took form as foundations, private wealth in the hands of professional foundation executives had played an important role in science. The foundations pioneered in the art of supporting science both by institutional grants, such as those by the Rockefeller Foundation's General Education Board, and by grants to individual projects—for instance, those that became common with the Rockefeller Foundation after 1928. Some had developed research departments of their own—for instance, the Carnegie Institution of Washington.

So dramatic had been the arrival of the great foundations on the American scene that they were for a time accustomed to function in areas that, in other periods, might be the responsibility of some other sector. The worldwide medical programs against yellow fever and hookworm were on a scale suggestive of government rather than private action. And, between the wars, grants from the foundations had supported such efforts at coordination of the national research structure as were being made by the National Academy of Sciences and the National Research Council. The support of President Franklin Roosevelt's Science Advisory Board by the Rockefeller Foundation, between 1933 and 1935, gave evidence of activity in an area very close to the public purposes of the government itself. The very effective National Research Council fellowships, earmarked for science, came from the private foundations. Yet in the late 1930's the foundations, their own capital funds battered by depression, could see little prospect of rapid expansion of their resources.

Thus the sectors of science support existed alongside one another in the late 1930's, each with a tradition and a self-sufficiency of its own. Each one felt that it had a clear mission independent of the others. The universities did basic research; the government did applied research related to its own missions and served a few special groups such as the farmer; industry applied science in its own laboratories; the foundations alone kept up a slight interchange with the other sectors, but even they thought in terms of special missions peculiarly appropriate to themselves. The interrelated system—the totality of arrangements by which the sectors of science support work together—which has developed since the 1930's consists of a tight interweaving of all the sectors, and the government has taken its place at the center of the system. The key link that will concern us

henceforth in this account is that between the government and the institutions of higher learning. It was a weak link in the late 1930's, so weak that many denied its existence at all, and its strengthening was a crucial factor in making the world a different place almost overnight.

Scattered Indications of Impending Change

A few portents in the 1930's foreshadowed the interrelated system as the postwar world has come to know it. In hindsight, one can almost see it coming even before the crisis of World War II, which intervened and hastened it. The establishment of the National Cancer Institute in 1937, as a part of the Public Health Service, brought with it grants-in-aid to private institutions as well as advanced training programs. The National Advisory Committee for Aeronautics had close ties with aeronautical engineering departments in leading universities and made a number of contracts for special investigations. A few scattered advisory committees to government agencies kept open a channel to university scientists. An unsuccessful try at a comprehensive organization was made by Karl T. Compton as chairman of the Science Advisory Board between 1933 and 1935. A new self-consciousness concerning the role of research is reflected in the studies of the National Resources Planning Board, which attempted an analytical and statistical profile of the sectors of science support and their relations. Indeed, the title of those studies, *Research — A National Resource,* was to become the watchword of the new system.

Yet, as warclouds gathered around the world before and after Munich, the critical question for science in the United States stood out starkly clear: Could research affect military events quickly enough to determine the outcome of the war? The modest research programs of the armed services were entirely inadequate in the new situation. There was no time to build new laboratories and train new career scientists to enter government service. The only realistic hope for deploying science lay with the university scientists and laboratories, and the weakness of the existing link between the government and university science made formidable the task of bringing the two together.

II

World War II: The OSRD Creates the Interrelated System

The Wartime Leaders of Science

By creating the National Defense Research Committee (NDRC) in 1940, and by expanding it into the Office of Scientific Research and Development (OSRD) in 1941, President Franklin Roosevelt provided the new framework of government-university relations even before Pearl Harbor. The link between universities and government research for national security had been established in a remarkably complete form. One of the many contributions the scientific community made to the war effort was the leadership that proposed this channel and then made it work. Four men from among a great many deserving scientists may be mentioned as providing this crucial administrative leadership: Vannevar Bush, James B. Conant, Karl T. Compton, and Frank B. Jewett. Chance plays a part in the good fortune of the United States here. The group possessed just the right combination of youth and seasoned experience. Only Jewett had played a role at high levels in World War I, and yet the others had had major administrative experience in the 1930's to season them.

Bush, Conant, Compton, and Jewett had an importance beyond their own personal qualities, impressive as those were. They were, in an unofficial way, representatives of the various sectors of

science support. Conant, of course, was a distinguished chemist and president of the oldest and most prestigious private university in the country. Compton had within a few years made the Massachusetts Institute of Technology into the nation's leading scientifically oriented technical institution. Jewett was both a senior leader of industrial research, as president of Bell Telephone Laboratories, and the recently elected president of the National Academy of Sciences. Bush had served as a professor of electrical engineering and as a vice-president of M.I.T., but he was now in the strategic position of president of the Carnegie Institution of Washington. He also was chairman of the National Advisory Committee on Aeronautics. Thus all the sectors of science were handsomely represented by men who commanded major respect, and Bush, an engineer at home in the universities, private foundations, and government research, was the natural spokesman of the movement. These men had an effective knowledge of the whole sweep of American research institutions and their scientists. Their job was to determine the military needs of the country and relate them to the research capability they knew to exist in the universities and industrial research laboratories. The need was so great that considerations of field of science and institutional affiliation made little difference. Nor could long-run effects on the science establishment, such as the supply of scientists for future years or the accumulation of basic knowledge, take precedence over the cardinal requirement of adequate weapons to win the impending war.

Policies of the OSRD

After a year's trial with the NDRC of 1940, an executive order of June 28, 1941, created the more comprehensive OSRD, of which Bush was director. This order set up the Committee on Medical Research as parallel to the weapons-oriented NDRC. Although many of the basic decisions were made between June 1940 and June 1941, we shall for convenience use the designation OSRD in describing the salient characteristics of the system. It operated no laboratories of its own. It did not supplant projects already under way under the Army and Navy. It made contracts with both universities and corporations. It early adopted the principle that the contracting institution should neither make a profit nor suffer a loss as a result of OSRD research. This led immediately to the allowing of a charge for overhead costs not easy to specify in the contracts. Since by definition these costs were hard to determine, the OSRD adopted for educational institutions the formula of 50 per cent of the actual labor payroll involved in a project.

The urgency of war placed its stamp on every OSRD decision. No distinctions were made between private and public uni-

versities, or between land-grant and non-land-grant institutions. Where work could be broken down into small lots, investigators were left at their own institutions. When great concentration was necessary, as in the case of the Radiation Laboratory at M.I.T., the institution was chosen purely on the ground of its ability to perform the work. In this case Karl Compton avoided a conflict of interest simply by refraining from taking part in either the discussion or the decision.

The OSRD was early confronted with the problem of delimiting its mission. Because in the twentieth century all parts of the spectrum of activities from basic research to its applications are dependent on one another, the OSRD could have gone off in a number of directions. Most of the key men, both on the panels doing the selecting and among the investigators chosen, were university-connected and had worked on basic research before the war, so that the organization might have been expected to favor basic research at least covertly. Or it might have sought immediate applications from the introducers of new designs and mechanisms, the inventors. Or it might have used its contracts deliberately to change the pattern of research institutions in the country along some preconceived path. It could have taken up the responsibility of providing general research service to industry in such fields as large-scale synthetic rubber production. However, it early set its face against those who wanted any or all of these things. As time went on, the OSRD became less and less concerned with the basic research end of the spectrum and more and more concerned with development, but no diminution in the reliance on university scientists accompanied this shift.

The OSRD Contract

The OSRD contract for research and development deserves special mention. As Irvin Stewart wrote at the end of the war, the "heart of the contract problem was to reconcile the need of the scientist for complete freedom with assurances that government funds would not be improperly expended." [6] The procurement contracts in use by the Army and Navy were not well adapted for research and development, so that the legal division of OSRD set out to provide an instrument of sufficient flexibility to accommodate both the government and the scientist.

The United States of America was one party to the contract, an institution the other. "Whereas, the Government desires that the Contractor conduct studies and experimental investigations

[6] Irvin Stewart, *Organizing Scientific Research for War: The Administrative History of the Office of Scientific Research and Development* (Boston, 1948), p. 19.

as hereinunder specified requiring the services of qualified personnel, and whereas the Contractor is willing to conduct such studies and experimental investigations on an 'actual cost' basis. . . ." described the essential transaction. By 1944, the OSRD made a distinction in function within its own staff by designating in the contract a "Contracting Officer," to be responsible for the business and fiscal aspects of the work, and a "Scientific Officer," usually a chief of division, to direct the scientific aspects. Not specifically mentioned but strongly implied, both by the phrase, "qualified personnel," and by the fact that an object of research was specified, was the existence of a scientist or group of scientists to take over the responsibility for the work at the contracting institution. Indeed, the principal investigator was often already at work gathering a staff and beginning operations, on the basis of a letter of intent, before the contract was signed.[7] Thus the OSRD by its contract assembled the entire cast of the new system of government support: the fiscal officer and the scientific officer on the government side; and the university administrative officer and the principal investigator on the university side.

The contract laid down the rules for cost determination (of salaries and overhead, for example), disposition of property, responsibility of the contractor, and patent and security provisions. In each of these matters the OSRD set important precedents and educated large numbers of people in the government and in the universities in the fundamentals of the new support system for research.

Congress and Science during World War II—the Kilgore Subcommittee

How did Congress and the American people get the opportunity to approve or disapprove the OSRD? Some had thought of asking for legislation in 1941, but the urgency of the times argued that it be done by executive order under temporary war powers. An announcement of the formation of the agency was published, but the need for security so sheltered it that Stewart, as executive secretary, could handle public information and Bush, as director, could handle congressional liaison all by themselves. A tacit agreement between Congress and OSRD tended to give force to Bush's insistence, which went all the way back to the beginnings of the organization, that it was a purely temporary agency. Once the emergency was over—once the narrow objective of weapons for this war had been accomplished—the OSRD had no thought but to place science and the agency before Congress for fundamental decisions about the shape of the future.

---

[7] Standard form 1001 of the OSRD contract appears in *ibid.*, pp. 339-346.

So great was the obvious relevance of science to the war effort, however, that not everyone was willing to wait until the shooting was over to find out whether the OSRD's strictly delimited program was adequate. Senator Harley Kilgore, Democrat of West Virginia, arranged major hearings before a subcommittee of the Senate Committee on Military Affairs in 1942, 1943, and 1944. Senator Kilgore and his staff came at the whole problem of science and government from the point of view of war industry. Hence they stressed patents, inventions, industrial research for small business, and the imperfect utilization of technical manpower. Since the OSRD started with a problem and tried to find the men best qualified to work on it, it took no responsibility for the scientists, often geologists or biologists whose specialties were not in great demand, who were left outside the war effort. And, since the OSRD had long insisted that it was not working on materials or methods of wide use in industry, it did not concern itself with supplying research support to war industry generally. Hence the Kilgore Subcommittee aimed at an organization to work in such an area. On July 8, 1943, a group of senators, headed by Kilgore and referring directly to his hearings, asked James F. Byrnes, then Director of War Mobilization, to set up a central scientific and technical body. Among the 23 signers, both parties and all major geographical regions were well represented.

Science—the Endless Frontier

Bush, already on record as opposing Kilgore's big agency for scientific and technical mobilization, became increasingly aware, as the successful conclusion of the war in Europe loomed up, that a major reorientation of scientific support was on the way. His oft-reiterated intention of closing down the OSRD at the end of the war had the effect of forcing a full-dress examination of science's role in American life. And that examination would eventually have to be made in the public arena, with fundamental legislation the result. But first the scientific community, if it did not wish to be caught unawares, should examine the postwar support of science and come forward with a program. Although the OSRD could not by itself take up the study of the shape of postwar science, it formed a natural framework. Therefore, President Roosevelt, in a letter dated November 17, 1944, asked Bush for his recommendations. The letter carefully referred to the OSRD as "a unique experiment of team-work and cooperation in coordinating scientific research and in applying existing scientific knowledge to the solution of technical problems paramount in war." The letter asked Bush to give his considered judgment personally, "after such consultation as you may deem advisable with your associates and others." Roosevelt thus

empowered Bush to convene an advisory committee-of-the-whole of the scientific community to answer four questions. They were:

"First: What can be done, consistent with military security, and with the prior approval of the military authorities, to make known to the world as soon as possible the contributions which have been made during our war effort to scientific knowledge? . . .

"Second: With particular reference to the war of science against disease, what can be done now to organize a program for continuing in the future the work which has been done in medicine and related sciences? . . .

"Third: What can the Government do now and in the future to aid research activities by public and private organizations? The proper roles of public and of private research, and their interrelation, should be carefully considered.

"Fourth: Can an effective program be proposed for discovering and developing scientific talent in American youth so that the continuing future of scientific research in this country may be assured on a level comparable to what has been done during the war?" [8]

Bush, having made his opportunity, took advantage to the fullest by appointing distinguished committees to study each of the four questions. The committees for questions three and four, headed by Isaiah Bowman and Henry Allen Moe, respectively, were the ones that considered in detail most of the features of the government-university link. A committee representing medical research in the universities had its say on question two. While university men, especially presidents, predominated on all the committees, the other sectors of science were also represented. The only major group not represented as such (although Bush, Conant, I. I. Rabi, and perhaps a few others bridged the gap) were the atomic scientists, still hidden even from the OSRD by compartmentation within the confines of the Manhattan project. As nearly as one could expect the scientific community to have a voice, it had one here.

Bush's report, *Science—the Endless Frontier,* attempted a profile of American science and a prescription for the future. The basic principle of the interrelated system appears in the body of the report.

"The Government should accept new responsibilities for promoting the flow of new scientific knowledge and the development of scientific talent in our youth. These responsibilities are the proper concern of the Government, for they vitally affect our health,

---

[8] Vannevar Bush, *Science—the Endless Frontier: A Report to the President on a Program for Postwar Scientific Research* (Washington, 1945, Reprinted 1960), pp. 3-4.

our jobs, and our national security. It is in keeping also with basic United States policy that the Government should foster the opening of new frontiers and this is the modern way to do it. For many years the Government has wisely supported research in the agricultural colleges and the benefits have been great. The time has come when such support should be extended to other fields.

"The effective discharge of these new responsibilities will require the full attention of some over-all agency devoted to that purpose. There is not now in the permanent governmental structure receiving its funds from Congress an agency adapted to supplementing the support of basic research in the colleges, universities, and research institutes, both in medicine and the natural sciences, adapted to supporting research on new weapons for both Services, or adapted to administering a program of science scholarships and fellowships.

"Therefore I recommend that a new agency for these purposes be established. Such an agency should be composed of persons of broad interest and experience, having an understanding of the peculiarities of scientific research and scientific education. It should have stability of funds so that long-range programs may be undertaken. It should be recognized that freedom of inquiry must be preserved and should leave internal control of policy, personnel, and the method and scope of research to the institutions in which it is carried on. It should be fully responsible to the President and through him to the Congress for its program."[9]

The National Research Foundation envisaged in the Bush report had about it a comprehensive nature that matched the situation into which it would move. It would have a Division of Medical Research and a Division of National Defense parallel to its Division of Natural Sciences. The Foundation was to have the power to "make contracts or grants for the conduct of research by negotiation without advertising for bids."[10] Many characteristics of the OSRD were included, such as the principle that the research should be "conducted, in general, on an actual cost basis without profit to the institution receiving the research grant or contract."[11] No geographical or other formula was proposed because the "Foundation must . . . be free to place its research contracts or grants not only with those institutions which have a demonstrated research capacity but also with other institutions whose latent talent or creative atmosphere affords promise of research success."[12] In general it was envisaged that the National Research Foundation would adopt

---

[9] *Ibid.*, pp. 8-9. [10] *Ibid.*, pp. 36-37.
[11] *Ibid.*, p. 39. [12] *Ibid.*

the historic goals of scientists in their relations with the government and extend them to the contract-grant system of tying the universities to public purposes. At the same time, the Bush report was explicit on the ultimate responsibility of the President and Congress. "Only through such responsibility can we maintain the proper relationship between science and other aspects of a democratic system. The usual controls of audits, reports, budgeting, and the like, should, of course apply to the administrative and fiscal operations of the Foundation, subject, however, to such adjustments in procedure as are necessary to meet the special requirements of research." [13]

The End of the War

Science—the Endless Frontier, which did not mention uranium or fission or nuclear energy, appeared the same month as the Alamagordo test—July, 1945—and only a month before the world learned of the atomic bomb with Hiroshima. Dramatic impact made atomic energy seem like a separate area of science policy to be dealt with as a thing apart. Indeed it proved to be, as the creation of the Atomic Energy Commission in 1946 showed. But meanwhile the problems attacked in *Science—the Endless Frontier* had their day in Congress. Senator Kilgore introduced a bill which represented his long-standing interests, while Senator Warren G. Magnuson introduced a bill embodying Bush's ideas.

On September 6, 1945, President Truman, in a special message to Congress on reconversion, set the keynote of the discussion when he said: "No Nation can maintain a position of leadership in the world of today unless it develops to the full its scientific and technological resources. No government adequately meets its responsibilities unless it generously and intelligently supports and encourages the work of science in university, industry, and in its own laboratories." In calling for a single federal research agency for science, Truman clearly confirmed the concept of an interrelated system of "universities, industry, and Government working together," and promised in unmistakable terms the freedom demanded by the nature of science. "Although science can be coordinated and encouraged, it cannot be dictated to or regimented. Science cannot progress unless founded on the free intelligence of the scientist. I stress the fact the Federal research agency here proposed should in no way impair that freedom." [14]

---

[13] *Ibid.,* p. 33.

[14] *Public Papers of the President of the United States, Harry S. Truman, 1946* (Washington, 1962), pp. 292-294.

The Kilgore-Magnuson Hearings

Senators Kilgore and Magnuson arranged jointly for hearings on science legislation which lasted through most of the fall of 1945, and gave the wartime leaders of science and many others a chance to express themselves on the shape of the future for science in the United States. The striking thing about these hearings is that every one of the witnesses except one supported the principle of some sort of science foundation in the government. Senator Kilgore led off by saying: "As the war has so dramatically demonstrated, science is a national resource of the greatest importance for our whole national life. Scientific skills and scientific know-how have enabled us to win rapid and decisive victory on the war fronts. The same skills and know-how must now be converted and expanded to meet the needs of peace—the improvement of our national health, the security of our national defense, the promotion of our prosperity." [15] As one eminent scientist put it, "we require the mass will of the people as expressed by the Government. Science and technology need the direct help of the Government. The Government needs ever more urgently the help of science and technology." [16]

Yet below the level of this large fundamental agreement, tensions predictable in a democracy's first public airing of an unfamiliar concept promptly emerged. *Science—the Endless Frontier* had proposed a part-time board of people otherwise unconnected with the government, not merely as an advisory body but as a responsible head of the agency—appointing the director, formulating over-all policy, and making grants and contracts. Senator Kilgore's bill favored a straight-line organization, with the director appointed by the President. Harold Smith, then director of the Bureau of the Budget, was strongly of the same opinion, equating the responsibility of the director with the control of public funds. "I believe that the most important principle involved in these bills is that an agency which is to control the spending of government funds in a great national program must be a part of the regular machinery of government. If the government is to support scientific research, it should do so through its own responsible agency, not by delegating the control of the programs and turning over the funds to any nongovernmental organization." [17]

President Edmund E. Day of Cornell University, representing the Association of Land-Grant Colleges and Universities, advo-

---

[15] "Hearings on Science Legislation," Hearings before a Subcommittee of the Committee on Military Affairs, U. S. Senate, on S. Res. 107 and S. Res. 146, 79 Cong., 1 Sess., October and November 1945, p. 1.

[16] Harlow Shapley, *ibid.*, p. 48. [17] *Ibid.*, p. 96.

cated a formula by which a percentage of the foundation's funds would be distributed to the land-grant institutions, making "as a counterweight an independent, Federally financed program administratively directed by the important public institutions in the several States. . . ." [18]

On this issue, Harold Smith and the Bureau of the Budget were on the side of *Science—the Endless Frontier* and geographically unrestricted grants and contracts. The "proposed foundation should be free to support the advancement of knowledge in any institution which, in the judgment of the foundation, is able to do effective and competent research." He went on to link the freedom of the foundation to support excellence, in specific packages wherever found, to the ability of the government to safeguard the use of the taxpayers' money.

"Only by specific contracts, rather than general purpose contracts, can it make sure that it is supporting in each institution only the type of research which that institution is qualified to perform. This is not to say that it will restrict the proper degree of freedom of research, or impose a narrow type of administrative supervision over the institutions with which it deals. But it would obviously be improper and ineffective to give funds to private institutions without some assurance of their ability to further the purpose of the program, and the foundation must have freedom to select the institutions that are able to do so." [19]

The patent problem occupied more hearing time than any other. In general, Bush stood for the OSRD practice of leaving patents in the hands of contractors whenever possible, while Kilgore hoped for government ownership of patents produced in the course of government-supported research. As it became clearer in the course of the hearings that the foundation would support basic research rather than industrial applications, more and more witnesses expressed doubt that science legislation was the place to reform the patent system.

The Failure to Make the National Science Foundation Parallel the Atomic Energy Commission

Despite the broad areas of consensus evident in the fall of 1945, legislation for a foundation did not clear both Houses of Congress until 1947. The seriousness of the organizational issue was demonstrated by the subsequent veto from President Truman.

"Our national security and welfare require that we give direct support to basic scientific research and take steps to increase the number of trained scientists. . . . However, this bill contains

---

[18] *Ibid.*, p. 794. [19] *Ibid.*, p. 96.

provisions which represent such a marked departure from sound principles for the administration of public affairs that I cannot give it my approval. It would, in effect, vest the determination of vital national policies, the expenditure of large public funds, and the administration of important government functions in a group of individuals who would be essentially private citizens. The proposed National Science Foundation would be divorced from control by the people to an extent that implies a distinct lack of faith in democratic processes." [20]

The failure of legislation to emerge in 1946, the last session of the Seventy-Ninth Congress, is partially explained by the bitter controversy over atomic-energy legislation. Two of the main issues dividing the May-Johnson bill from the MacMahon bill—organization of the commission, and patents—were parallel to the issues dividing the opposing forces on the science legislation, which reflected the dissension more faithfully than it reflected the urgency of atomic energy as a policy area. The closest students of the legislative history of the Atomic Energy Act of 1946 have noted that "many thousands of Americans had expended millions of words in public debate. . . . The final bill was not what any single one of them would have written. Yet, it was probably better than any individual could have produced. In this fact, perhaps, lay the secret vitality of American democracy." [21]

In the case of the science foundation, the congressional ability to be cautious in the face of conflicting philosophies dominated the result for the time being. But the vitality of American democracy had already been at work to create the interrelated system. The need for it had outrun the ability to create over-all institutions, and even before the war's end practical arrangements were being made by Congress and the Executive to insure the nation against the limitations in the organization of government-supported science that had prevailed in the 1930's. The OSRD would go out of existence, but the system it created had to live on.

---

[20] *Congressional Record,* Appendix (August 14, 1947), pp. A4442-A4443.

[21] Richard G. Hewlett and Oscar E. Anderson, *The New World, 1939-1946 (A History of the United States Atomic Energy Commission,* Vol. I, University Park, Pennsylvania, 1962), p. 530.

III

The Government–University Alliance, 1945-1950

Postwar Reconversion

The determination not to return to the 1930's, only dimly sensed by scientists who had served in the wartime projects, was explicit in the minds of those responsible for national science policy. Europe, for the first time in American history, could no longer be relied upon to send over a sufficient stream of basic research results relevant to the rapidly changing frontiers of science and technology. The need to revive a free flow of information was acute, but the need to begin new knowledge from the basic end of the scientific spectrum was the only hope for a healthy growth of technology. Because the universities had almost shut down graduate education during the war, a shortage of scientific manpower was also in everyone's mind; fellowships were needed to close the gap in the ranks created by the war's diversions.

Military and civilian leaders in all the services were especially insistent that the partnership with university scientists be continued. James V. Forrestal, Robert P. Patterson, and General H. H. Arnold emphasized it as a necessity when they appeared at the Kilgore-Magnuson hearings. General Eisenhower, as Army Chief of

Staff in 1946, made a particular point of the Army's commitment to basic research. He advocated a separation of "responsibility for research and development from the functions of procurement, purchase, storage, and distribution." [22] In short, the military itself did not wish to lose its new-found partnership with science. Without the OSRD, it had the choice either of building up its intramural laboratories or of maintaining by contract its liaison with the university scientists. And the choice was really not free, for few scientists in 1945 and 1946 were willing to accept civil service careers in the government laboratories. Therefore all the services had ultimately to think in terms not only of keeping as much classified and applied research as possible within their own laboratories, but also of making contracts with the men who, after having performed prodigies in the defense laboratories during the war, were now back on university faculties thirsting to work on basic research problems rather than hardware.

The Office of Naval Research

The Navy, for various reasons, made the clearest and earliest response to the necessity for a contract program after the end of the war. Men at several levels in the Navy had been thinking about the future of science in the Department at least since 1942.[23] As a result, the Office of Research and Inventions was, by September 1945, under way on re-allocated funds and ready with proposed legislation that would give congressional approval to its operations. The Vinson Bill, which became law in August 1946, became the charter of the Office of Naval Research. The act's preamble indicates the comprehensive vision of the founders of ONR:

" . . . to plan, foster, and encourage scientific research in recognition of its paramount importance as related to the maintenance of future naval power, and the preservation of national security; to provide within the Department of the Navy a single office, which, by contract and otherwise, shall be able to obtain, coordinate, and make available to all bureaus . . . world-wide scientific information and the necessary services for conducting specialized and imaginative research. . . ." [24]

The ONR Act provided, in addition to ample authority to make research contracts, for a Naval Research Advisory Committee.

Thus, the ONR possessed all the elements of a model program for the interrelated system. It had a direct administration

---

[22] Quoted in Don K. Price, *Government and Science* (New York, 1954), p. 57.

[23] The Bird Dogs, "The Evolution of the Office of Naval Research," *Physics Today*, XIV (1961), pp. 30-35.

[24] 60 Stat. 779. 79 Congress, 2 Sess. Ch. 727—August 1, 1946.

with a regular navy officer as director. In practice the chief scientist served as deputy director and headed a staff of program directors knowledgeable in particular fields. The advisory committee and a large number of subsidiary committees and panels brought eminent scientists in from the universities on a part-time basis to help the Navy decide what projects to support. As soon as word got around, ONR did not have to solicit proposals from the scientists; they came in a flood. The ONR officials did, however, have to establish rapport with university administrations to convince them to make the contracts which would allow the scientists to go to work.

In their missionary work with university presidents, the ONR representatives had to convince administrators, already harried by the dislocations of war and the returning flood of G.I.'s, that they should take on navy contracts for research. The document they used was already far from the straight military procurement contract. "Contracts are not new to the Navy, but the idea of conducting contractual relationships in the field of basic research with independent agencies and institutions . . ., using tasks instead of specifications, is a new departure in Government contracting." [25]

The men who made the ONR a success in the eyes of both the Navy and the universities had a driving belief in four major propositions:

"(1) The primary aim of much of the Planning Division's scientific program is free *rather than directed research. Instead of being pointed toward direct solution of some practical problem, its intention is to explore and understand the laws of nature, both animate and inanimate."* [26]

"(2) Practically none of the basic research work conducted by the Navy is in a confidential or secret status." [27]

"(3) We want to have listening posts in various scientific fields and we want to maintain contact with the most imaginative people in science." [28]

"(4) To date, there has not been established a unit similar to the proposed National Science Foundation; nor has any agency, other than the Office of Naval Research, indicated its willingness to accept even pro tempore *some of the associated responsibilities."* [29]

---

[25] Office of Research and Inventions, *Annual Report,* 1946, p. 63.

[26] *Ibid.,* p. 108.

[27] Admiral P. F. Lee, "National Science Foundation," Hearings before the Committee on Interstate and Foreign Commerce, U. S. House of Representatives, 80 Congress, 1 Sess., March, 1947, p. 209.

[28] E. R. Piore, "Some Thoughts on Federal Science," *Physics Today,* VII (1954), p. 13. [29] Office of Naval Research, *Annual Report,* 1947, p. 1.

University officials suspicious of military domination eventually came to believe the ONR.

It might be asked how a military agency could achieve rapport with scientists, even while the National Science Foundation legislation was stalled because too many scientists feared a single director appointed by the President, and insisted on a part-time board. The answer lies in the fact that the Navy recognized the level at which the independent advice of scientists was at that time most needed. No general board, or even the Naval Research Advisory Committee of fifteen members, could constitute an adequate representation of all the disciplines and subdisciplines of science. Therefore it set up an extensive network of advisory committees by fields of science to assist in the screening of research proposals. In 1948 the list of fields under consideration included: geophysics, astronomy, mathematics, chemistry, undersea warfare, fluid mechanics, psychophysiology, biochemistry, human ecology, physiology, microbiology, and psychology.

From the point of view of the government, re-establishing scientific merit as the major criterion for spending money, and obtaining the most reliable and experienced university scientists to make the decisions, meant the best available insurance to the taxpayer that there would be no waste. Who, other than a microbiologist, could judge the scientific worth of a proposal in the field of microbiology? From the point of view of the investigator making the proposal, the advisory committee represented one of the most ancient and cherished rights of the Anglo-American legal tradition—the judgment of his peers. From the point of view of the university, even the largest of which did not have enough microbiologists to form a disinterested jury, the national committee relieved the local administration of the necessity of making substantive decisions on individual projects. For the advisory committee members, who were by definition the men with the best reputations for research, life began to include periodic trips to Washington.

Other networks of advisory committees spread over Washington in the postwar years. The four groups brought together by the OSRD contract for weapons research—the scientific program director with his advisory committee in the agency, the agency's contract administrator, the administrative officer in the university, and the principal investigator in the university—were brought together in a close partnership in the name of basic research by ONR. By 1949, the agency had expenditures of the order of $20,000,000 for 1,200 projects in 200 institutions, engaging nearly 3,000 scientists and 2,500 graduate students. It was to that time "the greatest peacetime cooperative undertaking in history between the academic world and

the government." [30] If a serious flaw existed in the effective Navy program between 1945 and 1950, it was that the American people did not know that they had a productive parnership between government and their universities.

The National Institutes of Health

In the organization of the government-university partnership, medical research has always been a special problem area. The problems stemmed, on the negative side, from the increasingly heavy costs of both medical care and medical education. The medical schools in universities reflected these problems, and the OSRD was set up in part to give medicine special administrative handling in the Committee on Medical Research. On the positive side, no field offered more promise in the peacetime world envisaged in *Science—the Endless Frontier* than did medical research. A people who had entered the war without penicillin emerged from it with altered expectations. A reproach against the federal research establishment in the early 1900's had been "that more pains are now being taken to protect the health of farm animals than of human beings." [31] Because of the strength of the Department of Agriculture, this taunt was still valid in 1945, though clearly neither the Congress nor the people accepted the situation as an expression of their will. The result was pressure to do something in medical research. The National Research Foundation of *Science—the Endless Frontier* was not ready. The OSRD was closing down. The Public Health Service seized the opportunity, not merely because its leaders were ambitious, but also because the Congress had already prepared them for the task by statute.[32]

Much was made in the 1945 discussion of the inadvisability of a research agency with extramural contracts also operating in its own laboratories. *Science—the Endless Frontier* recommended against it, and the Atomic Energy Commission had only contract laboratories. Many old-line agencies that did not develop significant extramural programs—the National Bureau of Standards and the Geological Survey, for instance—have found the postwar decades a period of trial.

The Public Health Service was unimpressed by this seeming incompatibility. It had an impressive program of intramural research in its Hygienic Laboratory, which after 1930 was called the National

---

[30] Office of Naval Research, *Annual Report,* 1949, p. 1.

[31] Irving Fisher, *A Report on National Vitality: Its Wastes and Conservation* (Washington, 1909), p. 126.

[32] D. C. Swain, "The Rise of a Research Empire: NIH, 1930 to 1950," *Science,* Vol. 138 (1962), pp. 1233-1237.

Institutes of Health. It had begun making grants-in-aid to medical schools through the National Cancer Institute, established in 1937. Observation of the effectiveness of the Committee on Medical Research led the National Institutes of Health of the war period to become enthusiastic about research in universities as an adjunct to their intramural program. Therefore, in the Public Health Service Act of 1944, Congress conferred upon the Surgeon General of the Public Health Service the power to "make grants-in-aid to universities, hospitals, laboratories, and other public or private institutions, and to individuals for such research projects as are recommended by the National Advisory Health Council, or, with respect to cancer, recommended by the National Advisory Cancer Council." The next year, R. E. Dyer, director of the National Institutes of Health, testified at the Kilgore-Magnuson hearings that the Public Health Service already had "all of the authority in reference to health and medical research that is contemplated for the proposed foundation." [33]

Since authority is one thing, and money is another, the Public Health Service Act of 1944 did not assure the future of the National Institutes of Health as a major source of support of medical research; nor did it assure the future of the grant instrument as the most important means of linking university research to the government. In 1944 and 1945 the Bureau of the Budget withheld permission from the Public Health Service to seek funds for a grant program in general medical research. Only when the OSRD Committee on Medical Research went out of existence, and its contracts were transferred to the National Institutes of Health, did the nucleus of an extramural grant program come into existence. Thus it was the National Institutes of Health that carried on beyond OSRD in medical research. By 1951, when a National Science Foundation came into existence, the National Institutes of Health expenditures for health research were of the order of $30,000,000, more than half of which was spent through extramural grants. The pattern of the congressional appropriation exceeding the budget proposal sent up by the President had already put in an appearance.

The National Institutes of Health system of research support bore striking resemblances to that of the Office of Naval Research. The grant, a simple letter from the agency to the institution stipulating in broad terms the purpose of the research and the financial aspects of the transaction, brought the responsible officer of the government and the responsible administrative officer of the university into essentially the same relationship as that created by the Office of Naval Research contract. The investigator presented his proposal

[33] "Hearings on Science Legislation," p. 514.

describing his research in a similar way. The study sections of the National Institutes of Health, which corresponded to the advisory committees of the Office of Naval Research, were organized by fields of medical research to obtain the part-time advice of leading university research men. Thus the government again gained the assurance of quality and the investigator gained the judgment of his peers.

Some significant differences appear between the two operations, however. In the first place, while medicine depends on basic research in many sciences, it is itself an applied science with a highly specific object, the human being. The National Institutes of Health could argue for broad and fundamental studies, but it could also argue the practicality of its research in a way that the Office of Naval Research could not, at least if it were to maintain its flexibility. In the second place—also related to the nature of medicine—the National Institutes of Health could serve uniquely well in promoting certain lines of research. Diseases made such obvious targets that even the members of the appropriations subcommittees in the House and Senate could see areas such as cancer chemotherapy and virus study as worthy of special emphasis.

In the third place, the Office of Naval Research's Naval Research Advisory Committee, even though set up by law, had less specific authority than the Advisory Councils of the National Institutes of Health, which by statute had to recommend a grant before the Surgeon General could act. Thus the voice of the scientist was more authoritative in the National Institutes of Health than in the Office of Naval Research, however similar the practices of the two agencies. Finally, the grant-in-aid, as applied by the National Institutes of Health, was explicitly and unequivocally a support for research and not a purchase of research. In practice the Office of Naval Research contract also supported research rather than purchasing it, but the government's vast machinery for procurement contracts put the Office of Naval Research at a theoretical disadvantage.

Other Niches Occupied—AEC and Weapons Research

The period 1945 to 1950 saw other agencies profit by the example of OSRD and fill niches left by its demise. The Atomic Energy Commission could and did contract with universities for much research on a project basis. But it also built upon the university-operated laboratories inherited from the Manhattan District to create a system of national laboratories. Oak Ridge provided the site for one, close to operating plants of the Commission. Others, notably Argonne National Laboratory at the University of Chicago and the Lawrence Radiation Laboratory at the University of California, had close physical and intellectual ties with their universities.

In the case of Brookhaven National Laboratory on Long Island, the Atomic Energy Commission made its contract with Associated Universities, Incorporated, set up by several eastern universities for that purpose.

The national laboratories were technically institutions that conducted contract research, and much public commentary concerning the government-university interrelated system actually refers to incidents and arrangements at these famous institutions. Actually their work is not in the same category with project research performed by individual professors on campuses. A single contract may well cover an entire laboratory, with its large scientific and supporting staffs and its huge and costly machines. The laboratories have traditions of free research, and the red tape of administering such large organizations rests but lightly on the investigators. The laboratories play a significant role in graduate education, and they have carried the United States to pre-eminence in many fields of physics which, without large-scale government support for expensive and highly specialized equipment, could not have been entered at all.

The armed services, in the throes of unification and faced with the prospect of the cold war, had to evolve a weapons-research establishment after the end of the war without benefit of OSRD. The Office of Naval Research and contract programs in the other services provided for a continuing link between the military and the universities, but, as the diplomatic stalemate with the Soviet Union set in, and as weapons became so unconventional that research, relative to production, became an ever greater percentage of military expenditures, two major trends became evident. One was the heightened emphasis on intramural research by the military departments. The other was the increasing use of the research contract to purchase development on weapons systems from both profit and non-profit corporations. While not directly related to the government-university thread of this account, the contracts in the weapons area have had the indirect but sometimes almost overpowering effect of adding to the over-all cost figures for research and of increasing the demands on the scarcest commodity of all, brainpower. Moreover, the research and development contracting officers, becoming accustomed to dealing with profit corporations, tended to apply the same procedures to research contracts with universities.

The Steelman Report

In spite of the accomplishments at the working level which put the Office of Naval Research, the National Institutes of Health, and the Atomic Energy Commission laboratories and many university scientists to work, the failure of the immediate postwar reconversion to deal explicitly with the arrival of university science as a

major national resource aroused concern. A feeling of unease led President Truman to appoint a President's Scientific Research Board under the chairmanship of John R. Steelman. Urgency and a sense of competition still radiate from the major recommendations of that committee, dated August 27, 1947:

"(1) That, as a Nation, we increase our annual expenditures for research and development as rapidly as we can expand facilities and increase trained manpower. By 1957 we should be devoting at least one per cent of our national income to research and development in the universities, industry, and government.

"(2) That heavier emphasis be placed on basic research and upon medical research in our national research and development budget. Expenditures for basic research should be quadrupled and those for health and medical research tripled in the next decade, while total research and development expenditures should be doubled.

"(3) That the Federal Government support basic research in the universities and nonprofit research institutions at a progressively increasing rate, reaching an annual expenditure of at least $250 million by 1957.

"(4) That a National Science Foundation be established to make grants in support of basic research, with a director appointed by and responsible to the President.

"(5) That a Federal program of assistance to undergraduate and graduate students in the sciences be developed as an integral part of an overall national scholarship and fellowship program.

"(6) That a program of Federal assistance to universities and colleges be developed in the matters of laboratory facilities and scientific equipment as an integral part of a general program of aid to education.

"(7) That a Federal Committee be established, composed of the directors of the principal Federal research establishments, to assist in the coordination and development of the Government's own research and development programs.

"(8) That every effort be made to assist in the reconstruction of European laboratories as a part of aid to peace-loving countries. Such aid should be given on terms which require the maximum contributions toward the restoration of conditions of free international exchange of scientific knowledge."[34]

Any member of the public who wished to could read these recommendations, and, thus having before him the agenda for the next decade, should not have been overly surprised at the devel-

---

[34] President's Scientific Research Board, *Science and Public Policy* (Washington, 1947), I, pp. 6-7.

opment of federal support for science in the decade 1947-1957. In fact, the Steelman Report's target figures were in every case far under the actual totals for fiscal 1957.[35]

---

[35] A comparison of the Steelman Report target figures and fiscal 1957 shows: *Expenses Fiscal Year 1957*

	Projected in 1947	Actual 1957
I. Percentage of National Income for Science	1%	2.26% (1)
II. 1. Total Research and Development in U.S.	$2,240,000,000	$10,030,000,000(1)
2. *All* Basic Research in U.S.	440,000,000	834,000,000(1)
3. All Medical Research in U.S.	300,000,000	397,000,000(2)
III. Basic Research supported by Federal Government outside its Own Laboratories	250,000,000	311,000,000(1)

(1) National Science Foundation, *Reviews of Data on Research and Development*, No. 33 (NSF62-9) (April 1962) (Tables 1a, 2a, and 7).

(2) U.S. Congress Senate, *Federal Support of Medical Research*. Report to Subcommittee of Committee on Appropriations, United States Senate, 86 Cong. 2 Sess. (May 1960), p. 77, (Table 22).

IV

Maturation of the System, 1950-1957

The Belated Creation of the National Science Foundation

Since the interrelated system developed so vigorously in the late 1940's, the impulse for a National Science Foundation could have been sustained only by people who still felt that important values were involved. The friends of science in Congress never let the idea die even after the veto of 1947. The Senate passed a bill regularly, so that the main discussion shifted to the Interstate and Foreign Commerce Committee of the House, where the late Representative J. Percy Priest carried the main burden in behalf of the legislation.

On the scientists' side, an Inter-Society Committee for a National Science Foundation brought together a group through which the nation's scientific societies could scrutinize the complexities of the legislative process and keep in touch both with congressional staffs and with the Bureau of the Budget, who, of course, handled the examination of the drafts of legislation for the Administration. The patent issue was largely laid aside as the conviction grew that the Foundation would concentrate on basic research. The organization of the National Science Board and its relation to the Foundation gradually yielded to a compromise in which the President

appointed the director as well as the board, to whom certain direct powers of approval for grants were reserved.

As applied research dropped out of the concept of the Foundation, the bill became easier to pass because of the disappearance of the patent issue, but harder to pass because basic research was not clearly and obviously related to the missions of government agencies. The major addition to the concept of the Foundation in these years was the coordinating role in the government research establishment. This feature brought in the support both of those who feared inefficiency in government spending and of those who thought of over-all planning as a necessity if science was to be directed to national goals. In 1950, after the sponsors of the bill had accepted a $15,000,000 ceiling on appropriations (less than the Office of Naval Research was using for contracts and the National Institutes of Health for grants), the National Science Foundation Act passed both Houses of Congress and was signed by President Truman.

By 1950, Congress had clearly adopted the attitude that research required broad and flexible legislation. Under the National Science Foundation Act of 1950, the new foundation was authorized and directed:

"(1) to develop and encourage the pursuit of a national policy for the promotion of basic research and education in the sciences;

"(2) to initiate and support basic scientific research and programs to strengthen scientific research potential in the mathematical, physical, medical, biological, engineering, and other sciences, by making contracts or other arrangements (including grants, loans, and other forms of assistance) to support such scientific activities and appraise the impact of research upon industrial development and upon the general welfare. . . ." [36]

In some respects the Act said even more about government science policy than its substantive provisions stated. Geographical distribution of research funds by formula—the formula of the land-grant college system or other—was rejected. And the National Science Board was not specifically made representative of particular fields of science. But the legal requirements for membership carried with them the implied policies. Members "(1) shall be eminent in the fields of the basic sciences, medical science, engineering, agriculture, education, or public affairs; (2) shall be selected solely on the basis of established records of distinguished service; and (3) shall be so selected as to provide representation of the views of scientific leaders in all areas of the Nation." Implied here was a check on the power

[36] 64 Stat. 149 (1950). (Public Law 507–81 Cong.)

of the government and a safeguard to a free science. Indeed, a minority report by six senators on an earlier version of the bill had put this apprehension concerning too strong a director into words.

"The Administrator . . . will plan and direct a science program with the full force of two hundred or three hundred million dollars per year. He can ignore the Board's advice in any field he chooses regardless of his competence in that field; he can ignore their advice in all fields and dictate his own ideas. . . .

"Today our educational institutions are proud of their independence and freedom. If in a few years they become dependent upon funds from the Federal Government . . . they will not be able to resist the authority for dictation of this Czar of science,—the administrator. Only those schools . . . satisfying one man will receive the Federal money."[37]

If one proposition is fundamental to the whole postwar debate regarding the structure of science and its link to the government, it is that few—either in Congress or in the scientific community—wished a czar of science. The Act of 1950, by its construction of the National Science Board and the Division Committees, expressed the judgment of Congress that the system of advisory scientific panels was a legal and necessary part of the government's machinery.

The Young NSF and the Choice of the Grant Instrument

The first director of the National Science Foundation, Dr. Alan T. Waterman, moved not in the direction of becoming a czar, but to set up a system of support for basic research that would justify its stewardship of the taxpayers' money by careful scrutiny of each project by non-government scientists. As the former chief scientist of the Office of Naval Research, Waterman adopted many of its ground rules and practices.

At the same time, the young National Science Foundation was aware of the precedent in the National Institutes of Health for using grants in the support of research. Because of the breadth of the National Science Foundation Act, the Foundation was in a position to make a choice of the legal instrument best suited to the needs of supporting basic research in the universities. As a working paper used in the Foundation in July, 1951, put it, "recognizing the inherent heterogeneity of basic research and the difficulty of fostering its conduct through a single administrative mechanism, the Congress has provided the Foundation with a sufficiently liberal

[37] Kurt Borchardt, "Congressional Use of Administrative Organization and Procedure for Policy-Making Purposes: Six Case Studies and Some Conclusions," *George Washington Law Review*, XXX (1962), pp. 440-441.

grant of authority to meet almost any conceivable admixture of need." [38] According to the working paper analysis, "unquestionably the arrangement most widely used by governmental agencies for supporting research is the contract. . . . In theory, at least, there is a *quid pro quo* relationship between the parties to the contract; but in practice, through a gradual (evolution) of the contract form in recent years, this relationship tends to become less rigid and to take on some of the attributes of a cooperative or grant arrangement." [39]

A grant, on the other hand, according to the working paper, "is, in a formal sense at least, a unilateral action by one party by which a sum of money, property, or other valuable consideration is given to another party for accomplishment of an agreed-upon purpose." [40] After reviewing the "elaborate overload of financial and property accountability which has often proved excessively burdensome to both contracting parties" in the use of contracts, and pointing to the wide use of grants by private foundations as well as the Public Health Service, the working paper commended the grant to the Foundation's use. "Because of its flexibility, the grant is most appropriate to undertakings in which initiative and freedom of action play a decisive role and in which the production of *some* beneficial result is more to be sought than attainment of a set goal in a prescribed manner." [41] When the National Science Foundation chose the grant, it added a new dimension to the interrelated system. The Office of Naval Research definition of basic research and its organization of advisory committees were wedded to the legal instrument of the National Institutes of Health, creating an organization highly satisfactory for the continued alliance between university scientists and the government. With little money and an excellent system of advice, the National Science Foundation quickly established a reputation for responsibility in the administration of its grants.

Mission-Related Basic Research

A major problem that faced the National Science Foundation in its early years was finding a rationale for basic research independent of any of the particular missions recognized by the government. An assumption that had some currency in the early years was that the National Science Foundation would "take over" in the form of transfers the basic research already being performed by the Atomic Energy Commission, the Department of Defense, and various other agencies of the government. If this happened, one could say that the mission of the National Science Foundation was basic

---

[38] "Working Paper on Techniques of Fostering Research," dated 7/23/51, NSF Records. [39] *Ibid.*, pp. 3-4. [40] *Ibid.*, p. 5. [41] *Ibid.*, p. 6.

research, especially in the universities, while the Navy would support applied research related to its mission. Although some people took some time to get over this simple notion, it soon became clear that major transfers were impractical and that the well-established agencies could make a strong case for continuing their university contracts. The fundamental reason for this was that basic research activities and applied research activities had become so intertwined that the various agencies of the government felt a need that was no less urgent because it did not fit accepted definitions—the need for "mission-related basic research." If such a category were admitted, was there a real need for a National Science Foundation, after all?

The answer of the Eisenhower Administration to this question was "yes." In Executive Order number 10521, dated March 17, 1954, arrived at after extensive consultation, President Eisenhower said,

"As now or hereafter authorized or permitted by law, the Foundation shall be increasingly responsible for providing support by the Federal Government for general-purpose basic research through contracts and grants. The conduct and support by other Federal agencies of basic research in areas which are closely related to their missions is recognized as important and desirable especially in response to current national needs, and shall continue." [42]

While this did not say anything that the Congress had not already said in a number of organic acts, the reiteration confirmed the Foundation's mission as "general-purpose" basic research. At the same time it gave other agencies grounds to argue that they had full scope to conduct mission-related basic research. Such a plural system made possible the support of basic research in a variety of different ways, and assured those concerned with missions in health and weaponry of vigorous scientific activity in their areas among university scientists. A National Science Foundation that consolidated everything called basic research might have become rich and powerful quickly, but the plural linkage added much to the strength and flexibility of the interrelated system.

The National Science Foundation took the attitude that fostering mission-related basic research in other agencies strengthened science as a whole. To make the plural system described in Executive Order 10521 even more effective, and to make rapport between other government agencies and university scientists easier, the National Science Foundation encouraged the passage of legislation in 1958 by which Congress authorized all federal agencies to use grants

---

[42] Executive Order 10521, March 17, 1954, reprinted in National Science Foundation, *Fourth Annual Report, for the Fiscal Year Ending June 30, 1954*, pp. 118-119.

instead of contracts for the support of scientific research. The law, in effect, put both the National Science Foundation and Congress on record as favoring basic research in widely dispersed agencies of the government.

The Strengths and Limitations of a Plural System

The virtues of the plural system of the mid-1950's were many. The investigator had several chances to seek support for his ideas. The steady flow of proposals, the periodic gathering of the panels and study sections, the judgment of peers, the grant letters and contracts which emerged, became a settled and familiar pattern in the government. The interplay of actions that determined the proportion of federal funds allocated to each field tended to produce a kind of balance in which rapid changes of priority assigned to different fields were hard to accomplish. Indeed, no clear mechanism existed for making priority decisions, either among fields or among agencies.

Occasionally a special circumstance could produce some change in priority. The International Geophysical Year, an event that required the contribution of many countries to a coordinated series of experiments probing the entire environment accessible to man or his instruments, was occasion for a deliberate change in priority. Congress fully supported the emphasis by appropriations. But the plural system allowed such a shift to occur only when the most careful, vigorous, and foresighted action joined an especially appealing opportunity. An external event which disturbed the even tenor of the plural system was sure to create a demand for a more vigorous coordination of the government's role in science.

In a system in which a plurality of executive agencies supported science in a plurality of universities, that Congress should make a plural response is not surprising. The Congress, almost by definition, is largely engaged in resolving conflicts among the plural interests of American life as a whole. In addition, the committee system of Congress makes a single response difficult and a plural response the expected thing. Senators and congressmen gain respect and power by concentrating on a few areas which are the particular spheres of the committees on which they serve. In the early 1950's science policy as such did not have a high priority among the general issues on which all members of Congress have to be informed. Hence the number of full-dress debates on the floor concerning science were few, but there were always specialists who were following the development of parts of the interrelated system closely. Scientists were often confused by this combination of poor understanding of science in the Congress and intimate knowledge of the workings of the system on the part of a few congressmen.

Among the well-informed committees on science matters, the standing committees that had substantive cognizance over the great executive agencies naturally took first place, and of these the Joint Atomic Energy Committee is an outstanding example. It took a detailed interest in the affairs of the Atomic Energy Commission, and some of its members gained a high degree of expertise on the administrative side, and even, in a general way, on the scientific side, of the Commission. The committees of both Houses that had cognizance over the armed services became accustomed to the concepts that underlay the extensive research operations of the Department of Defense. And the committees on commerce and agriculture continued and deepened their historic interest in research.

One of the objectives of the scientific community in its dealings with the government had been, as we have already seen, to get away from short-term authorizations. Science sometimes requires abrupt and unforeseen changes in response to a changed research situation, but it equally requires the long-term support that makes sustained effort possible over periods of time up to several years before decisive results can be shown. Thus the provision of financial support for basic research on a year-by-year basis has often been the bane of science in government programs. In recognition of the need for greater stability, Congress has often appropriated funds for research programs on an open-ended basis—that is, to be available until obligated—so that commitments can be made for research extending over several years.

This practice, together with the practice of authorizing research programs with no definite dollar limitation, gives the appropriations committees a major role in the review of research programs. Some of the legislators most actively interested in scientific programs during the 1950's were members of the appropriations committees.

The mistrust that many rank-and-file members of the scientific community feel toward Congress reached a high pitch in the early 1950's because of the investigations by Senator Joseph R. McCarthy for the Senate Committee on Government Operations. The challenges of the loyalty of scientists, and of their ability to serve the government in sensitive areas, made them fear that the investigatory powers of Congress did not serve the government-science alliance well. Some other hearings of the period did nothing to allay the fears that had been aroused, or to make scientists feel that the investigatory powers of congressional committees were constructive forces.

Yet the pluralism of the government-science scene was so complete in the early 1950's that any channel of coordination might serve the potentially useful purpose of offsetting the sometimes conflicting interests and missions of the several science agencies. In

the Congress, the impulse toward coordination would not likely come through the standing substantive committees, linked as they were to individual agencies. The investigatory power, then in the hands of members of Congress outside the senior leadership on the standing substantive committees, was the main hope for an over-all look at the interrelated system and for raising questions about the coordination of its components.

The Committees on Government Operations of the House and Senate might not appear to headline readers as likely instruments to create increased coherence in the interrelated system. Yet even while the Army-McCarthy hearings filled the newspapers, a subcommittee of the House Committee on Government Operations raised many fundamental questions about research and development in the Department of Defense which would never have seen the light of day if the hearings had not been held. Furthermore, most of the leaders of the scientific community gained a chance to put their views before the Congress and the public, which they would otherwise not have had.

The Committee asked fifty leading scientists a series of questions; among them were: "To what extent should the Department of Defense contract with non-governmental institutions to carry on military research and development programs? To what extent should private, nonprofit institutions participate? To what extent should private industry participate? How much in-house research is required for the military services to be capable of exercising qualitative control over research and development conducted by outside laboratories?" [43] As research and development became an ever more prominent area of government activity, and its over-all organization became a cause for apprehension, the Committees on Government Operations became a natural focus for interest in science. If a major disturbing factor were to enter the picture, the Committees on Government Operations could be expected to step up their interest in the over-all organization of research and development.

[43] "Organization and Administration of the Military Research and Development Programs," Hearings before a Subcommittee of the Committee on Government Operations. House of Representatives, 83 Cong., 2 Sess., June 8-24, p. 2.

V

After Sputnik

Competition with the Soviet Union was the disturbing factor that put a new series of stresses on the now well-established plural and interrelated system of government-supported university research. Sputnik symbolized the competition and the challenge of the Soviet Union to the whole American people. The National Science Foundation had already discovered that Nicholas DeWitt's book, *Soviet Professional Manpower,* published in 1955, had a marked effect in interesting Congress in support of its program for education in the sciences. But, with Sputnik, millions who had not previously thought about the government's science policy developed a strong feeling that some priorities should at least be re-examined.

Changes in Organization by President and Congress

The Eisenhower Administration responded promptly with the appointment of Dr. James R. Killian, Jr., president of M.I.T., to the newly created post of Special Assistant to the President for Science and Technology. The President's Science Advisory Committee was reorganized to report directly to the President. Soon thereafter, as a result of the report of the President's Science Advisory Committee, *Strengthening American Science,* the President also set up the Federal Council of Science and Technology.

In the wake of Sputnik, the Congress took a lively and concerned interest in the plural interrelated system. It markedly strengthened the National Science Foundation and passed the National Defense Education Act. To a much greater extent than usual, congressional leaders took the lead in shaping the legislation which created the National Aeronautics and Space Administration and the National Aeronautics and Space Council. It also realigned its committee system by creating two new standing committees—Aeronautical and Space Sciences in the Senate, and Science and Astronautics in the House. The Democratic leadership of the Congress had thus worked with the Eisenhower Administration in creating a whole new set of institutions in both the executive and legislative branches. The senate committee limited itself to "Aeronautical and Space Sciences." But the house committee, by adopting the term "Science and Astronautics," projected a broader role than that of a

standing committee for the National Aeronautics and Space Administration.

In the stresses of 1958, with Soviet competition foremost in everyone's mind, with searching questions being asked about the whole range of American education, with the Congress and the Executive controlled by different parties, it would have been surprising if members of Congress outside the regular committees had not given close attention to the workings of the interrelated system. It would also have been surprising if the Committees on Government Operations had not come strongly to the fore with questions about over-all coordination. A subcommittee of the Senate Committee on Government Operations held hearings on a whole series of bills to create a Department of Science and Technology and a cabinet post of Secretary of Science and Technology. At the same time, the subcommittee and its staff became particularly interested in the coordination of scientific information. Their efforts helped in the creation of the Office of Science Information Services in the National Science Foundation through a provision in the National Defense Education Act of 1958. But their interest did not stop there. A series of reports on science information has continued to emanate from the subcommittee, a clear example of how sustained congressional interest can provide long-term stimulation to a matter of science policy.

Congressional interest in a Department of Science and Technology was given a particularly sharp edge because the coordinating structure, erected by the Eisenhower Administration around the Special Assistant for Science and Technology, was located within the White House, and thus was not available for questioning by congressional committees. A senator complained that when "a legislative subcommittee has to dig around and do its own investigation and sleuthing, that is when the trouble starts. That is when the half-truths come out. That is when you get the misrepresentation that takes place. . . . It seems to me somewhere, somehow, there ought to be the openness, the frankness of contact and of communication that the present situation requires, because the scientific program of this Government is no better than the knowledge of Congress about it, because we can either make it or break it either through our lack of knowledge or of enlightenment on the problems involved." [44] Although a consensus for a Department of Science and Technology never developed, either within the Congress or within the scientific community, the interest stirred up by the subcommittee had the great merit of indicating the need for coordination both in

[44] "Create a Department of Science and Technology," Hearings before the Subcommittee on Reorganization and International Organizations of the Committee on Government Operations. United States Senate, 86 Cong., 1 Sess., May 28, 1959, p. 129.

the Executive and in Congress, and of pointing up the necessity for good communication between the two branches. The proposal for a commission to study the creation of a department of science stemmed from these hearings and has passed the Senate regularly since then.

Another subcommittee of the Senate Committee on Government Operations also entered the post-Sputnik arena of science policy coordination through an investigation of national security machinery. This subcommittee sought the opinions of many members of the scientific community and included a section on science policy in its final recommendations, which appeared in the first days of the Kennedy Administration. The subcommittee saw the virtues of the science policy machinery set up within the White House, but urged the President to use his reorganization powers to move the structure out of the White House and into the Executive Office of the President, thereby allowing the Special Assistant for Science and Technology to appear before congressional committees. The step recommended by the subcommittee was taken by President Kennedy in Reorganization Plan No. 2 of June, 1962. With this change, the movement for a separate department of science has lost momentum.

Thus the Congress gained a regular channel of communication to the fourfold structure within the Executive which was concerned with over-all science policy. The President's Special Assistant for Science and Technology now serves as an adviser to the Chief Executive. As chairman of the President's Science Advisory Committee, he presides over a group of scientists from private institutions who provide the Executive with advice from the scientific community. As chairman of the Federal Council for Science and Technology, he presides over a group of high-level representatives from government agencies with major research and development programs. And finally, as director of the Office of Science and Technology in the Executive Office of the President, the Special Assistant is available to give information to congressional committees that seek it. Staff work organized through the Office of Science and Technology help the Special Assistant to coordinate his several roles in the service of the President.

On the House side, the Committee on Government Operations also responded to the post-Sputnik stimulus. As the Senate groups had done, it took a stance outside the regular committees that dealt routinely with the interrelated system. The Subcommittee on Intergovernmental Relations took a rather different tack from that of its Senate counterpart, but at its base was the same concern for an over-all congressional view of research and development. The House subcommittee chose the rapidly expanding health research area for a detailed examination of granting procedures. In 1961, after two years of investigation, it issued a report dealing with the major features of

the linkage between the government and universities supplied by the National Institutes of Health. It reviewed the administration of grants and training programs and the always thorny problem of indirect costs. The relation of this subcommittee to the present report is explained in the preface to this report.

In the post-Sputnik era, the alliance between the government and the universities had to acquire new dimensions, yet the basic relationship could not be forgotten in the urgent attempt to meet immediate national needs. Science was now a yardstick of Soviet-American competition, but the historic urge of the scientific community to preserve the conditions necessary for its creativity could not cease. In the fall of 1960, in the midst of a great national election, the President's Science Advisory Committee pointed to the bond that had grown up between the government and the universities.

"The truth is as simple as it is important:
Whether the quantity and quality of basic research and graduate education in the United States will be adequate or inadequate depends primarily upon the government of the United States. From this responsibility the Federal Government has no escape. Either it will find the policies—and the resources—which permit our universities to flourish and their duties to be adequately discharged—or no one will." [45]

As scientists, university administrators, government officials, and congressmen struggle to adjust the many strings that bind the interrelated system together, they can at least take comfort in a few generalizations drawn from a glance toward the past.

The interrelated system grew out of the actions of responsible people consciously responding to urgent problems, and responding to get maximum benefit from the most powerful tool available—research.

The plural system has many roots for its authority and many alternative administrative means of solving a given problem.

The scientific community has consistently insisted on the recognition of the principle of scientific freedom, and the American political community has recognized that this freedom is consistent with our form of society and responsible government.

The record shows a continuous regard for the government's responsibility for the money entrusted to it by the people. And the overwhelming majority of the scientific community has throughout the record respected that responsibility.

Freedom and responsibility are the twin necessities of a system that the American people have every reason to approve.

---

[45] President's Science Advisory Committee, *Scientific Progress, the Universities, and the Federal Government* (Washington, 1960), pp. 10-11.

CONTEMPORARY PROBLEMS IN THE SYSTEM OF GOVERNMENT SUPPORT

VI

Profile of the Government's Present Role in Science

Statistics: Expenditures

A profile of statistics delineating the government's role in science shows a continuation of the system of support already in existence in the 1950's. It also shows a series of new trends whose development has contributed substantially to the present over-all totals. The rise of total expenditures—public and private—for research and development from approximately $5 billion in 1953-54 to nearly $15 billion in 1961-62 (see Chart 1) is certainly striking enough in itself. But one must also note that applied research and development has been consistently the largest part of that total. Thus expenditures for basic research (on the order of $1 billion in 1961-1962) are a relatively minor part of the over-all total. The trends in federal obligations for research, development, and research and development plant, fiscal years 1947-1964 (see Chart 2), show both that the totals have gone up steeply and that a preponderance of applied research and development has characterized the federal government's program, as it has the total national investment.

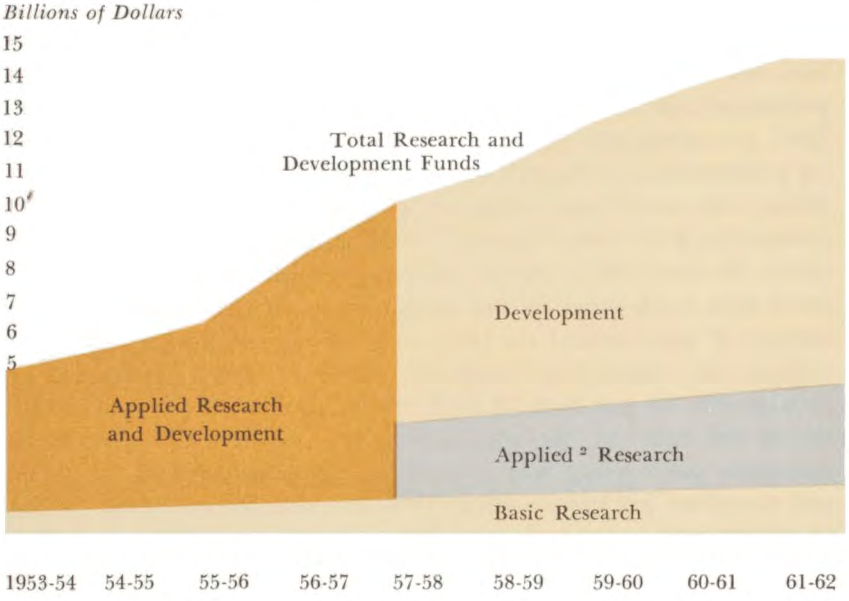
1964 statistics represented on the charts in this section are based upon budgeted figures, and thus do not reflect subsequent modifications resulting from congressional action and administrative decisions (see Table 1). These subsequent modifications do not, however, alter the essential trends of the curves as shown.

If one turns to an analysis of the funds used for research and development in the various sectors, 1952-1962 (see Chart 3), it is clear that industry has remained the major performer of research and development, with intramural research and development by the federal government second, although the latter's relative growth has been less than that of the other sectors. The colleges and universities performed research and development totaling $450 million in 1953-1954, as compared to $1.4 billion in 1961-1962. Federal obligations for performance of research and development, by sector (see Chart 4), reflects the same basic situation, with profit organizations in 1955 performing little more than the federal government in its own laboratories. By fiscal 1962, federal obligations to profit organizations were more than to all other sectors combined. From 1955 to 1961, the percentage of total federal research and development funds used by the colleges and universities remained relatively stable, representing approximately 10 per cent of total federal obligations. This stability lies at the heart of the approach of this report. The government-university partnership was a success at the beginning of the 1950's, and therefore has continued to grow in an orderly manner through the recent past.

The relations among the sectors of science support and the predominance achieved by the federal government as a source of funds are demonstrated by the table of intersectoral transfers for 1961-1962 (see Chart 5). The figure representing the operation of the government-university interrelated system is the $600 million for research and development (including $330 million for basic research) which stems from the federal government as the source of funds, with the colleges and universities proper (as opposed to research centers) as the performers. It is the relative rather than the absolute size of this figure that is a major concern of the scientific community. The graph of research and development performance by sector and type of work, 1962 (see Chart 6), shows the prominence of the universities in the performance of basic research, and the prominence of federally financed basic research in the universities. Thus it is clear that the fate of federal support to the universities and the fate of basic research are closely linked.

Turning to an agency breakdown of research and development (and research and development plant) expenditures for fiscal years 1940-1964 (see Chart 7), one can see the drama of the changing roles of individual agencies. The Department of Defense tops by far all the others in the postwar period, but it shows a decrease in its proportion of total federal research and development expenditures, from 73 per cent in 1960 to an estimated 51 per cent in 1964. The National Aeronautics and Space Administration meanwhile has risen to an estimated 28 per cent. The Atomic Energy Commission, while

CHART 1
TRENDS IN FUNDS FOR BASIC AND APPLIED RESEARCH AND DEVELOPMENT 1953-54—1961-62 [1]

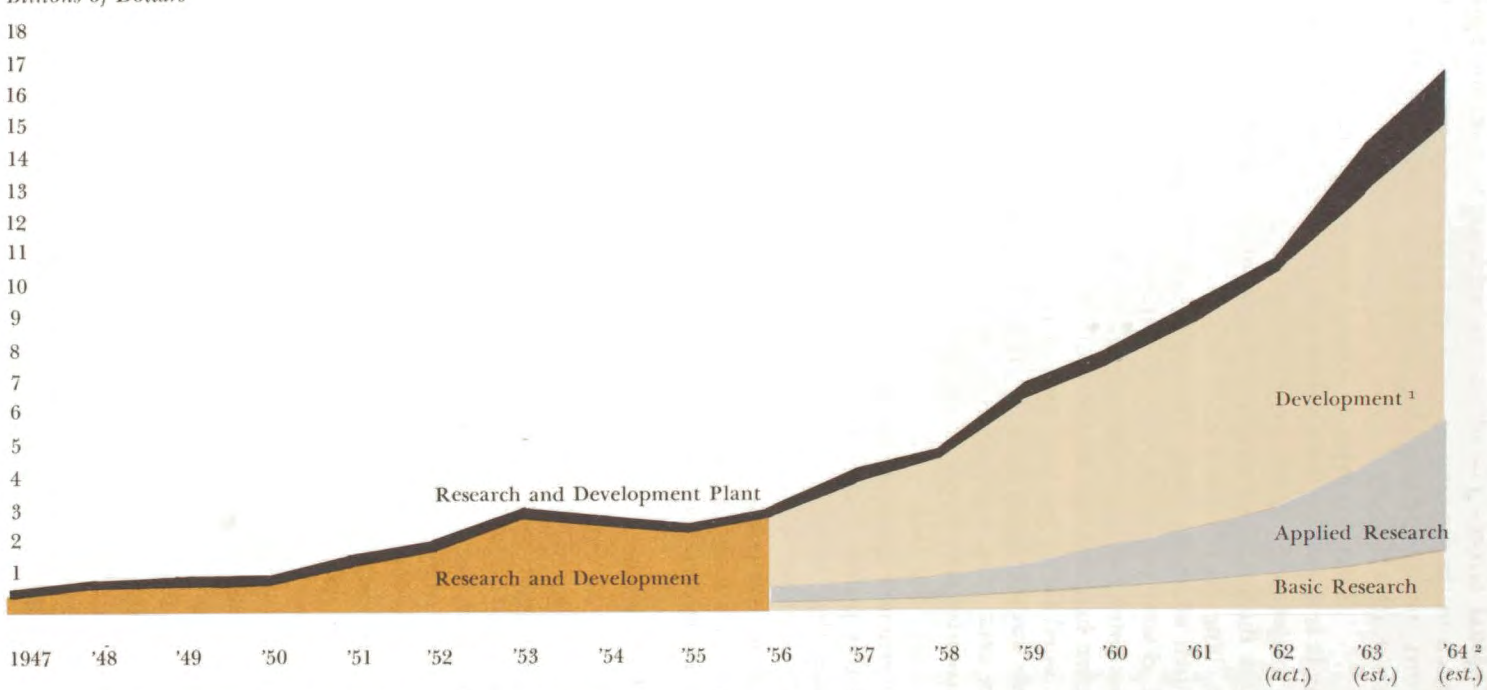


[1] Data are based on reports by the performers.
[2] Data separately identifiable for 1957-58, 1959-60, and 1961-62 only.
Source: National Science Foundation

rising from $1 billion to $1.5 billion from 1960 to 1964, nevertheless declined from 13 per cent to an expected 10 per cent of the total. The expenditures by the Department of Health, Education and Welfare (which, of course, includes the National Institutes of Health) and the National Science Foundation comprise only five per cent and one per cent, respectively, of total federal expenditures for research and development. The declining proportion for the Department of Defense and the rising proportion for the National Aeronautics and Space Administration are illustrated on the graph (Chart 8) showing research and development as a percentage of the gross national product.

Federal obligations for research and development by agency for 1962, 1963, and 1964 (see Chart 9) reflect the towering position of the Department of Defense and the growing role of the National Aeronautics and Space Administration. It is notable that basic research is well dispersed through the agencies of the government. The

CHART 2
TRENDS IN FEDERAL OBLIGATIONS FOR RESEARCH, DEVELOPMENT, AND RESEARCH AND DEVELOPMENT PLANT. FISCAL YEARS 1947-1964



[1] Includes pay and allowances of military personnel. [2] To be corrected. See Table 1.

Source: National Science Foundation.

National Science Foundation is neither the sole home of basic research in the government, nor the largest supporter of it. This graph shows statistically what Executive Order 10521 of 1954 stated in administrative language.

That the fields of science have not shared equally in federal funds is shown by the trends in federal obligations for total research by major fields of science, 1956-1964 (see Chart 10). Engineering has been the principal recipient throughout the period, obligations to it reaching an estimated $2.57 billion, or 44 per cent of the total research effort, in 1964. The overwhelming part of this goes into applied work related to large development efforts. The physical sciences accounted for 18 per cent of the total research effort in 1956, but this figure had risen to 26 per cent for 1964. Medicine and biology accounted for 12 per cent each of the total in 1956, but by 1964 medicine was scheduled to rise to 14 per cent while biology dropped to six per cent. The social sciences, at an estimated $352 million in 1964, accounted for two per cent of the total.

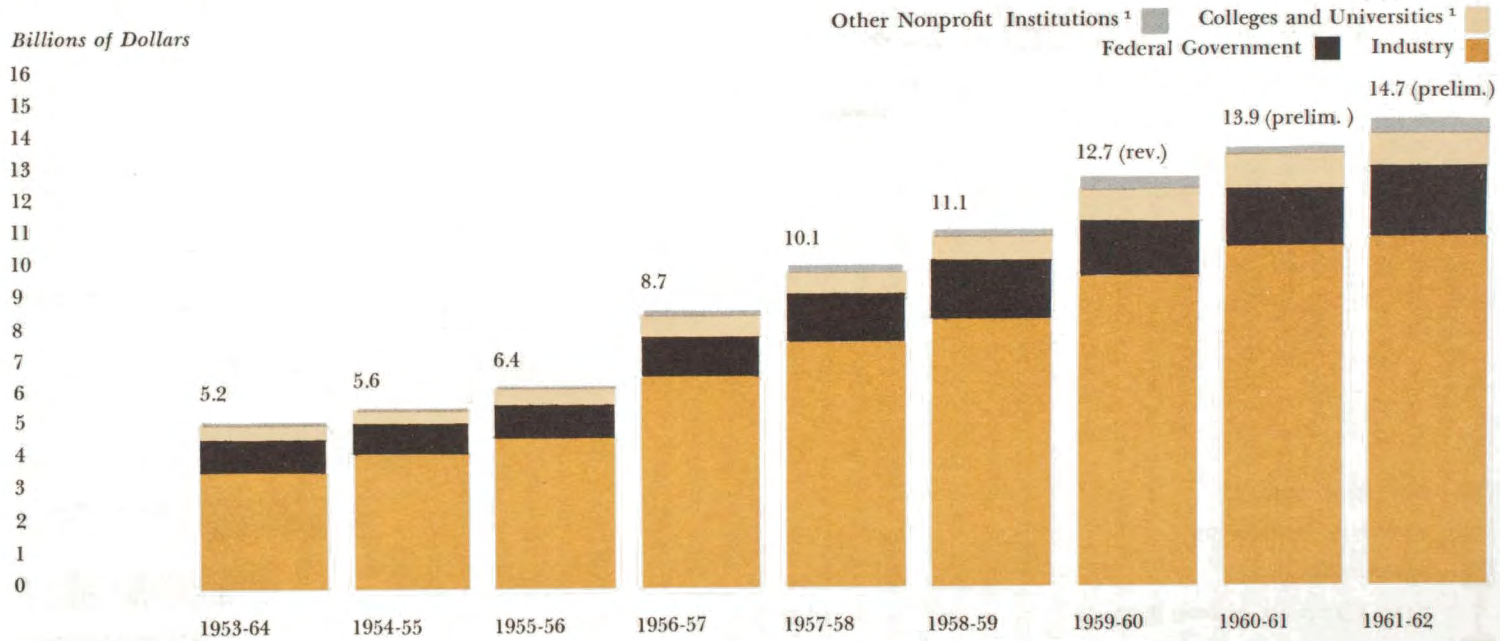
For those genuinely concerned with the critical elements in government spending for research and development, the great lesson of this profile is that the big totals come in parts of the spectrum other than basic research and in sectors other than the universities. The statistics show, however, that the link between the government and the universities does exist, that large funds are involved, and that the funds loom proportionately much larger for the universities than for the government as a whole.

Administrative Practices of Federal Agencies

As already shown, a number of federal agencies participate in the support of basic research, and, as one might expect from the various paths by which they entered the field and the variety of their missions, their administrative practices differ greatly. The agencies in the Department of Defense support basic research to maintain the military strength of the United States. The enabling legislation that paved the way for establishing the Atomic Energy Commission and the Department of Health, Education and Welfare recognizes the need for research in their respective areas. The National Aeronautics and Space Administration is charged with exploring outer space and making the results of this exploration useful. The National Science Foundation has responsibilities for the support of basic research generally.

It is important to note that the established tradition of statutory construction in the United States permits not only activities authorized by the language of the statutes narrowly construed, but also those authorized by reasonable inferences from the statutes. These may be drawn from the records of congressional hearings and reports

CHART 3
FUNDS USED FOR PERFORMANCE OF RESEARCH AND DEVELOPMENT IN THE U. S., BY SECTOR 1953-62

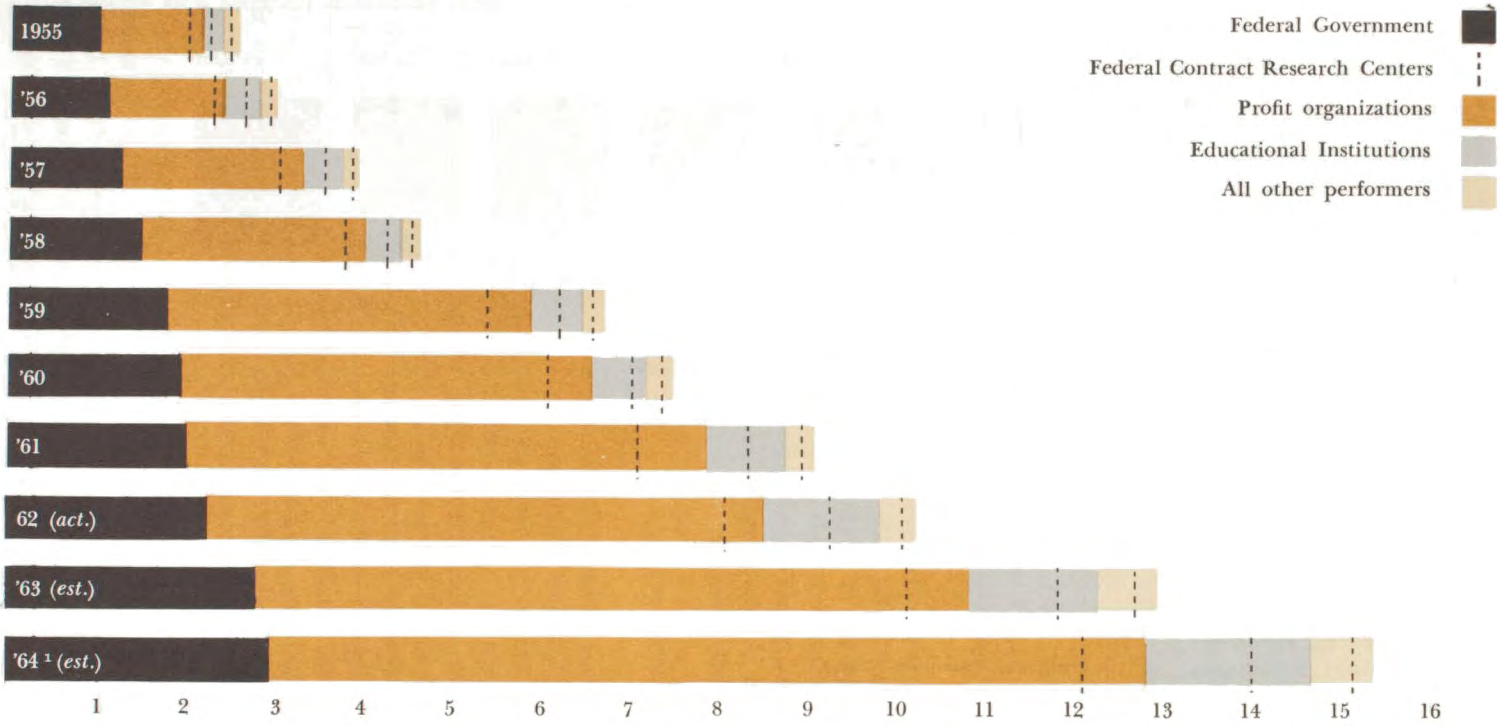


[1] Data include state and local government funds.

Amounts from the federal sector for research centers administered by organizations in the other three sectors are included in totals.

Source: National Science Foundation, 1963 Note: Data are based on reports by performers.

CHART 4 TRENDS IN FEDERAL OBLIGATIONS FOR PERFORMANCE OF RESEARCH AND DEVELOPMENT, BY SECTOR
FISCAL YEARS 1955-1964



[1] To be corrected. See Table 1 Source: National Science Foundation

of congressional committees. They are often drawn from the "common sense" of the situation. Such extended authority has often been sustained by judicial interpretation, by governmental practice in the absence of judicial challenge, and by congressional appropriation of relevant funds. What administrators have long done with government funds is a good index of congressional intent. Thus the nature of the work done by a contractor or a grantee and the degree of freedom of action permitted them do not depend upon the narrowest interpretation of the language of the statutes defining the mission of a granting agency. The basic research contract or grant is within the statutory authority if the agency judges it conducive to the success of its mission as defined by the statute. Thus, agencies with practical missions need not restrict the freedom of action of basic research contractors or grantees because of the practical nature of their missions.

Although all agencies have been authorized since 1958 to use the grant form of support for basic research, the actual practices in support of individual projects differ widely from agency to agency. The National Science Foundation uses grants of up-to-five years duration, the median being approximately two years. In the Department of Defense, the Office of Naval Research continues to use the fixed-price contract form of support, renewable at one-year intervals and sometimes for two or three years ahead. The Army Research Office uses grants or contracts of one-to-five years duration, two years being the median. The Office of Scientific Research of the Air Force uses both grants and contracts of one-year duration, but renewable for two more years. The Advanced Research Planning Agency (ARPA) uses annually renewable contracts. The National Institutes of Health uses annual grants renewable for up-to-seven years, with a median of three years. The Atomic Energy Commission uses contracts, usually of one-year duration and renewable. The National Aeronautics and Space Administration uses grants, mostly funded annually.

Both grantees and contractors are required to report the progress of their work. Implementation of this requirement actually varies greatly from one agency to another, from a simple submission of reprints of published work to frequent and more or less formal progress reports. All agencies use cost-type contracts for large projects and construction of research facilities. Some research contracts (for instance, those of the Office of Naval Research) state explicitly that their purpose is to support the conduct of research (as against purchase of research results). In these contracts, research objectives are described in broad terms only; thus no more restrictions are placed on the research freedom of the investigator than in grants. Other contracts are more restrictive.

All recipients of grants and contracts are required to keep records showing how funds have been spent. These may be inspected

CHART 5
RESEARCH AND DEVELOPMENT, 1961-62 INTERSECTORAL TRANSFERS OF FUNDS USED FOR PERFORMANCE (PRELIMINARY)

Research and Development Performers *(Millions of Dollars)*

Sources of Funds Used	Federal Government	Industry	Colleges & Universities		Other Nonprofit Institutions	Total	Percent Distribution R & D Sources
			Proper [1]	Fed'l Contr. Research Centers			
Federal Government	$2,090	$6,310 [2]	$600	$450	$200 [2]	$9,650	65
	238	*89*	*330*	*112*	*80*	*849*	*57*
Industry		4,560	55		90	4,705	32
		314	*25*		*12*	*351*	*24*
Colleges and Universities [2]			230			230	2
			180			*180*	*12*
Other Nonprofit Institutions [3]			65		90	155	1
			48		*60*	*108*	*7*
Total	$2,090	$10,870 [2]	$950	$450	$380 [2]	$14,740	100
	238	*403*	*583*	*112*	*152*	*1,488*	
Percent Distribution, R & D Performance	14	74	6	3	3	100	
	16	*27*	*39*	*8*	*10*		

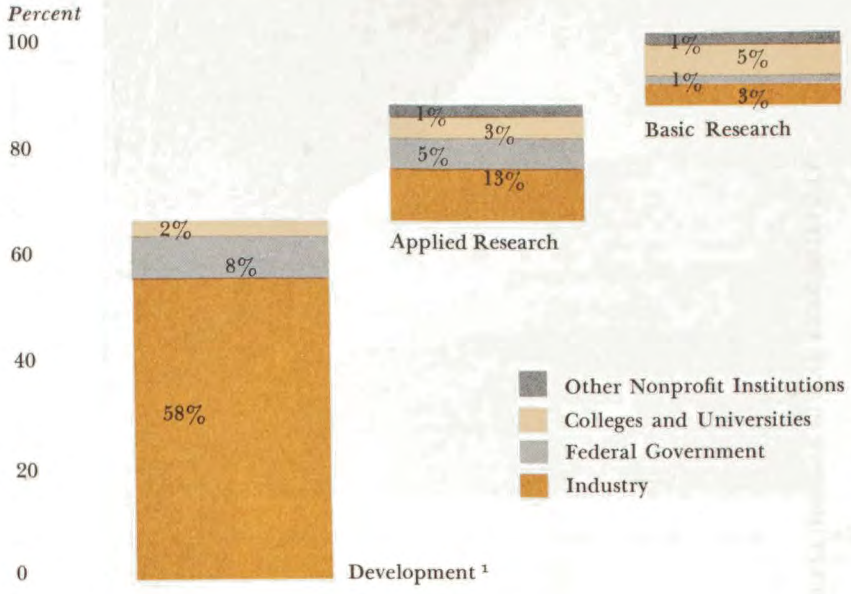
[1] Includes agricultural experiment stations. [2] This amount includes funds from the federal government for research centers administered by organizations under contract with federal agencies. [3] Data include state and local government funds.

Note: All data are based on reports by the performers. Source: National Science Foundation.

Basic Research

CHART 6
RESEARCH AND DEVELOPMENT PERFORMANCE, BY SECTOR AND TYPE OF WORK, 1962

Total Research and Development Expenditures: $14.7 Billion

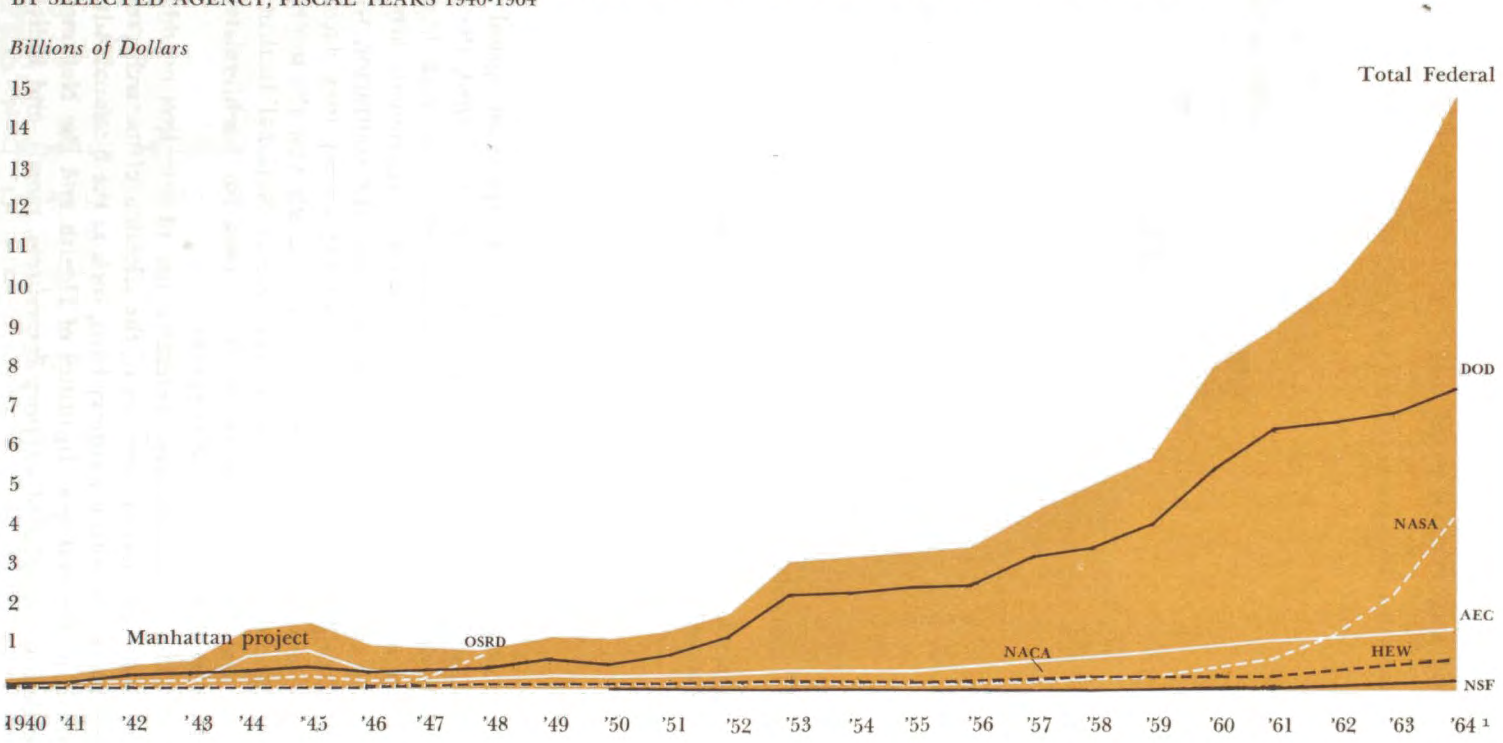


[1] Other nonprofit institutions reported less than 1 percent.
Source: National Science Foundation

by auditors to determine that money has been spent for agreed projects, and, in those cases where a budget has been specified, the auditors may determine that expenditures are consistent with budgets. Contracts usually vest the title to permanent equipment acquired under the contract in the agency rather than the contractor, who is required to keep property records until the agency may decide to turn the property over to him. Grants generally vest the ownership in the grantee institution but, in the case of National Institutes of Health grants, the equipment must be used for health-related research after the expiration of the grant.

Most agencies make extensive use of scientists outside the agency staffs for advisory services in the selection of research projects. Except for a few with a statutory basis, such as the National Advisory Councils in the National Institutes of Health and the National Science Board, the roles of advisory committees, panels, and individual

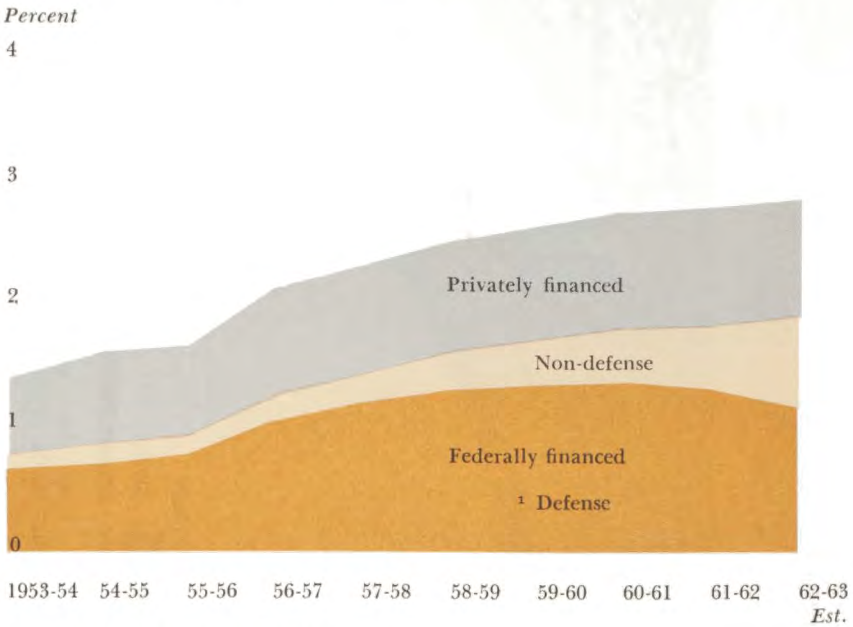
CHART 7
FEDERAL RESEARCH AND DEVELOPMENT AND RESEARCH AND DEVELOPMENT PLANT EXPENDITURES, BY SELECTED AGENCY, FISCAL YEARS 1940-1964



[1] To be corrected. See Table 1.

Source: National Science Foundation

CHART 8
RESEARCH AND DEVELOPMENT AS A PERCENTAGE OF THE GROSS NATIONAL PRODUCT, 1953-54—1962-63

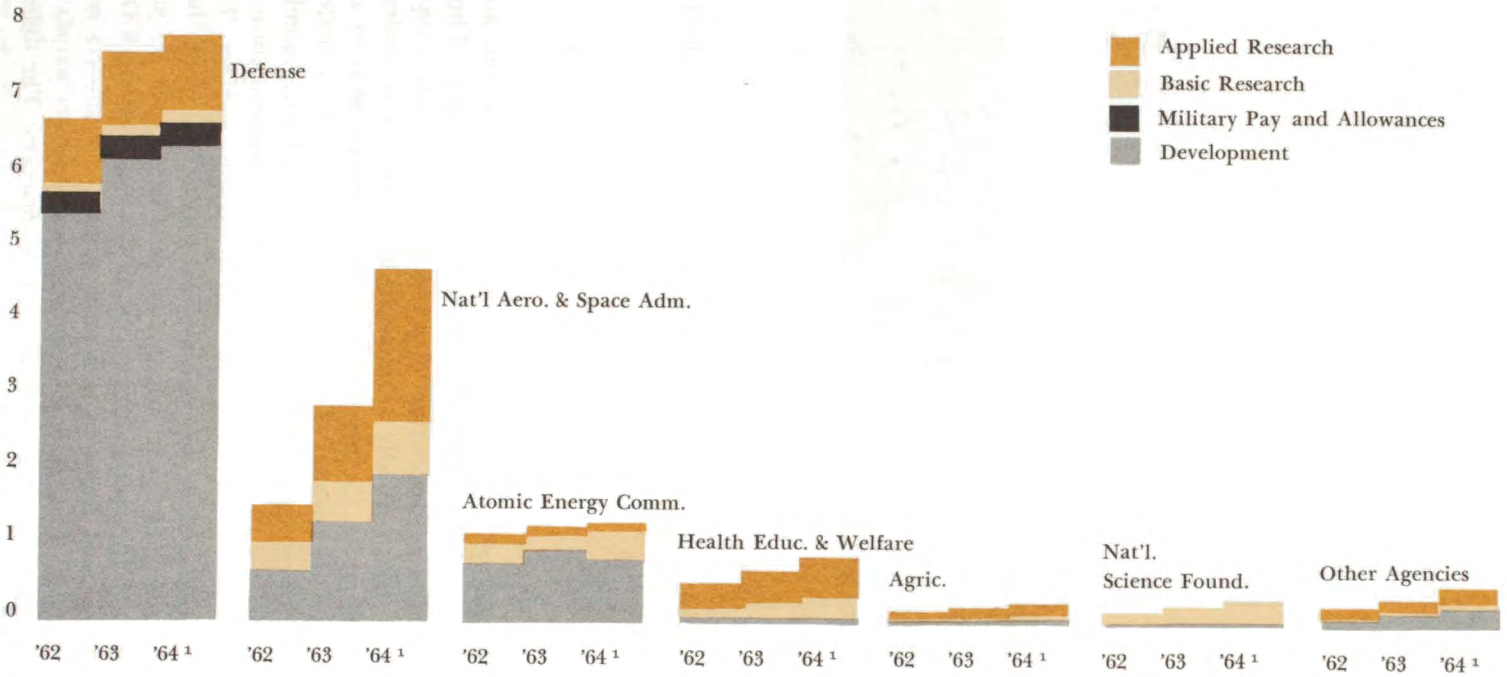


[1] Includes DOD and part of AEC.
Note: Data for the GNP refer to the earlier calendar year. Source: R. & D. data, National Science Foundation. GNP data, U.S. Department of Commerce.

referees are set by administrative decisions. The extent and form of practices differ greatly from one agency to another. Thus the National Science Foundation uses referees to evaluate proposals, and advisory panels usually arrange the proposals in an order of excellence. However, the practice varies from one division to another. In the National Institutes of Health the study sections evaluate proposals for scientific competence and arrange them in corresponding order. The Advisory Councils then make final recommendations based on relevance to the National Institutes of Health program. The Atomic Energy Commission uses only individual referees, while the National Aeronautics and Space Administration relies largely on advice from scientists in the centers it operates. In the Department of Defense, the Office of Naval Research uses some advisory committees and individual referees. The Office of Scientific Research uses panels of referees appointed by the National Academy of Sciences. The Office of Army

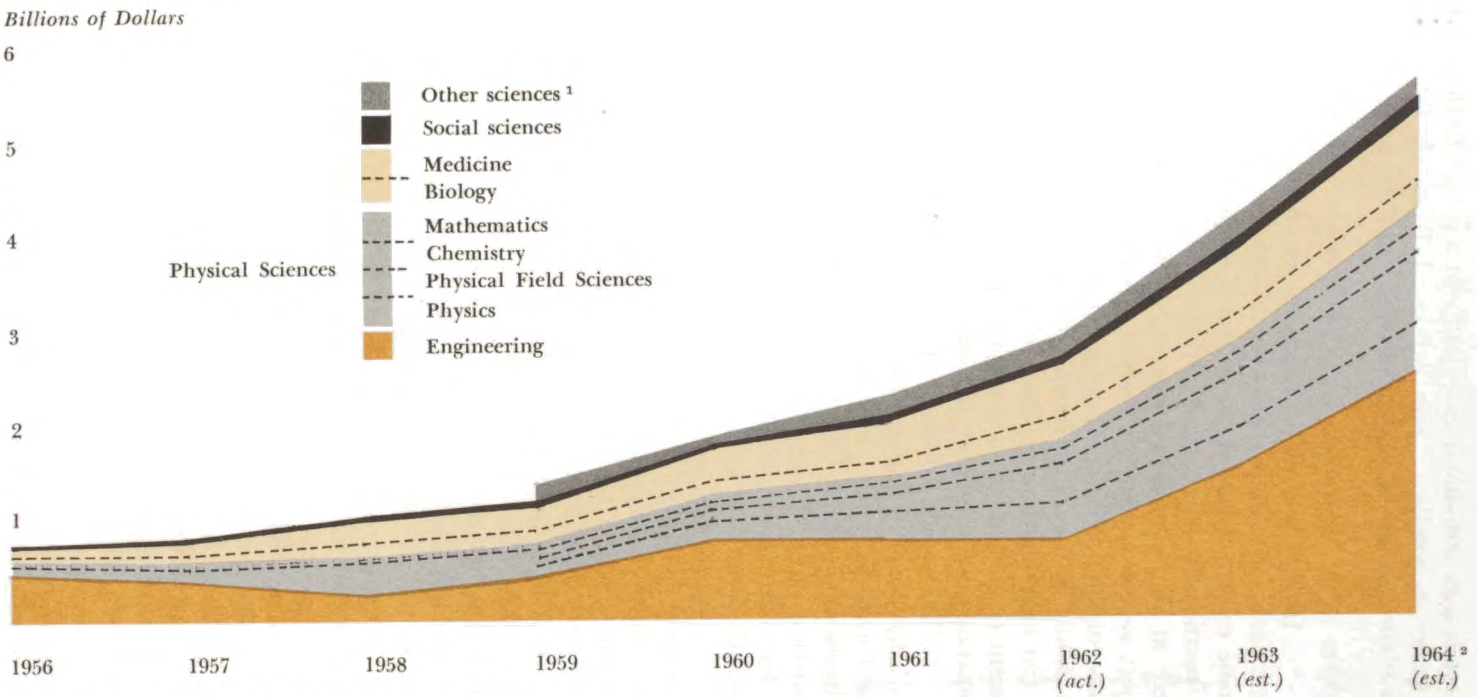
CHART 9
FEDERAL OBLIGATIONS FOR RESEARCH AND DEVELOPMENT, BY SELECTED AGENCY
FISCAL YEARS 1962, 1963 AND 1964

Billions of Dollars



[1] To be corrected. See Table 1. Source: National Science Foundation.

CHART 10
TRENDS IN FEDERAL OBLIGATIONS FOR TOTAL RESEARCH, BY MAJOR FIELDS OF SCIENCE
FISCAL YEARS 1956-1964



[1] Includes psychology [2] To be corrected. See Table 1.
Note: pay and allowance of military personnel not included

Research uses individual consultants in a manner differing from one discipline to another. The Advanced Research Planning Agency uses advisory committees and individual referees.

Problem Areas Surrounding the Interrelated System

In the changes of scale and emphasis in federal programs for research and development over the last five years, new strains have become evident. Some of these strains are in the government-university partnership itself. Many others, however, have developed elsewhere in the interrelated system. In some cases extension of the project system is clearly required. In others the indiscriminate extension of the project-grant system is an inferior solution to problems that should be faced directly and forthrightly by the makers of policy. We can only list some of the problem areas that we see developing adjacent to our subject, and emphasize that we consider them worthy of separate examination in their own right.

The object of federal support is not only increasing scientific knowledge but also strengthening of the universities themselves. The trained men and strong institutions produced by federal support are in themselves a major national resource in peace or war. Thus, the production of future scientists and strong, independent universities broadens both the opportunities and the problems of federal support beyond the bounds of basic research and related graduate education.

Construction and major facilities. Since the institution of the interrelated system during World War II, the government has increasingly felt the necessity of providing support for research by major plant investment. Chart 2 reflects this federal interest, and the 1963 legislation for college aid will doubtless accentuate the trend. When institutions of higher learning accept support for large buildings and other facilities, the uses to which the buildings are put are often related to other missions of the institutions as well as to federally supported research, and the formulae and legal instruments by which the arrangements are made must take these complexities into account.

Programs in science education. Always present as a direct adjunct to research at the graduate level, programs in science education have developed greatly since Sputnik. They have followed the quest for new scientific talent down into the grade schools, in recognition of the fact that the beginnings of scientific careers are made early. Indeed, the important decisions regulating the supply of scientific manpower are often made by boys and girls in school. Institutes for teachers and programs for improving courses of instruction have gained wide support in Congress, in the universities, and in elementary and secondary education. These educational improvements not only assist the training of future scientists, but also have the effect of bettering the quality of the education of all.

TABLE 1
RELATION OF FEDERAL OBLIGATIONS FOR RESEARCH AND DEVELOPMENT AND R&D PLANT, BASED ON *THE BUDGET, 1964,* TO THOSE BASED ON SUBSEQUENT CONGRESSIONAL ACTION AND ADMINISTRATIVE DECISIONS, BY SELECTED AGENCY, FISCAL YEAR 1964 (ESTIMATED) [1]

(Millions of dollars)

Agency	The Budget 1964			Subsequent Congressional and administrative decisions			Actual change		
	R&D	R&D Plant	Total	R&D	R&D Plant	Total	R&D	R&D Plant	Total
TOTAL, ALL AGENCIES	15,329	1,672	17,001	14,566	1,763	16,329	−763	+90	−672
Department of Agriculture	184	2	186	184	2	186			
Department of Commerce	69	58	127	56	56	112	−13	−2	−15
Department of Defense	7,868	97	7,965	7,636	96	7,732	−231	−1	−232
Department of Health, Education, and Welfare	842	77	919	791	85	876	−51	+8	−43
Department of the Interior	125	10	135	120	9	129	−5	−1	−6
Atomic Energy Commission	1,195	299	1,494	1,237	407	1,643	+42	+107	+149
Federal Aviation Agency	60	17	77	109	19	128	+50	+2	+52
National Aeronautics and Space Administration	4,672	976	5,648	4,175	1,027	5,202	−497	+51	−446
National Science Foundation	211	130	341	166	59	225	−45	−71	−116
Veterans Administration	33	7	40	34	3	37	+1	−4	−3
All Others	70	[2]	70	57	[2]	57	−13		−13

[1] In a few instances, R&D and R&D Plant do not add up precisely to the totals shown, due to rounding of figures.

[2] Less than $500,000

Source: National Science Foundation.

Science information. Unless the results of research reach the people who need to know about them promptly and efficiently, the best of research projects will not be effective. The responsibility for science information is shared by the government, the universities, and the scientific community. A report of the President's Science Advisory Committee, issued January 10, 1963, and entitled *Science, Government, and Information: The Responsibility of the Technical Community and the Government in the Transfer of Information,* deals with this responsibility comprehensively.

The humanities and the social sciences. Healthy universities are more than just collections of departments of mathematics, physics, chemistry, and biology. Their programs in the humanities and the social sciences must also develop their full potentials in the interest of scholarship as a whole. Even the education of scientists cannot neglect other fields of learning, if the scientists of the future are to contribute fully both in their professional capacities and as citizens.

Civilian industrial technology. Means by which the results of research may be brought to bear on the everyday needs of the civilian economy, as they have been on the requirements of military and space programs, should be given careful consideration.

National facilities. In some fields of science, the trend toward national facilities instead of installations at individual universities has been apparent. Special area requirements, expensive equipment, and inter-disciplinary approaches often make the creation of such facilities desirable. They pose special problems, however, for the government agencies and the universities that participate in them.

Experiments requiring large outlay for supporting technology. The cost in dollars per scientist engaged in research has been rising astronomically in some areas. Actually included in the total costs are necessary large outlays—often totaling many millions of dollars—for supporting technology. Some projects involve military personnel and large labor forces. For lack of explicit classification of costs, however, these massive totals are charged entirely to basic research.

Basic research in governmental laboratories. Our general belief that basic research is most often at home in a university setting should not obscure the fact that it also is done in government laboratories and that, in certain fields, the government laboratory has both special equipment and skilled investigators. Also, applied research, which is the usual activity of many government laboratories, may gain significantly in range and effectiveness if some basic research projects are also conducted in those laboratories.

Basic research in industrial laboratories. Like government laboratories, industrial research organizations need basic research results and the breadth of vision created by basic research work.

Patents appear to concern only a small fraction of investigators involved in basic research in universities. This is a very complex problem that cannot be resolved without involving questions of patent rights arising out of applied research in industrial laboratories and universities. We note that on October 10, 1963, President Kennedy issued a memorandum announcing liberalized policies for all federal agencies insofar as existing statutes allow changes in current policies. We believe that discussion of the patents situation as it affects basic research should await changes in agency procedures.

Having taken cognizance of these problem areas, however (and others could be added), we have no hesitation in focusing our attention squarely on the mechanism by which the investigator in the university and the federal government are bound together, because the individual investigator remains, as he has been for decades, the most important person in the interrelated system. In his hands remains most of the research at the farthest edge of the frontier. As a teacher and leader of graduate students, the future is also in his hands.

VII

Principles for the Project System

The Project and the Judgment of Merit

The project system refers to the unit of organization—the project—which defines a particular research activity's size, shape, duration, and personnel as a rational basis for support. Projects may exist in laboratories and research establishments in every sector, and they draw the support of funds from every sector. The experience of two decades has given the project a definite status and fixed it firmly in the rules and customs that govern the interrelated system. The use of the project is consistent with our belief that the investigator's ability and creativity is the crucial ingredient in all research. The project proposal is an important index of the investigator's ability and creativity. Since there is never a sufficient amount of support available for all conceivable research, the evaluation of the project proposal nearly always becomes the basis for judgment in the situation we are considering here—support of the university investigator by a federal agency.

The use of project support as the principal means of aiding basic research has advantages of great practical importance. Through the project system the federal government can finance research in institutions of higher learning in the way that relates the award of funds as closely as possible to scientific merit and minimizes the effects of po-

litical pressure. There is no way for the federal government to make general grants to universities with unspecified purpose, on the basis of merit, without undertaking to rate or accredit the universities, either as a whole or with respect to the quality of their scientific programs, and, when large sums of money are granted, the problem becomes particularly acute. The federal government (like the great private foundations) has always sought to avoid this kind of judgment, having no desire to come into conflict with the independence of the national associations through which the colleges and universities maintain and defend their own academic standards.

Through the project system, the federal government can, after the general purposes of research funds have been defined, decide to award funds on the basis of the scientific merit of investigators and their proposals. The ultimate responsibility remains with the duly constituted authorities—the Congress, the President, and the heads of departments and agencies—who decide on the purposes, procedures, and dollar volumes of the several programs. None of these decisions directly determines the distribution of funds among institutions, or infringes upon their independence. The decisions on individual awards can be made with the advice of professionally qualified specialists in the various disciplines, so that each scientist's application is judged by a panel of his peers; and thus no one, in the name of the government, makes an administrative or political decision on the fate of a college or university as a whole. Thus, this competition avoids the perils of overcentralization of planning and management, which are particularly dangerous where the freedom of inquiry inherent in the nature of science is involved.

The decision to ask for and accept a grant in aid of his research can pose a complex problem to the scholar-scientist who values the full freedom of inquiry traditionally fostered by universities. If the grant, from federal or private sources, is made under rules that tend to hamper his wide-ranging studies of natural phenomena, or to curtail his need to teach and work with graduate students, then he sacrifices valuable ingredients that characterize effective research. On the other hand, unless he finds a source of funds, his work is seriously hampered. At present, the project system is the most flexible of fiscal arrangements permitting the federal government to utilize the talents of scientists in our universities. It permits each scientist to decide on the extent of his commitment to governmental support by balancing his scholarly duties to the university with his need for financial support of his research.

We are therefore convinced that, for the foreseeable future, the major emphasis in the federal government's support of basic research in science in institutions of higher learning should continue to be given to the project system.

Grant and Contract

The grant, as the instrument for government support of research in the universities, has continued in favor since 1958. The Bell Report to the President, on government contracting for research and development, concluded that "in our judgment the grant has proved to be a simpler and more desirable device for federal financing of fundamental research, where it is in the interest of the government not to exercise close control over the objectives and direction of research." The arm's length between the government and the scientist, praised in this quotation, has to do with objectives and direction of research rather than with fiscal accountability. A contract can provide—and in many cases has—the same freedom for science, coupled with fiscal responsibility, that the grant does. Long-standing contract procedures, such as those of the Office of Naval Research, use the contract in the freest possible way for the support of research. Yet wide use of the contract in procurement of goods and services by the government has made it a more usual instrument for the purchase of research results than for support of research. Therefore we favor the more widespread use of the grant made possible by the legislation of 1958, so that the increase in its use as the principal instrument for federal support of basic research in the universities will be continued.

The grant-in-aid is traditionally and symbolically different from a contract. It is the basis for a cooperative relationship under which the grantor and the grantee share a common purpose of public service. This is not a relationship between buyer and seller, and not a hierarchical relationship between superior and subordinate, but a relationship between agencies that, differing in financial resources, are equally concerned with serving a public purpose. For instance, the federal government makes grants to states for public welfare programs, and states make grants to local school districts for the support of education. The recipient of funds is indeed expected to account for their use by proving that the funds have been spent for the intended public purpose—and not as if reporting to an administrative superior. Because the contract has most frequently been used for the purchase of commodities from businesses operating for profit, the habits of contract administrators in government agencies sometimes tend to a more detailed and restrictive type of direction and accountability than is appropriate for the support of basic research.

Whether the grant or contract is used in the project system, the same principle should obtain: the terms should never be such as to make it impossible to deliver the goods. The worst way to waste federal money in this system is to give funds to support basic research with conditions attached that handicap the perform-

ance of the research, or that reduce the ability of institutions to encourage the utmost scientific imagination and inventiveness.

It is fundamental to both a grant and a contract that the agency and the university enter into the agreement only for some agreed purpose. The only question that can arise concerning the purpose is with regard to its breadth. No agency of government can or should make a grant or otherwise disburse public funds without some definition of the reason for their expenditure. The practical problem is the expression of governmental purpose in such terms as will produce the optimum scientific result. We cannot emphasize too strongly that every grant or contract has a purpose, and that the fulfillment of that purpose is the responsibility of the government, the university, and the scientist. The scientist participates actively in the definition of the purpose in the preparation of his research proposal. In the remainder of this chapter we shall trace the life cycle of a grant, giving special attention to the way in which the purpose is unfolded.

Grant Negotiations

An accepted pattern of negotiation should precede the approval of a grant. For simplicity in describing the process, we shall adopt a single set of terms that are not to apply to any specific agency but rather to an idealized situation. We shall speak of the instrument as a grant, even though much of what we say applies equally well to fixed-price contracts. We shall speak of the university, even though other institutions of higher learning do participate in the system. The four essential officers involved in the negotiation we shall call: (1) the principal investigator, the scientist whose ideas are both the origin and the end-product of the whole process; (2) the administrative officer of the university, the president or his deputy, sharing responsibility with his governing board; (3) the program director, an officer of the government agency with scientific knowledge and standing in the scientific community; and (4) the grants administrator, an officer of the government agency responsible for handling government funds in accordance with the rules laid down by the President and Congress.

Each of the four officers plays a vital role in the negotiation, and each performs a function that none of the others can perform. We believe that each needs a better understanding than he now shows of the roles played by all the others. The grants administrator should be uncompromising on the fiscal responsibility of government, but respectful of the scientific purposes of the agency, mindful of the fiscal procedures and broader responsibilities of the administrative officer of the university, and sensitive to the uncertainties that face the principal investigator in the lab-

oratory. The program director, representing the general scientific purposes of his agency, should use the services of the grants administrator as a fellow officer of the government, join the administrative officer in an understanding of the nature of the university, and work with the principal investigator as a fellow scientist.

The administrative officer of the university, when he accepts a grant, places his university in a position of direct legal responsibility for government funds, for their care and proper disbursement. At the same time he bears a direct responsibility for the institution. One of the proper missions of the university is the research for which the grant was made. It also has other proper missions—the education that is a part of federally supported research, the education that lies beyond the federal support, and many kinds of public service.

The principal investigator is in the most complex position of all. He is at the center of a network of obligations. He (as well as the administrative officer) takes responsibility for the proper use of federal funds when the grant is accepted. He has a responsibility toward the graduate students, postdoctoral fellows, and other staff who work with him on the project. He is a professor of the university, with duties as a teacher both to those graduate students who work with him on the grant and to many students, both graduate and undergraduate, who do not. He is a member of a faculty and may have faculty committee assignments. He may have administrative duties in the university, such as the chairmanship of a department. He is a member of the scientific community, with offices or duties in a variety of learned societies, including such posts as advisory editor on one or more journals. Yet, in the midst of this maze of duties, one thing is clear: the principal investigator's work *as a scientist* is the determining factor in achieving the national purposes envisaged in the grant.

The negotiation of a project grant begins and ends with the principal investigator. He starts with an idea for research and ends with the support that allows him to go ahead with it. If the process were frictionless, negotiation would not be the right word for it. The administrative officer of the university may be faced with severe decisions as to the use of space and facilities for a federally financed project rather than for competing functions. He must guard against derogation of the teaching mission of the university. He must be sure that nothing in a grant agreement frustrates the university's own fiscal procedures (themselves sometimes determined by state law). The program director, who can arrange the support of only a fraction of the proposals that come to him, faces such severe choices that, in our opinion, he always needs help, as the following discussion of panels will show. The

grants administrator must be aware of special legal provisions that must appear in grant letters.

The principal investigator may have a friendly relationship with the program director of the federal agency. He may be in a position to exchange views with the administrative officer of his university and his staff, but as a faculty member he is not likely completely to share the administrative point of view or be aware of all the competing considerations. He is least likely to know personally or negotiate informally with the grants administrator. Thus the participants in grant negotiations come to their task with divergent attitudes and responsibilities, often leading to frictions in the negotiation process. A campaign of education for all four groups of officials would pay beneficial dividends.

We believe that the health of the project system requires that three principles remain inviolate, *never* becoming subjects of negotiation or giving rise to restrictive clauses in grants. They are: (1) the responsibility of the government for the expenditure of public funds; (2) the independence of the universities; and (3) the freedom of the scientist to conduct his research, reach his conclusions in his own way, and make them public.

The Proposal

The purpose of a project, which provides the test of the propriety of the use of federal funds throughout the life of the grant, is first defined by the principal investigator himself in the body of a proposal. Too often this fundamental fact is not well enough understood by the scientist seeking support. He may avoid later difficulties in making his budget conform to the scientific realities of his research by his own action in broad, yet careful, description of his project. Federal granting agencies should make it plain in their instructions that the content of the project proposal is the basis of the purpose of the research as it will be stated in the grant letter. Approval of the proposal by the university and by the agency means that the investigator will be expected conscientiously to try to reach the scientific objective defined in his proposal. If the proposal sets out a highly specific method of investigating a scientific problem, rather than the fundamental nature of the problem itself, even small changes in tactics may cause trouble. Thus, investigators can do themselves a major service in the very beginning by presenting carefully conceived proposals, or they can lose the opportunity and bind themselves in ways that will prove unfortunate later on.

We believe that the impact of administrative restrictions can be minimized if project proposals consist of the following elements:

(1) Broad objectives of the proposed research in terms of areas of scientific knowledge to be advanced.
(2) Specific early research objectives stated as illustrative of the broader aims.
(3) Scientific tactics (experimental methods) to be employed.

With such a proposal, only a deviation from the broad objectives of the project proposal should be considered the kind of change requiring special approval from the federal agency.

The Panel and the Consultant

When a proposal comes to the desk of the program director in a federal agency, he must take action to determine whether the proposed project should be supported by the government. Each program director is knowledgeable in a particular field of science, and previous budgetary decisions by the administration, the Congress, and the agency have determined that his particular field has only a finite sum at its disposal, usually only a fraction of the total budgets of all the proposals in hand. A decision must be made, in the interest of both the taxpayer and the investigator, on the *scientific* quality of the proposal. We believe that no agency has or should have sufficient funds to avoid making this decision. We also believe that, in general, program directors can seldom make the required judgment of scientific quality without assistance. That assistance must come from the scientific community itself.

Agencies have usually recognized, some more formally than others, that a judgment of scientific quality can be adequately defended only when the scientific community has participated. Selection of advisers from the national pool of scientists in a particular discipline, avoiding undue regional or institutional concentration, is the best means of securing competent judgments and freedom from irrelevant considerations. We use the word "panel" to mean a group of scientists qualified in a particular field, who hold appointments to regular terms and meet periodically to pass on the merit of proposals. Their names should be well known to the scientific community, and they should have all pending proposals in a given field before them for comparative ranking. Some agencies informally use consultants with special competence to pass on particular proposals. Consultants usually render judgments of proposals by mail, without knowledge of other referees or of other proposals. We believe that consultants can usefully supplement the information otherwise available for the judgment of proposals, and that agencies that do not use the panel system would benefit by calling upon them.

While we can see certain difficulties in the present functioning of the panel system of review, we feel strongly that it

should be retained and also improved and expanded. The overwhelming majority of scientists who have commented to us on the evaluation methods of federal agencies have praised their fairness, wisdom, and success. Among the difficulties we see in the functioning of the system, however, we especially note the following:

(1) It makes a heavy additional demand on the time and energy of the very scientists who have the most to contribute as investigators.

(2) It tends to be cumbersome and to increase the period of waiting from the time of an original proposal until work can begin.

(3) When some individuals serve too continuously on the panels of one or several agencies, and when a few universities are regularly over-represented, the burden is too concentrated on the individuals involved and the system is open to the charge of favoritism in judgment.

(4) With the constant shifts in the boundaries of disciplines and the interdisciplinary nature of much current research, panels may not always reflect the current frontiers of research, and proposals may be sent to the wrong panels for judgment.

We believe that the shortcomings of panels can be corrected if the federal agencies are alert to the fundamental reasons for consulting the scientific community, and if they take steps along the following lines:

(1) The burdens on individual advisers must be kept to a minimum, by using more advisers and rotating them often. The pool of competent scientists from which panels can be drawn is not only large but expanding.

(2) Every effort should be made to give younger scientists their turns on panels, both to spread the work and to infuse new points of view.

(3) The constitution of panels should represent perspective as well as specialty. Panels in given fields of science should include some members from allied fields.

(4) While the final responsibility for action rests with the federal agency, the advice of the panels must be consistently taken seriously to maintain the conviction among advisers that their services, even though part-time, are important.

(5) The judgment of panels as to the general reasonableness of proposed budgets is a part of their judgment of proposals, but the talents of panelists are not being properly utilized when they are requested to make detailed decisions on fiscal matters, properly an agency responsibility.

(6) The plural system, in which several agencies support basic research in the same broad scientific areas, should be continued because, in addition to its other advantages, it permits individual investigators to appeal to more than one panel. This

multiplicity of opportunity is worth more than its increased cost in money and in scientist-man-hours served on panels. It tends to reduce charges of personal or institutional bias on particular panels. Moreover, in the face of different approaches of different agencies, dictated by their missions, new ideas that may be at variance with a current consensus have several chances for appreciative examination.

Agency Staff

The program directors, while in general avoiding judgments of scientific quality without the advice of the scientific community, have a crucial role to play in the project system. Every agency has an important and delicate task in building its program staff. Program directors must be sufficiently knowledgeable about their fields to command the respect of the scientists with whom they deal. At the same time, their full-time presence as agency employees means that they are withdrawn from the ranks of active investigators even more completely than panel members. Extended service away from direct contact with research problems eventually impairs the program director's essential grasp of the state of the frontier in his area. Agencies can minimize this problem by utilizing scientists on leave from university positions; the rotation from campus to agency has done much over the last few years to broaden understanding of the complexities of the project system. Yet the agencies must beware of filling key positions continuously with temporary and partially committed people, thus impairing continuity of policy. To maintain the quality of agency staffs, the career service should be improved by providing compensation at satisfactory levels, and staff members should be encouraged to continue their scientific and professional advancement.

The decisions leading to the granting of funds already allocated to a field are only half of the essential duties of the program director. He must also closely observe research trends within his area and form judgments on proper levels for the future allocation of funds to the field. With the frontiers of research always changing, and with the fission and recombination of disciplines always going on, continuous review of trends is necessary if the agency director, the Bureau of the Budget, and the Congress are to have a rational basis on which to make support allocations in budgets for future years. Program directors, with their intimate links with the scientific community, are in the best position to provide the data necessary for sound program planning.

The administrative staff of an agency—including the grants administrators, the comptrollers, and the counsels—has an important role to play in the processing of proposals. It deals with proposals

at the point at which they are brought into detailed agreement with the fiscal practices of the government. We believe that a completely strict and proper fiscal administration of federal funds under the project system is entirely compatible with the scientific flexibility so often emphasized in this report. Detailed, repetitive reporting and requirements of advance specifications are familiar administrative devices to ensure responsible performance in many procurement activities of the government, but their application, even occasionally, in the project system is a violation of proven management practices in the support of basic research.

Duration, Size, and Multiplicity of Grants

Since the duration and size of grants vary not only with agency policy but with field of science, we can set forth here only general principles. The durations of projects range from one to seven or more years. The money involved in single grants ranges from a few thousand to millions of dollars. Since the time and effort required in the preparation of proposals, panel consideration, and agency work tend to be the same regardless of the amounts of money and time specified in grants, it is natural to regard larger and longer grants as preferable.

We believe that important economies can be achieved by using grants of longer term than a single year, and by refraining from calling for reports and reviews at too-frequent intervals, especially early in the life of a project. The necessary periods of uncertainty that immobilize investigators waiting to know whether staffs can be engaged and orders placed for equipment can be minimized if new proposals are not required at frequent intervals.

We have already stated our approval of the plural sources of federal support as represented by the several agencies. However, the multiple accounting and reporting required by multiple grants for closely related facets of an investigator's program are wasteful, and this system has, in our opinion, gone well past the optimum point for best results. We believe that vigorous efforts should be made to reduce the need for multiple-agency support by inter-agency agreements, with a single agency providing total support of that portion of an investigator's work that has a single, broad, scientific objective.

While we recognize that fewer, longer, more stable grants save the investigator's time and reduce the high cost of administration in both university and government agency, we are convinced that the health of the national research effort requires availability of small grants. By means of such grants, the project system must provide support for young, relatively untried principal investigators. It must also provide for continuous entry into the system of

untried ideas that lie outside the current consensus as to where the frontier in a given area lies.

Therefore we suggest a program of special, small research grants for individual independent research, with preference given to junior scientists. These grants should be awarded on the basis of outlines of research interests, supported by letters of endorsement from senior scientists personally acquainted with the work of applicants. Aside from reimbursement for the time of the investigator and indirect payment to his institution, the budget should provide only for supplies, travel, and smaller items of equipment as a single budget item. The investigator should be allowed to pursue whatever lines of research appear most fruitful to him within the broadly described field. Such a program would be based on the recognition that many original ideas and discoveries in science have come from very young investigators, and we as a nation cannot afford to tie all our well-trained young people to narrowly defined objectives or to routine work in subordinate positions on big projects.

Termination of awards by an agency should be given as careful and serious consideration as approval of applications. Abrupt termination can thoroughly disrupt a research organization and scatter valuable personnel. Such devices as notice of the beginning of a terminal year and tapering off of grants over reasonable periods of time give opportunity to conclude the current stages of projects, to develop new proposals for further work, or for skilled personnel to find other places of employment.

Changes in Budget Items

Two types of projects run no risk of having to make changes in budget items during the life of a grant. In one of these the investigator is so completely unimaginative that he can foresee and describe in detail both his results and his methods before he begins. This kind of "efficiency" we do not recommend. The other type of project that runs no risk of change is that of a creative investigator who describes his project strictly according to the rules we have discussed; whose proposal moves through its review by both university and agency in zero time; and who executes the research so fast or works in a field of such gradual change that the state of knowledge and technique does not change while he is at work. In actual practice, however, some risk of changes in budgets is inherent in every project, no matter how well conceived and executed.

Often an interval of nine months or more elapses from the time an investigator writes his proposal until support is assured and the research can begin. During this time the state of knowledge may have changed in unanticipated ways. Scientific papers are published; new instruments become available. The personnel available

for assistance may shift. New ideas emerge that require modification in the direction and emphasis of the project. The original design of the project no longer quite fits the state of knowledge or the tactical position in the field.

After the grant is awarded, external factors continue to change the configuration of the field. In addition, the investigator's own understanding of related problems should begin to sharpen rapidly. Even if the larger generalizations with which the investigator began are confirmed, many details will appear in different lights as he progresses. Even tactical decisions to change a method may affect the budget. And changes stemming from changed university regulations and the uncertainties that go with employing several people may affect the precise sums spent in particular categories.

The granting agency has the responsibility of assuring itself that inevitable changes made in budget items during the life of a grant do not constitute a change in purpose as originally described in the proposal and approved by the agency. Some regulation of the transfer of funds from one budgetary item to another is necessary if the agency is to have this assurance. We believe that the regulations limiting changes in the compensation of senior personnel, in travel (especially abroad), and in improvements in the facilities of grantee institutions are quite proper. On the other hand, we believe that principal investigators should be given maximum latitude in modification of other items in their budgets. We also believe that any limit on the purchase of initially unspecified equipment should be proportional to the total values of a grant.

If the principal investigator, in his application for renewal or continuation of a grant, explains substantial shifts in the specific budget items of his project, and thus justifies them on scientific grounds, adequate safeguards will be provided against diversion of funds. (We believe that a requirement for such explanations would be appropriate and sufficient.) Thus, projects will not be delayed pending approvals from federal agencies, and agency staffs will be spared the dilemma of making either perfunctory approvals or arbitrary refusals.

Total Professional Effort

Nearly every project grant provides for the payment of federal funds for the compensation of professional and technical personnel. Since these people are all employees of the university that receives the grant, the rules of the university rather than the rules of the government (through civil service regulations or otherwise) govern the rates of pay and conditions of employment. This fact is a cornerstone of the whole project system.

Accounting for the time or effort of technical and supporting personnel who carry out assigned work on a single grant is quite clear-cut. The supporting personnel can be hired in a non-academic status on the basis of a standard work week—for instance, forty hours. The personnel supported by funds provided by a federal grant should be subject to the same regulations, salary scales, and working conditions as those that apply to employees in comparable positions with salaries paid from university funds. For both types of employees, the university must require the same adherence to standards of attendance and quality of performance. The university should keep, and make available to officers of the granting agency, appropriate records of the working time and salaries of all technical and supporting personnel working on a grant. This accounting should be annual rather than for briefer periods.

For principal investigators and other scientists with academic appointments, the problem of time-accounting is more delicate, whether they are reimbursed from government funds or not. The results in research for which they are paid cannot be measured in days or hours, or in percentages of them. Scientists do not "put in" a specific number of hours per week on a project. Insights and ideas do not "come in on schedule." They come to scientists, just as they come to politicians and poets, while driving to work, while discussing unrelated problems with colleagues at a convention, or even while attending committee meetings. Thanks to long-established scholarly traditions, most universities have met the demands of free inquiry by establishing an atmosphere free from restraint and regulation, with no percentage time assignments and with research work freed from administrative direction. It is the total professional effort that counts, and, in the last analysis, the progress achieved by an investigator over a three- to five-year period is the most reliable measure of his effort.

Under some circumstances a simple fraction of total professional effort in university duties can be assigned to a grant. Three cases will illustrate a range of possibilities for a professor who is a principal investigator.

Case 1. During the summer, the professor is not being paid by the university and has no formal teaching or administrative duties. He can be paid a salary from his research grant based on a fraction of his regular salary for that portion of the year for which the extra (grant) salary was drawn.

Case 2. During the regular university year, the professor finds his research project so demanding that he requests the administration of the university to lighten his teaching responsibility and other duties by a definite proportion, and to reduce his salary from local funds by the same proportion. The university then is obliged

to seek replacement personnel. The funds of the research grant having been budgeted to pay the corresponding portion of the investigator's salary, he is then properly committed to the government to spend a commensurate portion of his total professional effort for that year on the project for which the grant was made.

Case 3. During the regular university year, the investigator undertakes his full teaching responsibility and his full range of duties as a professor, for which he is paid full salary from local funds. Among the duties for which he is being paid by the university is research. It may be an active year for the experiments in process under his grant, and he may spend what time he can working on it himself. He has full-time responsibility for the supervision of supporting personnel, who will continue to work through this period. Because of the fluctuations of activities geared to the academic calendar, the professor may be completely engaged in teaching duties and examinations one week, and then, because of a laboratory emergency, spend 80 hours on his research project the next. Because some of his research assistants are probably also his graduate students, much of the time he spends with them cannot be assignable separately to teaching or research. The two are intimately intermingled. Under case 3, any effort at time-accounting, even in terms of a fraction of total effort, is unrealistic, and should not be demanded by the agency.

We recognize that many variations in the patterns of compensation described in the three cases can be produced by multiple grants, each claiming their fraction. We also recognize that professional schools and large facilities, with many non-teaching appointments for senior scientists, produce difficult problems of application. However, we believe that the concept of total professional effort, when properly defined by academic institutions, contains within it not only a realistic measure for the scientist but an adequate safeguard for the government.

This tracing of the grant through its life cycle has enabled us to illustrate the principles that should govern every federal agency in supporting basic research in institutions of higher learning. The plural system of support, which we have praised and which we wish to see continued, precludes a government-wide uniformity in every detail of policy and procedure. Nevertheless, uniformity in the *principles* of support will foster the diversity of research patterns which contributes to the strength and glory of contemporary American science.

VIII

The Role of the Institutions of Higher Learning in the Operation of the Project System

Improving the Administration of Grants in the Universities

Because the grant is a cooperative arrangement of trust between the government and the university, the health of the project system and the achievement of national purposes through it depends upon enlightened policies both within the universities and among the government agencies. We believe in the importance of the universities' traditional self-disciplined freedom and in federal support on terms that will protect this freedom, because this combination has proved to be the most productive of increasing effectiveness in basic research which, in turn, is absolutely essential to the well-being of the nation and of civilization.

It is desirable to protect the freedom of a university scientist to choose a subject of research according to his own interests, because it will let science deploy more rapidly and effectively along the new and moving frontiers of knowledge. This freedom is not inconsistent with continuing federal government plans for a total national research program involving the selection of particular fields for special financial support. Moreover, this freedom of the investigator does not relieve the university administration of making responsible and discriminating judgments in deciding which projects or types of research to approve. Administrative officers should consider the relationship of proposals to the development of long-range university interests.

Weak university administration is no more in the interest of the government than it is of the universities themselves. Nor is it desirable to develop grant-supported university programs so heavily specialized in a few fields that the universities fail to fulfill their traditional function of providing an environment for education and free inquiry in all fields of knowledge. But the administrations of universities, both in the way in which they get their funds and by the nature of their faculty appointments, are, to a much greater extent than business corporations, or some private foundations, limited in the freedom with which they can commit their resources. A large part of their money comes (from the states and private sources as well as from the federal research programs) for particular purposes which cannot be changed by administrative decisions. The general structure of expenditure is set by the appointment of professors on permanent tenure, whose independence is the basic guarantee of academic freedom.

A university can make a major contribution to the cause of fiscal responsibility by maintaining a business and accounting staff with both high professional standards and knowledge of the granting procedures of the various federal agencies. The touchstone of the university stewardship of government funds is the rule that federal grant money should be expended with the same prudence, economy, and probity that governs the expenditure of university funds from other sources. This rule works well only to the extent that the university has clear policies for the expenditure of large sums. Unfortunately, where federal research money now equals the entire university budget of a few years ago, adequate mechanisms for supervising its proper, productive use are sometimes lacking.

An able business staff can do much to relieve principal investigators of the detailed bookkeeping and financial reporting required by grants. It can also keep abreast of the latest interpretations of grant requirements by the various agencies. It can advise the investigator, when he draws up his proposal, as to the provisions in the grant that will ensue from the content of his application. It can serve as a watchdog to be sure that the investigator, unaware of the niceties of legal phraseology, does not give away some essential freedom of action to a government agency in the course of negotiation. It should educate the investigator in the legal responsibilities he assumes when his university accepts a grant. It can direct the investigator to the agency whose program is most relevant to the project proposed.

Even with punctilious attention to the fiscal side of the federal grants on his campus, the administrative officer has not exercised his full responsibility if he does not give some kind of

academic review to project proposals. He cannot, however, give direct orders to faculty members about the substance of their research, any more than a government agency can. The national panels are in a much better position than are administrative officers to rank proposals by scientific quality. The university has, of course, reviewed a professor's general capability as a scholar and teacher when it bestowed a tenure appointment on him. The academic review of project proposals addresses itself to the question whether a grant is consistent with the concept of the university as a community of scholars engaged in the education of youth and in public service, as well as in the advancement of knowledge.

We believe that all universities will do well to examine their mechanisms for the review of grant proposals, and that nearly all these mechanisms require drastic improvements. While specific measures to be taken depend upon previous accomplishments and local circumstances, we believe that some form of research board, representing both administration and research faculty, might be found widely useful. No university that does not now have a large program of federally supported research projects can realistically hope to gain one if it tries to manage its research grants by haphazard and outmoded policies.

Graduate Education and Basic Research

The 1960 report of the President's Science Advisory Committee, *Scientific Progress, the Universities, and the Federal Government,* examined carefully the connection between basic research and graduate education. We believe that this connection requires re-emphasis, because its relevance to the health of the project system is just as great today as it was in 1960.

Graduate education can be of highest quality only if it is conducted as a part of the research process itself. The research must not be in the form of mock problems; it must be a part of the exploration of the unknown, with all the uncertainties and challenges that go with it. By the same token, research can remain truly a quest, with freedom to follow unexpected lines, if the tentative conclusions of recent scientific research are tested in the interplay of advanced teaching.

Two trends are discernible which, if extended far enough, would lead to the impairment of the fruitful combination of research with graduate education. In some fields, basic research has moved into laboratories that have lost close touch with university teaching departments. Special conditions of geography or size sometimes dictate that a basic research facility be located away from a university center. Some of these facilities have done distinguished work in basic research. Nevertheless, we do not believe that the

pattern of the intellectually isolated research facility should be encouraged without compelling reason. We agree with the President's Science Advisory Committee Report in its call for invention of ways to bring about further interpenetration of these institutions with the universities.

The other trend that may impair the fruitful combination of research and graduate education stems from a lack of strong policy within the universities themselves. Administrations, under pressure to retain distinguished scientists who are tempted by the simplicities of life in non-teaching laboratories in government, research institute, or industry, find that the easiest counter-offer is a promise of reduction in teaching. Some scientists retire from virtually all contact with students, while others only a little less distinguished are so overloaded with teaching that they are forced out of research. Administrations, hoping to add to the prestige of their universities by encouraging large-scale research projects of high visibility, may expect faculty members to buy large amounts of released time from the university. If the administration then allows a professor buying released time to use grant money to run up his salary far above the regular university scale, the stage is set for teaching of all kinds—graduate and undergraduate—to become a "poor relation" to research in the university.

University administrations need courage to be far-sighted in maintaining a balance between teaching and research. They also need the active help of enlightened policies in the federal agencies, for these agencies affect both basic research and graduate education by their fellowships and grants. Research professorships and postdoctoral fellowships that specifically exclude teaching should be carefully weighed for possible schismatic effects on research and education in the universities.

Indirect Costs

One of the most serious fiscal problems to develop in the operation of the project system has grown up around the payment of indirect costs to universities. The roots of the overhead payment or indirect cost problem go all the way back to the OSRD. Because it conducted federally supported research, a university clearly incurred some expense that could not easily be separated from other institutional expenses. Thus, the difficulty of description in accounting terms is precisely what made indirect costs indirect. The no-gain-no-loss principle for research contracts indicated that the government should defray these costs, which, as the amount of federal support grew, became a real drain on the institution. Clearly, the vastly expanded research program owed some share to the universities for administration buildings, maintenance services, account-

ing systems, libraries, and dormitories, in a way that the finest distinctions of the accountant could never quite pinpoint. The realization gradually dawned that no absolute difference exists between direct and indirect costs, and, as accounting procedures have developed, some items, retirement benefits for instance, have moved from one category to another. As different agencies developed different patterns of reimbursement, comparability became ever harder to achieve.

The introduction of the grant instrument for the support of research initiated a different pattern for the reimbursement of indirect costs. Ideally, the grant makes only a partial contribution toward a purpose to which the grantee institution is already fully committed, and on which it is willing to spend some of its own funds. We believe that this principle is correct, and, as we noted earlier, the institution often does make a sizable investment of its own funds in the form of the investigator's salary. But indirect costs have become so large that the universities cannot easily assume these costs on every research project that a faculty member arranges. A generation ago, when outside funds provided only a few minor supplementary research expenses, an administrative officer could quite properly encourage every professor to seek funds from any possible source and in any amount that he could get. But when federal research expenditures reach many millions of dollars per year on a single campus, the administrative officer can no longer afford to take the old approach. The university must be maintained as a community of scholars dealing with all aspects of knowledge, and there are not enough unrestricted funds from non-federal sources to provide for that and also for the management of massive new programs.

The administrative officer with a large federal grant program is tempted to do several dangerous things if indirect costs are not adequately covered: (1) He may divert funds from work in other branches of knowledge. (2) He may divert funds from the teaching function of the university. (3) He may neglect the proper administration of federal funds. (4) He may divert federal funds to questionable uses. In partial recognition of these dangers, the government agencies that use grants have been allowed to pay a flat rate, a percentage of the direct costs of the grant. In recent years, the percentage paid by the National Institutes of Health and the National Science Foundation, for instance, has ranged from 15 per cent to 25 per cent. Since actual overhead on individual projects varies, and the costs at different institutions vary, the flat rate can easily produce individual instances of overpayment and underpayment.

The contract pattern of reimbursement, developed by the Department of Defense and adopted in Circular A-21 of the Bureau

of the Budget, is a negotiated rate based on an audit of the expenditures of the institution. Hence the administrative officer of the university, in general preferring the flexibility of the grant, looks wistfully at the contract when he thinks of indirect costs. Most universities have felt that on grants with a flat rate they have been undercompensated, and thus forced into cost-sharing for government-financed research, in a way not chosen by themselves and not advantageous to the over-all health of their institutions. A report to Harvard University comments, "Research can be carried on effectively in the long run only if a university maintains its overhead in an intellectual and academic, as well as an administrative, sense . . . . It is not a question of asking the government for more money, but rather, of asking it to give its funds with a proper regard for the total function of the university."

The indirect cost issue unfortunately has become a wedge not only between the government and the universities but also between investigators and administrators on university campuses. The investigator can see where direct costs go in his project, and he realizes that the national panel in his discipline has only a finite number of dollars to grant, so that, the more money paid into indirect costs by the government, the less remains available for research. All that goes to the university in indirect costs simply disappears, as far as the investigator is concerned. The administrative officer, on the other hand, concerned with institutional balance and with those parts of the university that would be deprived of funds from other sources if the federal projects drain off local funds, is likely to be quite as emphatic as the investigator, but in the other direction. We suggest that university administrations should make special efforts to explain their use of funds from indirect cost payments to their faculty members.

We believe that federal agencies should pay for indirect costs, on grants as well as contracts, at a rate substantially equivalent to audited costs. We also believe that an institution that accepts payments for indirect costs should accept the obligation for those institutional functions that, in fact, give support to the research activity, thus supporting the investigator and his department adequately.

Institutional and General Research Grants Tied to the Project System

Almost from the beginning of the project system, it became obvious that, while the independence of the universities was being reasonably preserved, the effects on the institutions that received the grants were great simply because the research was done there. Often these effects were of greater significance than the results of research,

which in a given case might not be decisive. The effects showed up where the institutions, with the help of project funds, were able to build up a "capability" for the future with the faculty personnel they had attracted and facilities they had established. The kind of grant that, as its main object, would build up an institution's capability has therefore seemed attractive to some universities during the last two decades. Yet institutional and general research grants have always entailed the judgment of scientific excellence on an institutional basis. The project system has brought satisfactory resolution of the problem of judging scientific quality. The advocates of institutional grants have always to meet the charge that they will depart from the highest standards of excellence, and hence waste the taxpayer's money. Yet every institution, no matter how many projects its faculty members attract, could increase its capability if it had free funds with which to supplement project grants.

The National Science Foundation and the National Institutes of Health have, in a modest way, recognized the need for supplementary grants somewhat similar to institutional grants. We believe that an extension of this type of grant is desirable and that, if the purpose is broadly enough defined, it would enable a university to support many types of activities that do not fit neatly into the project system. The fact that institutional grants of this type are awarded in direct proportion to the volume of project grants received by an institution means that the judgment of scientific quality supplied by the scientific community carries over indirectly to provide a standard of quality.

Development Grants to Alter
the Geographical Distribution of Federal Funds

Supplementary institutional grants do nothing to protect the project system from the charge that it makes the rich richer and the poor poorer. We consider it a most unfortunate effect of the application of the interrelated system that it historically has led to concentration of federal support funds at relatively few institutions. The country would be stronger and national purposes more nearly fulfilled if there were many more good investigators at many more institutions. If there were no place in the country from which an institution of higher learning of great distinction was inaccessible, the general welfare of every citizen would be vastly increased. As John Wesley Powell told the Congress nearly a century ago, "The learning of one man does not subtract from the learning of another, as if there were a limited quantity of unknown truth. Intellectual activity does not compete with other intellectual activity for exclusive possession of truth; scholarship breeds scholarship, wisdom breeds wisdom, discovery breeds discovery."

We are convinced, however, that a desirable pattern of distribution of research capability cannot be achieved by wholesale redistribution of the federal funds which the Congress, for important national purposes, has made available through the project system. To deprive investigators who have proved themselves worthy of support, in order that those who have not proved themselves may have a share of support, would mean a lowering of national capability in science. And even if large amounts of federal money were available for the purpose, support to institutions that do not have sound policies to foster research would be wasteful. The local university must provide academic freedom, proper salaries, and reasonable work loads before federal support, either in projects or institutional grants, will work in the direction of excellence.

Therefore, we believe that a program of development grants should be launched in support of research and graduate education in institutions with potentiality for becoming strong in the future. We recognize that the framing of criteria by which these grants should be awarded is not an easy task. We suggest that development grants should not be extensively used until principles and the criteria for such awards have been carefully studied by a competent special task force. Since controversial questions are at issue, the membership of this task force should be drawn primarily from two groups: scientists from leading academic institutions not eligible for such development grants, and lay citizens of broad national interests, representative of various geographical areas and of various economic interests. The criteria should be kept distinct from those used by the selection panels in the present project system. Judgment of quality by established standards of excellence gives the project system its present integrity, and the loss of those standards would not help emergent institutions at all, in the long run. Judgment of potentiality and the stimulation of excellence can succeed only if the development grant is awarded for its proper purpose.

The Permanent Interrelated System

When development grants have done their work and increased the number of strong universities in every region of the nation, they should be phased out to let the project system, modified by supplementary institutional grants, take over. Thus we are advocating here, as we have throughout this report, a strengthening of the partnership that has served the nation well for two decades. The achievements of the investigators who perform research will be greater if the institutions in which they work are stronger. If the government's ability to ensure fiscal responsibility is secure, its ability to assist both the investigator and his institution will be increased. The system will be stronger if not one but several agencies have

strong policies in support of basic research. And the system will be strengthened with the solution of other pressing problems which the Congress, the Executive, and the universities must meet forthrightly. The one feature of the partnership of the federal government and the institutions of higher learning that dominates the future, as well as the past, is the immense productivity in scientific discovery and the great strength that the presence of science brings to our national life. The federal government, the universities, and the scientific community still have far to go together.

Clearly the government and the universities have essential responsibilities—both separate and joint—for the success of the system. So, too, the scientific community has an essential role to play. That part of the total scientific community with which we are concerned in this report—the scientists in the institutions of higher learning—are a part of a larger society of scholars. As such, their responsibilities are multiple. They have obligations to advance scientific knowledge, but also for the education of youth. They must give conscientious and enlightened service on panels and other advisory bodies, and as individuals they must often give advice on the selection of research proposals. We urge that the members of the scientific community look upon this service as advancing science as significantly as if they had spent the same time in their laboratories. By defining the purpose of the grant or contract in his proposal, the scientist participates in the process that brings him support. When he accepts support funds, he accepts a trust to render conscientious effort to achieve the purpose of the grant or contract. He acquires no other rights to the funds. The responsibility of the scientist as a member of the scientific community works in the direction of harmony with the responsibilities of the government and the universities. To reduce the incidental mutual irritations of the system, the simple guidelines of this report have been put forward. We hope that they will help the partnership of the federal government, the universities, and the scientific community in the grand purpose of advancing the welfare of the nation, and with it the welfare of all mankind. ■