CONTENTS

Page

Ray G. Daggs Award Announced 111

Membership Status 112

Porter Predoctoral Fellowships 116

Travel Plans to the International Physiological Congress 117

Regulation and Control in Physiological Systems 118

APS Fall Meeting - Rochester, New York 119

1972 Fiscal Reports 120

1973 Divers' Gas Purity Symposium 122

Handbook of Physiology - Two New Volumes 123

APS Member Receives Passano Award 124

Three APS Members Receive Scientific Achievement Awards 125

Regulation of Splanchnic Blood Flow In Man
Loring B. Rowell 127

Cerebral Cortical Control of Movement
Hiroshi Asanuma 143

Muscle-Nerve Transplants ... Ethel Cosmos 167

The Physiology of Weightlessness
Symposium Proceedings, April 14, 1972 178

News from Senior Physiologists 234

2nd Workshop on Contractile Behaviour of the Heart 246

Mabel Purefoy FitzGerald 247

Subscribers to The Physiologist will note that a Supplement - "Audiovisual Aids Useful in the Teaching of Physiology" is included with this issue.

RAY G. DAGGS AWARD ANNOUNCED

President Dr. Robert Berne made the following announcement at the Business meeting of the Society at Atlantic City on April 17, 1973.

As you know Ray Daggs was a guiding force in the American Physiological Society from 1956 until his retirement in January of this year. Under his direction as Executive Secretary and Treasurer, the Society has grown in size, extended its activities and achieved considerable financial stability. Elected officers of the Society come and go. By the time they have acquired a minimum of knowledge about the running of the Society, their term of office expires. However, Ray Daggs has always been on hand to lead the officers down the right path. Ray has always been devoted to the Society and has placed its interests foremost. He is a direct individual who has the knack of getting to the heart of the matter quickly and succintly. Telegrams were sent to former Presidents of the Society who served with Ray Daggs, telling them of the Daggs Award. Most of these individuals were able to attend this meeting but unfortunately all could not. I received a telegram from Alan Burton which sort of sums up our feelings about Ray and I would like to read it to you.

"Regret I cannot be present. Please convey to Ray Daggs my very great admiration for his work for the Society and Physiology. I first knew him forty years ago when he was contributing by research in nutrition. Using his great sense of humor, integrity and reasonableness, Ray Daggs steered and successfully managed a succession of ignorant and opiniated Presidents like me. Congratulations on a well deserved and fitting tribute. May Ray and his wife enjoy many more years of rewarding work and play."

The Society will very much miss Ray and hope that he will honor us by visiting us at some of our future meetings.

As an expression of our appreciation on behalf of the American Physiological Society I present you with this scroll which establishes the Ray G. Daggs Award, an annual Award to be presented beginning next year to a physiologist who is judged to have provided distinguished service to the science of Physiology and to the American Physiological Society. Please accept this scroll with my congratulations.

MEMBERSHIP STATUS

April 1, 1973

Regular Members	3614
Retired Members	234
Honorary Members	15
Associate Members	420
	4283

SUSTAINING ASSOCIATES

Abbott Laboratories
Ayerst Laboratories
Burroughs Wellcome & Co., Inc.
CIBA-GEIGY Corp.
Eli Lilly & Co.
Gilson Medical Electronics
Grass Instrument Co.
Harvard Apparatus Co.
Hoechst Pharmaceutical Co.
Hoffman-LaRoche Laboratories
Lakeside Laboratories, Inc.
Merck Sharp & Dohme Research Laboratories
Narco Bio-Systems, Inc.
The Norwich Pharmacal Co.
Chas. Pfizer and Co.
A. H. Robins Co., Inc.
Smith Kline and French Laboratories
Warner-Lambert Research Institute
Waverly Press-Williams & Wilkins Co.
Wyeth Laboratories

DEATHS SINCE 1972 FALL MEETING

Thomas C. Barnes - 8/14/72 - Res. Associate, Philadelphia State Hosp.
Solomon A. Berson - 4/11/72 - Prof. Med., Mt. Sinai Sch. Med., N.Y.
Loren D. Carlson - 12/12/72 - Chrmn., Div. Sciences Basic to Med., Univ. California, Davis
Howard J. Curtis - 9/13/72 - Sr. Biologist, Brookhaven Natl. Lab.
Frederick L. Hisaw - 12/3/72 - Prof. Emeritus Biol., Harvard Med. School
John H. Grindley - 12/14/68 - Prof. Surgery, Mayo Fndn. & U. of Minn.
Louis N. Katz - 4/1/73 - Dir. Emeritus, CV Inst., Michael Reese Hosp.
Benjamin Kramer - 9/29/72 - Prof. Emeritus Pediatrics, Maimonides Hosp. of Brooklyn
Bernard Leboeuf - 10/30/72 - Assoc. Prof. Med., Univ. of Montreal
Edward Lodholz - 12/6/72 - Prof. Emeritus Physiol., Grad. Sch. Med., Univ. of Pennsylvania
Wade H. Marshall - 11/14/72 - Retired Chief Neurophysiol., Natl. Inst. Mental Health
Russell W. Morse - 2/25/73 - Dir., Neurobehavioral Science, Med. College of Georgia
Louis H. Nahum - 7/25/72 - Lecturer Emeritus, Yale University
Charles G. Neumann - 10/19/72 - Assoc. Prof. Clin. Surg., N.Y. Univ.
David W. Northup - 3/13/73 - Prof. Emeritus Physiol. & Biophys., West Virginia Univ.
Wiktor W. Nowinski - 12/28/72 - Res. Prof. Biochem., Texas Univ. Med. Sch., Galveston
Dickinson W. Richards - 2/23/73 - Prof. Emeritus Med., Columbia Univ.

Charles D. Snyder - 3/21/73 - Prof. Emeritus Exptl. Physiol., Johns Hopkins Univ.
S. Smith Stevens - 1/18/73 - Prof. Psychophysics, Harvard Univ.
Price E. Thomas - 9/2/72 - Prof. Physiol., Kirksville College of Osteopathic Med.
Claude V. Winder - 8/10/72 - Asst. Dir. Pharmacological Res., Parke Davis & Co., Ann Arbor, Mich.
M. X. Zarrow - 1/23/73 - Prof. Behavioral Science & Biology, Univ. of Connecticut

50-YEAR MEMBERS

Edward F. Adolph
Walter C. Alvarez
Joseph C. Aub
J. Percy Baumberger
Olaf Bergeim
Charles H. Best
George H. Bishop
Harold C. Bradley
McKeen Cattell
George R. Cowgill
Lester M. Dragstedt
Dayton J. Edwards
Mable P. FitzGerald
Carl H. Greene
Frederick R. Griffith, Jr.
Charles M. Gruber
Harold L. Higgins
Paul E. Howe
Andrew C. Ivy
Dennis E. Jackson
Norman M. Keith
Nathaniel Kleitman
Henry Laurens
Chauncey D. Leake
David Marine
Jesse F. McClendon
Walter R. Miles
Frederick R. Miller
Clarence A. Mills
Ann S. Minot
Stuart Mudd
Leonard B. Nice
David Rapport
Alfred C. Redfield
Andrew H. Ryan
Norman B. Taylor
Joseph T. Wearn
George H. Whipple
Harvey L. White
Rosalind Wulzen

NEWLY ELECTED MEMBERS

The following, nominated by Council, were elected to membership in the Society at the Spring Meeting, 1973.

REGULAR MEMBERS

ALEXANDER, Edward A.: Asst. Prof. Med., Boston Univ. Sch. Med.
BAHLER, Robert C.: Asst. Prof. Med., Case Western Reserve Univ.
BAILIE, Michael D.: Asst. Prof. Dept. Human Development, Michigan State Univ.
BARRETT, Terence W.: Asst. Prof. Physiol. & Biophys., Univ. of Tennessee
BEEUWKES, Reinier III: Asst. Prof. Physiol., Harvard Med. Sch.
BELL, Curtis C.: Asst. Prof. Neurol., Univ. of Oregon Med. Sch.
BERNSTEIN, Marvin H.: Asst. Prof., Dept. Zool., Duke Univ.
BINDER, Henry J.: Assoc. Prof. Internal Med., Yale Univ.
BLOOMQUIST, Eunice I.: Asst. Prof. Physiol., Tufts Univ. Sch. Med.
BUCKLEY, Ramon D.: Asst. Prof. Biochem., Univ. Southern Calif.

BUERGER, Alfred A.: Asst. Prof. Physical Med. & Rehab., Univ. of California, Irvine
CASTANEDA, Aldo R.: Prof. Surg., Univ. of Minnesota Med. Ctr.
CHANG, Chin-Chuan: Staff Scientist, The Rockefeller Univ.
COELHO, Jaime B.: Res. Assoc., Dept. Med., Columbia Univ.
COTHRAN, LaVal N.: Asst. Prof. Surg., Howard Univ. Coll. Med.
DHINDSA, Dharam S.: Res. Assoc., Dept. Med., Univ. of Oregon
DiCARA, Leo V.: Prof. Psychiatry & Psychology, Univ. of Michigan
DORN, Janice B.: Asst. Prof. Physiol., Univ. of Missouri Sch. Med.
DOUSA, Thomas P.: Consultant, Physiol. & Biophys., Mayo Clinic
DUNN, Jon D.: Asst. Prof. Anat., Louisiana State Univ. Med. Ctr.
ETTINGER, Philip O.: Cl. Asst. Prof. Med., Med. Coll. New Jersey
FABIATO, Alexandre: Asst. Prof. Med., Harvard Med. Sch.
FISHER, H. Kenneth: Asst. Prof. Med., Univ. of Washington
FORSTNER, Gordon G.: Asst. Prof. Physiol., Univ. of Toronto
FRIZZELL, Raymond A.: Asst. Prof. Physiol., Univ. of Pittsburgh
GAREY, Walter F.: Asst. Res. Physiol., Scripps Inst. Oceanography
GARNER, Harold E.: Prof. Vet. Med. & Surg., Univ. of Missouri - Columbia
GILLARY, Howard L.: Asst. Prof. Physiol., Univ. of Hawaii
GREGA, George J.: Asst. Prof. Physiol., Michigan State Univ.
HAKIM, Anwar A.: Res. Assoc., Univ. of Illinois Med. Ctr.
HAMMER, Charles E., Jr.: Assoc. Prof. OB-GYN, Univ. of Virginia
HAWKINS, Richard A.: Staff Res. Fellow, St. Elizabeth's Hosp., Washington, D.C.
HOFFMAN, Lee: Asst. Prof. Med., Albert Einstein Coll. Med.
HOLLOWAY, James A.: Asst. Prof. Physiol. & Biophys., Howard Univ.
HOTCHKISS, Julane: Adjunct Asst. Prof. Physiol., Univ. of Pittsburgh
HUNTER-KRAFT, Frances: Asst. Prof. Physiol., Howard Univ.
JONES, LeeRoy G.: Science Technical Dir., US Army Res. Inst. Environ. Med.
KENT, Kenneth M.: Sr. Invest., Natl. Heart & Lung Inst., NIH
KUMADA, Manoru: Asst. Prof. Biomed. Engr., Johns Hopkins Sch. Med.
LaFARGE, C. Grant: Asst. Prof. Pediatrics, Harvard Med. Sch.
LERNER, Robert G.: Asst. Prof. Med. & Pathol., New York Med. Coll.
LEVISON, Henry: Assoc. Prof. Pediatrics, Univ. of Toronto
LINDHEIMER, Marshall D.: Assoc. Prof. Med. & OB-GYN, Univ. of Chicago
LYNNE-DAVIES, Patricia: Assoc. Prof. Med., Univ. of Alberta
McCROREY, Henry L.: Assoc. Prof. Physiol., Univ. of Vermont
MacINTYRE, William J.: Prof. Biophys., Case Western Reserve Univ.
MAGLEBY, Karl L.: Asst. Prof. Physiol. & Biophys., Univ. of Miami
MENKES, Harold A.: Asst. Prof. Med. & Environ. Med., Johns Hopkins
MILLER, Josef M.: Asst. Prof. Otolaryngology, Univ. of Washington
MUGGENBURG, Bruce A.: Physiologist, Dept. Vet. Med., Lovelace Fndn. for Med. Education & Research
NEWHOUSE, Michael T.: Asst. Prof. Med., McMaster Univ.
NOORDERGRAAF, Abraham: Prof. Biomed. Engr., Univ. of Pennsylvania
PERLMAN, Robert L.: Assoc. Prof. Physiol., Harvard Med. Sch.
PHILBIN, Daniel M.: Asst. Prof. Anesthesia, Harvard Med. Sch.
POLOSA, Canio: Assoc. Prof. Physiol., McGill Univ.
PRUSCH, Robert D.: Asst. Prof. Div. Biol. & Med., Brown Univ.
RANKIN, John H.G.: Asst. Prof. Physiol., Univ. of Wisconsin Med. Sch.

RANNEY, Helen M.: Prof. of Med., State Univ. N.Y., Buffalo
RATNER, Albert: Assoc. Prof. Physiol., Univ. of New Mexico
REEDER, David D.: Asst. Prof. Surg., Univ. of Texas, Galveston
REICH, Theobald: Assoc. Prof. Clin. Surg., New York Univ. Med. Ctr.
RICHMOND, Jonas E.: Biochemist, Univ. of California, Berkeley
RITCHIE, Brenda: Assoc. Prof. Biol., Quinnipiac College
ROSE, Richard C.: Asst. Prof. Physiol., Milton S. Hershey Med. Ctr.
ROVETTO, Michael J.: Res. Assoc. Physiol., Pennsylvania State Univ., Hershey
SALLEE, Verney L.: Asst. Prof. Physiol., Univ. of Texas, S.W.
SCOBEY, Robert P.: Asst. Prof. Behav. Biol., Univ. Calif., Davis
SEELY, John F.: Asst. Prof. Med., McGill Univ.
SHANBOUR, Linda L.: Assoc. Prof. Physiol., Univ. Texas, Houston
SHANNON, Roger: Asst. Prof. Physiol., Univ. of New Mexico
SONG, Seh-Hoon: Instr., Dept. Biophysics, Univ. of Western Ontario
SOULE, Roger G.: Assoc. Prof. Health Dynamics, Boston Univ.
SPEAR, Joseph F.: Asst. Prof. Animal Biol., Univ. of Pennsylvania
STILES, Robert N.: Asst. Prof. Physiol. & Biophys., Univ. Tennessee
STRONG, Cameron G.: Asst. Prof. Med., Mayo Clinic
SYBERS, Harley D.: Asst. Prof. & Asst. Res. Pathol., Univ. of California, San Diego
WALKER, Franklin D.: Asst. Prof. Psychiatry, Indiana Univ.
WALL, Betty J.: Res. Assoc., Dept. Biol. Sciences, Northwestern Univ.
WEISS, Gerald K.: Asst. Prof. Physiol., Univ. of New Mexico
WILEY, Ronald L.: Assoc. Prof. Zool., Miami Univ., Oxford, Ohio
YING, Shao-Yao: Instr., Dept. Anat., Harvard Med. Sch.

ASSCCIATE MEMBERS

ALBERT, Thomas F.: Asst. Prof. Vet. Science, Univ. of Maryland
BANASZAK, Edward F.: Asst. Prof. Physiol. & Med., St. Luke's Hosp., Milwaukee
CHAUDRY, Irshad H.: Instr., Dept. Surg., Washington Univ. Med. Sch., St. Louis
COLTON, Joel S.: Postdoct. Fellow, Inst. of Psychiatric Res., Indiana Univ. Med. Ctr.
DIXON, Earl Jr.: Teacher of Physiol., Tuskegee Inst.
DOUGLAS, Everett L.: Asst. Prof. Biol., Univ. of Missouri, Columbia
DREES, John A.: Asst. Prof. Physiol. & Biophys., Temple Univ.
DUBROVSKY, Bernardo O.: Asst. Prof. Psychiatry, McGill Univ.
FERGUSON, John H.: Asst. Prof. Neurol., Case Western Reserve
FOREMAN, Robert D.: Grad. Student, Physiol., Stritch Sch. Med., Loyola Univ.
GORSKI, Marianne E.: Grad. Student, Physiol., Stritch Sch. Med., Loyola Univ.
GRUBBS, Clinton J.: Grad Student, Physiol. & Biophys., Univ. of Tennessee Med. Units
KHAN, Qamar A.: Asst. Prof. Physiol., Meharry Med. College
LIPPINCOTT, David B.: Grad. Student, Physiol., Stritch Sch. Med., Loyola Univ.
LEWIS, Lon D.: NIH Spec. Res. Fellow, Physiol. & Biophys., Colorado State Univ.

MALIK, Asrar B.: Instr. Physiol., Jewish Hosp. of St. Louis
MANN, Michael D.: Senior Fellow, Dept. Physiol. & Biophys., Univ. of Washington
MAUDERLY, Joe L.: Vet. Physiologist, Dept. Radiobiol., Lovelace Fndn. for Med. Education & Res.
MOHRMAN, David E.: Res. Assoc., Dept. Physiol., Univ. Michigan
MYERS, Joseph B.: Asst. Prof. Biol., Atlanta Univ.
PICKRELL, John A.: Physiologist-Biochemist, Lovelace Fndn.
ROSENBERG, Alberto: Res. Assoc., GI Lab., VA Ctr., Los Angeles
SCOTT, Mack T.: Prof. Physiol., Meharry Med. College
SPRAY, David C.: Ph.D. Candidate, Physiol., Univ. of Florida, Gainesville
TACKER, Willis A., Jr.: Instr. Physiol., Baylor Coll. Med.
WEATHERS, Wesley W.: Asst. Prof. Environ. Physiol., Rutgers, The State Univ.
WEBBER, Charles L., Jr.: Grad. Student, Physiol., Stritch Sch. Med., Loyola Univ.
WINET, Howard: Res. Fellow, Div. of Engineering, Cal. Tech.
YIPINTSOI, Tada: Assoc. Consultant, Dept. Physiol., Mayo Clinic

****

PORTER PREDOCTORAL FELLOWSHIPS

The Porter Development Committee of the American Physiological Society announces that predoctoral fellowships for the current year have been awarded to the following students for graduate studies at the institutions indicated:

Lura D. Altheimer, Department of Physiology, Emory University

Jean L. Flagg, Department of Physiology, Harvard Medical School

Cordell S. Fray, Department of Physiology, Harvard Medical School

Pamela J. Gunter, Department of Physiology, Emory University

Lorraine M. Miller, Neuro- and Behavioral Sciences Ph.D. Program, Stanford University

Nathaniel G. Pitts, Department of Animal Physiology, University of California, Davis

Shirley D. Sharrock, Department of Physiology, University of Florida

These fellowships are supported by a grant from the Harvard Apparatus Foundation to the American Physiological Society. For further information please write to Dr. Edward W. Hawthorne, Co-Chairman, Porter Development Committee, Department of Physiology, Howard University College of Medicine, Washington, D. C. 20001.

TRAVEL PLANS TO THE INTERNATIONAL PHYSIOLOGICAL CONGRESS NEW DELHI, INDIA - OCTOBER 20-26, 1974

The following flight and tour plans are proposed for the Congress. We would appreciate your cooperation in completing the enclosed form and returning it to Chevy Chase Travel, our official travel agent, in order to determine the interest in the various options. The final travel plans will then be announced.

1. 14 DAY EXCURSION

Oct. 18 - New York/Delhi
Nov. 2 - Bombay/New York
Round trip air fare per person - $475.00

This will allow time to attend Satellite Meetings which will be held in various cities within India. If you do not wish to return with the group on Nov. 2, you can return individually within 120 days.

2. 21 DAYS (Based on the GIT fare of 20 persons travelling together)

a. Oct. 14 - New York/London
Oct. 18 - London/Delhi
Oct. 30 - Delhi/Athens — Air fare per person - $617.00
Nov. 4 - Athens/New York

b. Oct. 18 - New York/Delhi
Nov. 3 - Bombay/London — Air fare per person - $617.00
Nov. 8 - London/New York

On these tours, land arrangements in London and Athens will be included.

3. AROUND THE WORLD

30 Days - Depart from home town to New York. Visit Athens, Istanbul, Bombay, Delhi (for the Congress), Kathmandu, Bangkok (for Symposium), Hong Kong, Tokyo, Honolulu, to West Coast and continue to home town.

Air fare per person (based on 15 persons travelling together) - $1507.00

A complete land tour (for each country visited) will be arranged in connection with this departure.

4. PAN-CONTINENTAL CHARTER FLIGHT (Using regular scheduled carriers, 707 equipment for approximately 170 passengers)

Approximately 30 Days - West Coast/Hawaii/Tokyo/Sydney/Delhi/Johannesburg/Rio/Miami

A three or four day stop will be included in each city (one week in Delhi) during which time Symposia will be arranged with the local Physiological Societies. Price to be announced later.

PLEASE NOTE: The individual, regular all year fare - New York/Delhi round trip is $1398.00 per person.

The American Physiological Society
and
The American Automatic Control Council
invite your attention
to the following International Symposium

REGULATION AND CONTROL IN PHYSIOLOGICAL SYSTEMS
August 22-24, 1973
University of Rochester, N. Y.
(In conjunction with the APS Fall Meeting)

Commentary and discussion of 21 sessions will be led by outstanding practitioners:

TOPIC - COMMENTATOR

Biochemical regulation
J. Higgins (U. Pa.)
Pharmacokinetics
W. Jusko (Millard Filmore)
Membrane transport
K. Kornacker (Ohio State U.)
Microvascular dynamics
M. Intaglietta (U. C., La Jolla)
Growth, Nutrition
R. Suddith (U. Colo.) and F. Yates (USC)
Visual Processing
J. Lettvin (MIT)
Auditory, Vestibular
R. Llinas (Iowa U.)
Muscle control systems
D. McRuer (Syst. Tech.)
Respiratory system, aspects
G. Longobardo (IBM)
Overall respiratory regulation
F. Grodins (USC)
Aspects of heart regulation
M. Levy (Mt. Sinai, Cleveland)
Aspects of CV regulation
K. Sagawa (Johns Hopkins)
Local CV regulation
R. Cox (U. Pa.)
Kidney regulation
D. March (USC)
Water system
H. Weed (Ohio State U.)
Glucose metabolism
D. Gann (Johns Hopkins)
Endocrinology, metabolism
E. Stear (UCLA)
Neurons, neuron populations
M. Cohen (Einstein, N. Y.)
Single units, CNS complexes
G. Moore (USC)
Nervous system, behavior
S. Grossberg (MIT)
Thermoregulation
L. Senay (St. Louis U.)

Overall commentary and discussion will be led by:

A. Guyton, A. Iberall, J. DiStefano, J. Urquhart, W. Topham

For Information, write to General Chairman:

General Cochairmen	Program Cochairmen
E. Adolph, Univ. of Rochester	A. Guyton, U. of Mississippi
G. Cohen, Univ. of Rochester	A. Iberall, General Tech.

APS FALL MEETING - ROCHESTER, NEW YORK

AUGUST 20-24, 1973

The 24th annual "Fall" meeting of the APS will be held jointly with the International Symposium on Dynamics and Controls in Physiological Systems on August 20-24th at the University of Rochester.

The refresher course, which is scheduled for Monday, August 20th, is being organized by Dr. Bodil Schmidt-Nielsen on the subject "Physiological Adaptations to the Environment." This program will be divided in three parts: Altitude and Air Pollution, Osmoregulation, and Temperature Regulation.

On Tuesday there will be two symposia. In the morning Dr. Leon Farhi will chair a session devoted to "Diffusion of Gases in the Gas Phase of the Alveoli." In the afternoon the topic will be "Molecular Mechanisms of the Sodium-Potassium Pump" and is being planned by Dr. Joseph Hoffman.

The Dynamics and Control Symposium will begin on Wednesday and continue through Friday. This symposium was previously scheduled to take place in Rochester the week before the APS meeting which had been planned for Montreal. Now that the APS meeting has been moved to Rochester, it was decided to have a single registration in order to encourage interchange between engineers and physiologists. This symposium has the joint sponsorship of the International Federation of Automatic Control, American Society of Mechanical Engineers, APS, and International Union of Physiological Sciences. Drs. Gerald H. Cohen and Edward F. Adolph are general chairmen. Papers will be presented in several concurrent sessions. A major purpose of the symposium is to focus the attention of engineers and physiologists on topics of common interest. A preprint of the symposium will be available at the time of the meeting. Those who purchase this volume will receive an addendum containing the discussion at a later date.

At the Federation meetings in the Spring the APS has often organized a symposium on some aspect of the teaching of physiology. Speakers at such sessions have been invited. At this year's Annual Fall meeting a similar session has been organized on teaching, but composed of papers which are volunteered. Members have been invited to submit an abstract of their planned ten minute presentation. The subject matter might relate to equipment, description of a demonstration, a new approach to a subject, or methods to evaluate the effectiveness of teaching. The only restriction is that the subject is related to the teaching of physiology. Contribution of an abstract to the Teaching Session does not disqualify a member from submitting an abstract for the scientific sessions.

The traditional scientific sessions with ten minute presentations will begin on Tuesday August 20th and end at noon on Friday.

1972 FISCAL REPORTS

The bylaws of the Society (Article VII) identify the three principal funds which are used for the fiscal management of the Society's affairs. The behavior of these funds during the year 1972 are summarized below.

SOCIETY OPERATING FUND

This fund is used for direct services to members through arrangement of meetings, programs, etc.; the expenses and activities of Council and its committees (other than publications); the generation and distribution of educational materials; and the supervision of the business affairs of the Society.

INCOME

Membership Dues	$80,641	(68%)
Sustaining Associates Contributions	5,125	(4%)
Reimbursement for Services rendered in connection with the Fed. Spring meeting	17,981	(15%)
Interest (on advance monies received)	7,859	(7%)
Fall Meeting (net)	791	(1%)
Other Income (sale of educational and other material, etc.)	5,577	(5%)
Total Income	$117,974	

EXPENSES

Salaries and Benefits	$52,722	(32%)
Dues to Fed. and other Organizations	21,719	(13%)
Office Rental (Paid to Fed.)	4,660	(3%)
Travel and Subsistence for Officers and Committees (other than publications)	9,194	(6%)
Education Committee and Office	38,950	(24%)
Cost of Member Physiologist Subscr.	20,611	(12%)
Bowditch Lecture	500	-
Mail, Telephone, Supplies & Misc.	4,143	(2%)
Business Office Expenses (11%)	13,127	(8%)
Total Expenses	$165,626	

Excess of Expenses over Income (deficit)	($ 47,652)
Subsidy for Education and Physiologist 1/72 from Savings	42,140
Actual Deficit	($5,512)

PUBLICATIONS OPERATING FUND

This fund represents the functions of the Society as a publisher of scientific journals.

INCOME

Subscriptions	$659,040	(73%)
Sale of Reprints (net)	51,306	(6%)
Sale of Back and Single Issues	14,000	(2%)
Page Charges	123,230	(14%)
Advertising (net)	14,198	(2%)
Interest (on advance subscriptions, etc.)	20,115	(2%)
Royalties	9,201	(1%)
Miscellaneous	4,808	-
Total Income	$895,898	

EXPENSES

Printing and Engraving	$473,605	(54%)
Salaries and Benefits	169,401	(19%)
Mail, Telephone, Supplies, Etc.	60,085	(7%)
Office Rental (Paid to Fed.)	13,806	(1%)
Section Editor Expenses & Professional Services	63,057	(7%)
Travel & Subsistence for Officers, Committee, and Editors	12,464	(1%)
Miscellaneous	766	-
Business Office Expenses (89%)	87,846	(11%)
Total Expenses	$881,030	
Allocated to Publications Special Fund	(8,405)	
Adjusted Total	$872,625	
Net Income	$23,273	

PUBLICATIONS CONTINGENCY AND RESERVE FUND

This is a reserve fund which the Society has accumulated over many years. Its existence is dictated by prudent business practice, in case of any severe reversals etc. the journals can continue to be published for at least one year following such reversals. The Society has very few tangible, salable assets that could be used as collateral for borrowing money. The fund's size should be from one to two times the annual operating costs of the publication operations, including the Handbooks. It is held in long term investments managed by an investment counselor. Its uses are carefully spelled out in Article VII, Section 3 of the Society Bylaws.

Balance Dec. 31, 1971 (market value)	$1,211,521
Dividend and Interest paid to APS in 1972	47,022
Balance Dec. 31, 1972 (market value)	1,358,307
Gain in market value during 1972	146,786

1973 DIVERS' GAS PURITY SYMPOSIUM

The 1973 Divers' Gas Purity Symposium will be held at Battelle-Columbus on November 27 and 28, 1973, sponsored by U.S. Navy Supervisor of Diving.

The call for papers seeks answers to the following questions:

1. What are the limits of human tolerance to various forms of hyperbaric-gas contamination?
2. How can sources of contamination be found and identified?
3. How can gas systems be built clean and kept clean?
4. How may better equipment and/or procedures contribute to gas purity?
5. How may units of measurement be clarified and improved?
6. What are some legal aspects of divers' breathing gas contamination?
7. What new areas of research should be explored?

The interdisciplinary Symposium group will include representatives of the medical, engineering, diving, manufacturing, and legal professions. As attendance at the Symposium will be limited to 120 people, by invitation only, presentation of a paper will assure participation of those who wish to attend.

About 15 to 20 papers will be used. Those that are used will be bound and distributed before the Symposium and commentary will be solicited from registrants. Commentary will be forwarded to the authors so that each may be aware of his audience's specific interest in his paper and can concentrate his presentation on those areas in which the group's interest lies. In this way, they hope to avoid authors reading their papers to the audience, and achieve meaningful exchange of information between authors and audience.

For further information please contact:

Peter S. Riegel
Program Coordinator
1973 Divers' Gas Purity Symposium
Battelle-Columbus Laboratories
505 King Avenue
Columbus, Ohio 43201

HANDBOOK OF PHYSIOLOGY: TWO NEW VOLUMES

The staff of the Handbook Editorial Office is working on page proof for two new volumes of the Handbook of Physiology: the second volume in the section on endocrinology and a new section on renal physiology.

The central theme of the two separate books that make up the volume entitled Female Reproductive System is the absence of a steady state in the female reproductive system. The underlying morphological and biochemical processes that manifest the events producing a reproductive cycle, and the neural and endocrine mechanism that generate the cyclicity form the base upon which the volume is built. The fifty chapters in the volume include eight on the central nervous system-pituitary-ovarian interrelationship, three on the effect of hormones on sexual behavior, eighteen on the ovary, nine on the female reproductive tract, nine on pregnancy, one on immunoendocrinology, and two on fertility control. (One of the chapters on fertility control has been translated into French and will be distributed by The Population Council to medical and paramedical family planning workers, demographers, and others in developing countries.)

Roy O. Greep, who is serving with Edwin B. Astwood as editor of the section on endocrinology, also served as volume editor. He has assembled chapters written by a diverse group of authors. This volume is truly an example of physiology in the broadest sense and we expect that the volume will be useful to all involved in the study of reproductive biology. It is scheduled for publication in the summer of 1973.

The second volume for which page proof is being received is entitled Renal Physiology. This single volume of more than 1000 pages constitutes a new section of the Handbook, edited by Jack Orloff and Robert W. Berliner. Publication is scheduled for the fall of 1973.

The volume encompasses what is known of renal physiology today. It begins with more than 100 pages and 85 electronmicrographs on the ultrastructure of the kidney, providing a basis for that which follows regarding transport across membranes and through intercellular channels The discussion of the numerous investigative techniques that are a cornerstone of research in the field, begins with an assessment of clearance methods in intact animals and continues with analysis of the techniques of stop-flow, micropuncture, and the in vitro perfusion of isolated tubule segments. Acidification and ammonia excretion are presented in depth, as are discrete tubular transport processes and electrophysiology. Glomerular-tubular balance, the role of aldosterone in electrolyte transport, of antidiuretic hormone on water movement, and current views on blood flow and filtration, are covered in detail by those responsible for the major developments in these spheres. Comparative physiology is discussed. The renin-angiotensin system, the physiology of diuretic agents, and even the conduit system out of the kidney proper are treated. Renal metabolism has also been covered in detail.

Members of the Society will recognize the authors of the chapters in the section on renal physiology and in the volume on the female reproductive system, as the distinguished physiologists from this country and abroad, who have contributed so much to that which is described in the volumes.

Order forms for these volumes will be sent to members later this year. Remember that volumes of the Handbook of Physiology are offered to members of the Society at a sizable reduction in price, if they are ordered directly from the APS business office in Bethesda.

****

APS MEMBER RECEIVES PASSANO AWARD

Dr. Roger W. Sperry, biologist at the California Institute of Technology, is the recipient of the $10,000 Passano Award for 1973, one of the highest awards in American medicine.

The award was made to Dr. Sperry on the basis of his studies demonstrating that the functions of surgically disconnected hemispheres of brains in animals, as well as human beings, can co-exist as two distinct minds in mutual ignorance of each other within one skull. His research has led to a better understanding of the mind/brain relation and the neurological basis of human behavior.

Dr. Sperry received his award on April 19 at a dinner held during the week of the annual meeting of the Federation of American Societies for Experimental Biology in Atlantic City.

THREE APS MEMBERS RECEIVE SCIENTIFIC ACHIEVEMENT AWARDS

Dr. John A. Clements, Dr. James O. Davis, and Dr. Robert D. Dripps, were among 10 medical educators and researchers who have received 1973 Awards for Distinguished Achievement from Modern Medicine, a leading national medical journal.

More than 200 men and women were nominated for the prestigious Awards, which originated in 1934. Nominations come from U.S. Medical school officials, leaders of medical organizations, physician-readers of Modern Medicine, and members of the journal's worldwide editorial faculty.

Dr. John A. Clements, professor of pediatrics, University of California Cardiovascular Research Institute, San Francisco, was cited "for pioneering work indicating the presence and function of lung surfactants."

A Career Investigator of the American Heart Association, he was born in 1923 in Auburn, New York. He received his M.D. degree at Cornell University in 1947, served as a research assistant in physiology at Cornell for two years, and began investigative work on the lung in 1949 at the Army Chemical Center, Edgewood, Maryland.

According to Modern Medicine, Dr. Clements' work "led to a basic understanding of the mechanical operation of (the lung) in both normal and abnormal states. The knowledge accumulated through two decades of research now offers methods of relief for children who are afflicted with the respiratory distress syndrome."

Before his appointment at the University of California in 1961, Dr. Clements served at Roswell Park Memorial Institute as principal cancer research scientist, and at Johns Hopkins University and Hospital in the anesthesiology department. He is a frequent guest lecturer, a consultant to governmental health agencies, and a member of editorial boards of several scientific journals.

Dr. James O. Davis, professor and chairman, department of physiology, University of Missouri, was cited "for proof of the involvement of the kidney in the production of aldosterone."

Dr. Davis, who is chairman of the National Council for High Blood Pressure Research, American Heart Association, was born in 1916 in Tahlequah, Oklahoma. He received a B.S. degree in 1937 at Northeast Oklahoma State College, an M.A. degree in 1939 and a Ph.D. in zoology in 1942 at the University of Missouri, and his M.D. degree in 1945 at Washington University.

According to Modern Medicine, a program on experimental heart failure Dr. Davis set up in the late '40's at the National Heart Institute "was the beginning of his long series of studies in this area of cardiovascular research." From 1957-1966, when he took his present post, he was chief of the Institute's section on experimental cardiovascular disease, and during the last five years was visiting professor of physiology at Johns Hopkins University, University of Virginia and Temple University.

In his current research, Dr. Davis has shifted more to the field of hypertension. In addition to his post with the American Heart Association, he is a member of the Endocrine Society.

Dr. Robert D. Dripps, vice president for health affairs at the University of Pennsylvania was cited "for many years of important work in the science of anesthesiology."

At Princeton he majored in chemistry, and in 1936 he received his M.D. degree from the University of Pennsylvania. Dr. I. S. Ravdin showed him the "attractions and needs" of anesthesiology and Dr. Carl F. Schmidt obtained for him a Commonwealth Fund fellowship for training in anesthesiology with Dr. Ralph M. Waters at the University of Wisconsin. In 1942 he returned as physician anesthetist to the Hospital of the University of Pennsylvania.

His research includes the first work on the safety of spinal anesthesia as far as neurologic complications are concerned and circulatory effects of many other anesthetic agents.

"Introduction to Anesthesia" written with Drs. James E. Eckenhoff and Leroy D. Vandam has been voted the best text on the subject by teachers of anesthesiology.

Dr. Dripps was professor of anesthesia and chairman of the department at the University of Pennsylvania from 1949 to 1972 and director of anesthesia of the Hospital of the University of Pennsylvania from 1943 to 1972.

REGULATION OF SPLANCHNIC BLOOD FLOW IN MAN*

LORING B. ROWELL
Dept. of Physiology and Biophysics
University of Washington School of Medicine
Seattle, Washington

During rest, blood flow to the splanchnic organs (stomach, spleen, pancreas, large and small intestines and liver) exceeds that to any other region. Total splanchnic blood flow (SBF) averages 1.5 liters/min or about 25% of resting cardiac output in an average size man. The region extracts only 15-20% of the O_2 it receives. Thus, SBF can be markedly reduced without sacrifice of adequate local O_2 supply (29, 45).

The splanchnic region vasoconstricts when man's cardiovascular system is challenged by a variety of stresses. This response is important in blood pressure regulation and in the redistribution of cardiac output during exercise, heat stress, and in disease-induced states of low cardiac output. In this discussion, major findings from a number of experiments on normal young men and some selected cardiac patients are summarized. In each case clues pertaining to the causes of splanchnic vasoconstriction are discussed. All findings are fitted into one general scheme which reveals a common and predictable pattern of reflex splanchnic vasomotor response to a variety of stresses.

I. Splanchnic Vascular Response to Exercise

Figure 1 summarizes the response of SBF to graded exercise in three groups of individuals with very low, normal and very high values of maximal oxygen uptake ($\dot{V}_{O_2}$ max) (3, 29, 38). These are patients with "pure" mitral stenosis (3) (no congestion or cardiac failure), sedentary young men and endurance athletes ($\dot{V}_{O_2}$ max = 25, 45, and 65 ml/kg min, respectively). $\dot{V}_{O_2}$ max is an index of cardiovascular capacity for O_2 delivery (maximal blood flow and tissue O_2 extraction) (2). Two major points are: a) SBF is reduced in proportion to the severity of exercise expressed as $\dot{V}_{O_2}$ per kg body weight (7, 14, 29, 30, 38, 46). b) The extent to which SBF is reduced at any given $\dot{V}_{O_2}$ depends upon the individual's $\dot{V}_{O_2}$ max per kg body weight (3, 29). Scaling SBF with respect to the per cent of $\dot{V}_{O_2}$ max required shows the underlying similarities between individuals. Thus, somehow SBF during exercise is regulated in proportion to the individual's circulatory capacity for O_2 delivery. Grimby (10) observed a similar relationship between renal blood flow and $\dot{V}_{O_2}$ max.

A.) Significance of Splanchnic Vasoconstriction

At or near V_{O_2} max, SBF is reduced by almost 80% (29, 45); this reduction redistributes 250-300 ml/min of O_2 to working muscle.

---

* Taken from the introductory remarks given at the session on Peripheral Circulation I at the 1973 Federation Meetings.

Together with the kidneys, non-working muscle (4, 45, 52) and skin (8, 45, 52) which also vasoconstrict, a total of about 600 ml of O_2 can be redistributed each minute. This reduction has the greatest significance in those with low $\dot{V}_{O_2}$ max. For example, in the three groups shown in Figure 1 who all had similar resting SBF, 42% of the total capacity for O_2 delivery (or $\dot{V}_{O_2}$ max) could be achieved by this redistribution. Equivalent values would be 17% in the sedentary men and 11% in the athletes.

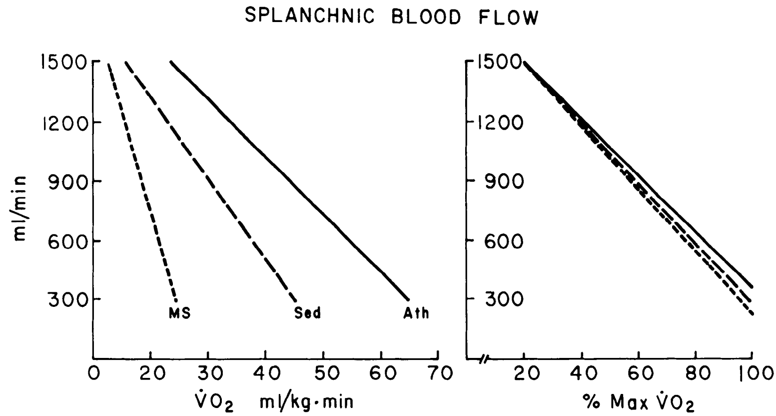


Fig.1. Decreases in splanchnic blood flow (SBF) with increasing oxygen uptake ($\dot{V}_{O_2}$) (per kg of body weight) up to maximal oxygen uptake ($\dot{V}_{O_2}$ max) in three groups: MS, patients with pure mitral stenosis; Sed, normal sedentary young men; and Ath, endurance athletes. Each line on the left ends at the average $\dot{V}_{O_2}$ max/kg of the group. On the right, lines are superimposed when data is related to per cent of $\dot{V}_{O_2}$ max. Adapted from Rowell et al. (26,29,38) and Blackmon et al. (3).

Regional vasoconstriction can also serve to counteract muscle vasodilatation and maintain arterial blood pressure. The significance depends upon the individual's maximal cardiac output or total vascular conductance. Were total regional vasoconstrictor tone lost and resting vascular conductance restored to non-working regions during maximal exercise, arterial blood pressure would fall 42 mm Hg in the mitral stenosis patients, 20 mm Hg in sedentary men and only 12 mm Hg in the athletes. Thus, reduction of SBF and RBF during exercise serves a potentially major role in redistributing O_2 to working muscle and in regulation of arterial blood pressure during exercise.

B.) Cause of Splanchnic Vasoconstriction

1.) Baroreflex. Is regional vasoconstriction triggered by a fall in arterial blood pressure at the onset of exercise? Occasionally blood pressure does fall at this time, but more often it does not (13, 31). Rather, arterial mean and pulse pressures tend to rise immediately; thus, a baroreceptor stimulus is unlikely.

2.) Receptors in Working Muscle. Recent findings (12, 18, 20, 21, 22, 23, 49, 50) point to receptors in working muscle (probably unmyelinated c-fibers) which respond to local changes in K^+, PO_2, pH, osmolality, etc. Accordingly, the response of such receptors should be proportional to the adequacy of muscle blood flow which at any level of exercise should in turn depend upon the capacity of the circulation for O_2 delivery. This is an attractive postulate for it could explain the close proportionality between heart rate, vasomotor responses, etc. and the individual's $\dot{V}_{O_2}$ max.

II. Splanchnic Vascular Response to Heat Stress

Figure 2 shows the time course of SBF in seven men and their average splanchnic vascular resistance (SVR) and right atrial blood temperature during direct whole body heating (32, 36) in which body skin temperature was clamped (using water perfused suits), raised to 40-41°C as rapidly as possible and then held there for 30-50 min. Initially, the fall in SBF was primarily passive, accompanying a fall in blood pressure (see Fig. 3). As blood temperature rose (Fig. 2), SVR increased progressively to 39% above the control value (32, 36).

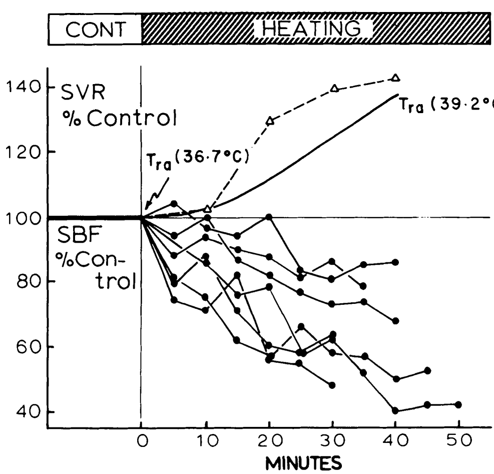


Fig.2. Splanchnic vascular resistance (SVR) and SBF during direct, whole body heating in seven men (32,36). Upper portion shows average increase in SVR during heating (Δ---Δ). Solid line shows the time course of right atrial blood temperature (T_{ra}) with average values at beginning and end of heating. SBF for each subject is shown in the lower half.

A.) Significance of Splanchnic Vasoconstriction

Figure 3 shows that direct whole body heating caused in 12 men a 6.6 liter/min increase in cardiac output which must go to skin as other major vascular beds vasoconstricted (9, 32, 34, 36). Since cardiac output and total vascular conductance were so high, the 40% decrease in SBF could make only relatively minor contributions to increased skin blood flow (approximately 0.6 liters/min out of 7.8 liters/min (9) and to blood pressure regulation. But splanchnic vasoconstriction may play a major role in redistributing blood volume to skin. As recently

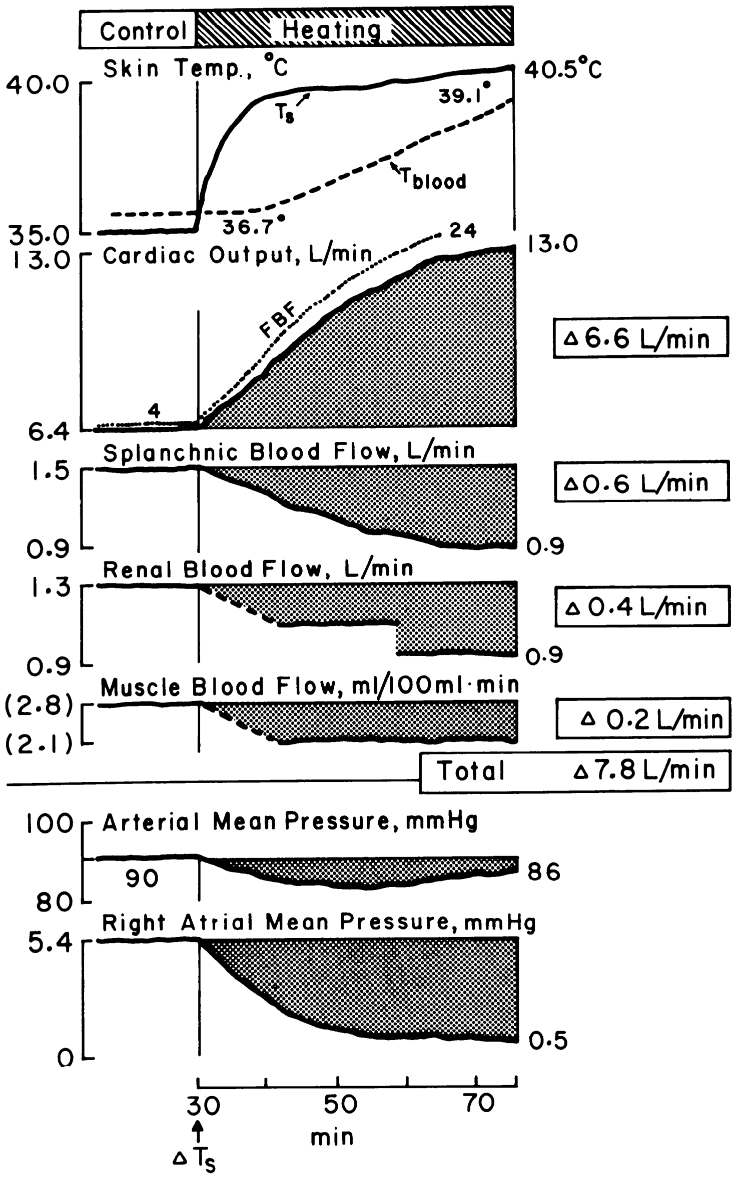


Fig.3. Average circulatory changes in men directly heated for 30-50 min with skin temperature at 40-41°C (9,32,34,36). In boxes are average changes (Δ) in cardiac output and blood flow to each region studied in 7-17 men (renal flow from 1 man). The sum of these changes, total Δ, is 7.8 liters/min which must go to skin (9).

shown in dogs (6), constriction of splanchnic resistance vessels causes a passive reduction in splanchnic venous volume since venous distending pressure is reduced. This effect combined with the fall in right atrial mean pressure (see Fig. 3) during heating will favor further passive collapse of splanchnic veins and should displace blood volume toward the heart. Splanchnic veins (in dogs) do not actively constrict during heat stress (48).

B.) Cause of Splanchnic Vasoconstriction

1.) Fall in Arterial Blood Pressure. Assuming for now that the splanchnic region in man responds to baroreflexes, the fall in blood pressure with heating could trigger splanchnic vasoconstriction. To test this, blood pressure was restored to control levels during body heating by total arterial occlusion of the legs (36) (Fig. 4). Since restoration of blood pressure to control levels did not alter the rise in SVR (Fig. 5) - a fall in pressure appears not to be the primary stimulus (36).

2.) Thermoregulatory Reflex. The close association between splanchnic vasoconstriction and increasing blood temperature (Fig. 2) suggests that splanchnic vasoconstriction is a reflex effect of central heating. This is supported by recent observations in animals wherein either brain or spinal cord heating increases the firing rate of splanchnic vasoconstrictor nerves, reducing SBF (15, 16, 42, 47).

Although details of the methods used to measure SBF, etc. are beyond the scope of this discussion, Figure 5 illustrates the method wherein indocyanine green dye (extracted exclusively by liver) concentrations are repeatedly measured in arterial and hepatic venous (from catheter in the largest right hepatic vein) blood samples during constant infusion of the dye. In non-steady states, difference in dye infusion rate (I) and hepatic removal rate are computed according to Bradley (5) from the rate of change in arterial dye concentration ($\dot{C}_A$) times plasma volume (PV) - that is,

$$SBF = \frac{I - \dot{C}_A\,(PV)}{C_A - C_{HV}} \qquad (1)$$

where $C_A - C_{HV}$ (hepatic venous dye concentration) is hepatic dye extraction. Theoretical analysis of the errors inherent in this method reveal that the dynamics of the system are such that with a minimum sampling interval of 2 min, true changes in SBF over that interval can be determined with less than a 10% error (27, 35).

III. Splanchnic Vascular Response to Heat Stress Plus Exercise

When exercise and heat stresses are combined, effects on SBF and SVR are additive (30, 33). Figure 6 shows the relationship between SBF and per cent of V_{O_2} max required during exercise in both neutral (25.6°C) environments (30). At any given "relative" V_{O_2} in the heat, SBF was reduced an additional 20% or 300-400 ml/min below the resting value. A corresponding increase in SVR occurred as blood pressure was only 4-7 mm Hg lower in the heat. Note also in Figure 4 the much higher heart rate in the heat.

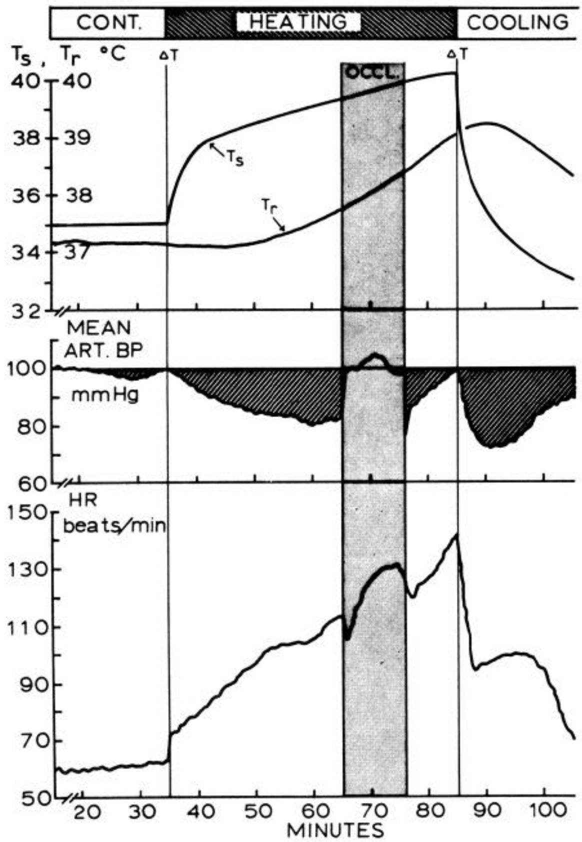


Fig.4. Response to direct heating in one supine resting subject. Shown are skin and rectal temperatures (T_s and T_r) (top), mean arterial blood pressure (BP) and heart rate (HR). Heating began at 35 min and ended at 85 min. Shaded vertical bar marked OCCL. shows period of arterial occlusion of both legs. Note the rise in mean pressure during OCCL. (From Rowell et al. (36) - by permission).

A.) Significance of Splanchnic Vasoconstriction

The importance of splanchnic vasoconstriction here was the requirement for redistribution of a greater fraction of cardiac output to skin. Because of reduced stroke volume, cardiac output was not increased in the heat (37), so that skin blood flow could be increased only at the expense of reduced SBF - and also renal blood flow (24).

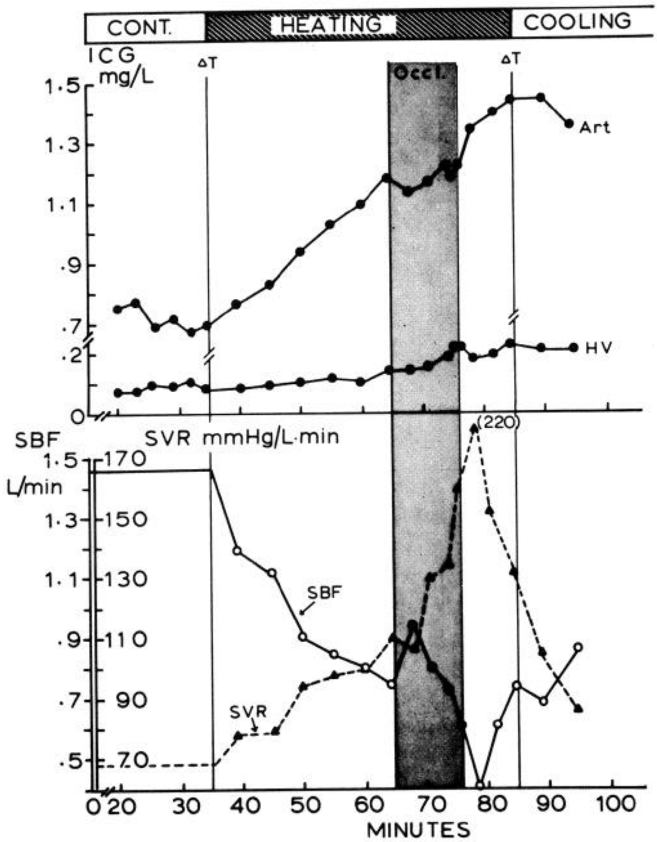


Fig.5. Data from the same subject continued from Figure 4. Upper section (ICG) shows changes in arterial (Art) and hepatic venous (HV) indocyanine green dye (ICG) concentration. The shaded bar (OCCL) marks the period (see Fig.4.) when blood pressure was restored to control. Lower section shows SBF (o——o) (outer y axis) and SVR (▲---▲) (inner y axis). Note the continued rise in SVR despite restoration of blood pressure. (From Rowell et al. (36) - by permission).

B.) Cause of Splanchnic Vasoconstriction

Since aortic pulse pressure was unaffected by the added heat stress and mean pressure fell only 4-7 mm Hg (19), reflex effects of increased body temperature are a likely cause. But one cannot rule out effects of heat and altered chemical environment in working muscle upon those nerves in muscle (unmyelinated c-fibers?) which may elicit some reflex cardiovascular responses to exercise.

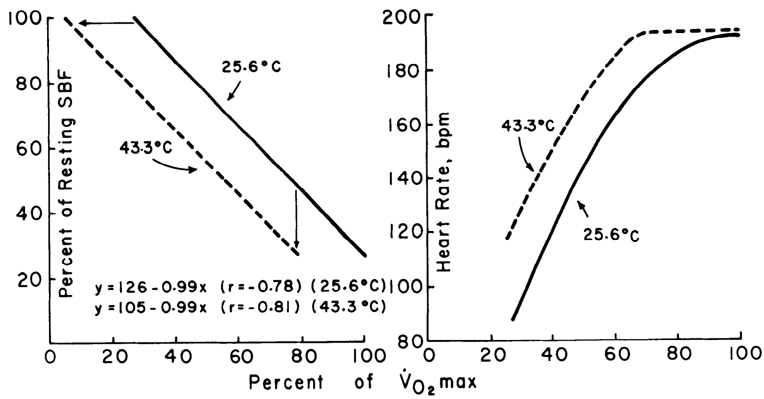


Fig.6. Decrements in SBF, expressed as per cent of resting SBF (100%) versus the per cent of $\dot{V}_{O_2}$ max required during exercise in a neutral environment (25.6°C). Arrows indicate that SBF began to fall at a lower per cent of $\dot{V}_{O_2}$ max and also reached minimum values sooner in the heat. Regression equations for the two lines are given where y = per cent of resting SBF. The marked elevation of heart rate in the heat is shown on the right. (Adapted from Rowell et al. (30)).

IV. Splanchnic Vascular Participation in Blood Pressure Regulation

Earlier studies suggested that the splanchnic region in man vasoconstricts in response to reduced arterial blood pressure. For example, head-up tilting caused splanchnic vasoconstriction which, in hypertensive patients, could be abolished by splanchnic sympathectomy (51). The time course and quantitative significance of splanchnic vasoconstriction induced by baroreflexes was recently investigated in five normal young men by subjecting them to lower body negative pressure (LBNP) (-50 mm Hg) applied below the iliac crests (35). LBNP, or simulated hemorrhage, caused a decrease in SBF and a rise in SVR while arterial mean pressure remained almost constant. SVR tended to rise immediately when arterial pulse pressure fell suddenly. When pulse pressure fell gradually, the rise in SVR was delayed. Figure 7 summarizes the overall response to LBNP. Note the fall in right atrial pressure and the immediate vasoconstriction of forearm which includes both skin and muscle responses (1, 39). At the end of LBNP (before any signs of syncope) SVR rose 30%, SBF decreased 33% and cardiac output fell 28% on the average in five men.

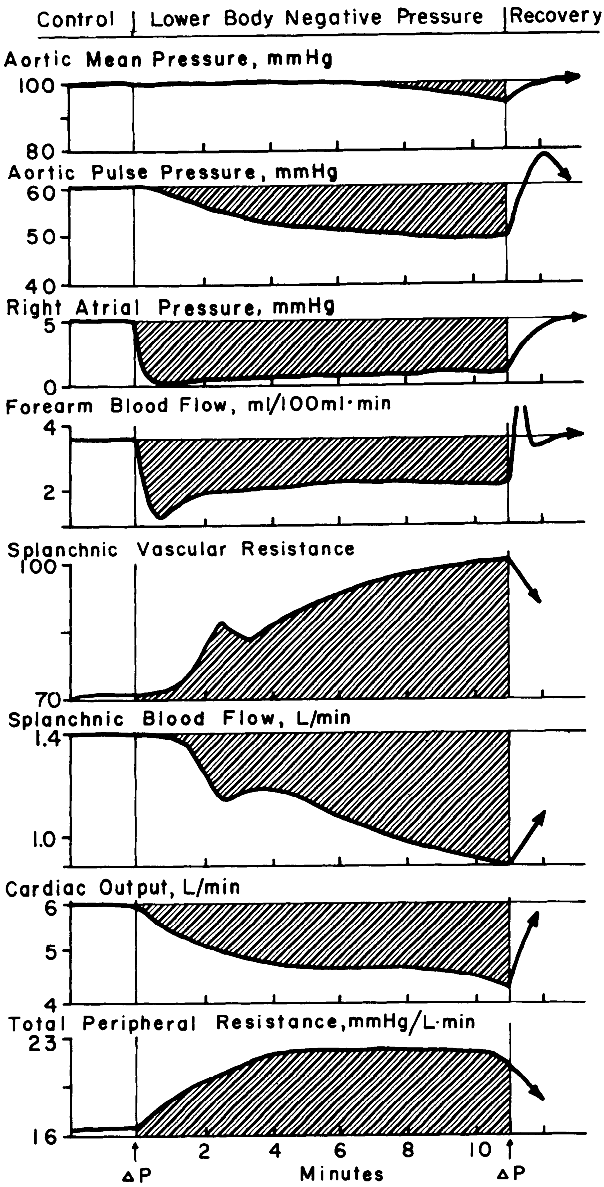


Fig.7. Schematic illustration of overall cardiovascular response to lower body negative pressure at -50 mm Hg applied below the iliac crests (simulated hemorrhage). This represents the response of a subject showing a gradual fall in pulse pressure with a gradual increase in SVR. Note the sudden fall in right atrial pressure and forearm blood flow. (Adapted from Rowell (28).)

A.) Significance of Splanchnic Vasoconstriction

The quantitative significance of splanchnic vasoconstriction is illustrated in Table 1. Of the decrease in total vascular conductance ($^1/R$) of 13.5 units, 4.4 units or 33% was attributable to splanchnic vasoconstriction. Thus, one-third of the compensatory regional vasoconstriction required to maintain mean pressure occurred in the splanchnic region (35).

Table 1

Changes in Total and Regional Vascular Conductances
During Simulated Hemorrhage (LBNP)
(Arrows point between flows measured before and during LBNP)

	CO	SBF	Skin, Musc* BF	Other**
$\dot{Q}$ L/min	6.8 ↓ 4.9	1.6 ↓ 1.0	1.5 ↓ 0.9	3.7 ↓ 3.0
Δ Conductance ΔC × 10^3	13.5	4.4	5.3	3.8
%total ΔC	100%	33%	39%	28%

*Total skin and muscle blood flows estimated to be 1.5 liters/min. The total change was estimated from the per cent change in forearm skin and muscle blood flows.

**Other presumably is mostly renal.

B.) Cause of Splanchnic Vasoconstriction

These studies suggested that in contrast to skin and muscle which vasoconstricted immediately with the fall in right atrial pressure, that splanchnic vasoconstriction was triggered by the fall in aortic pulse pressure (mean pressure had not changed at the time). Presumably skin and muscle vasoconstriction is reflexly elicited by low pressure baroreceptors in the right atrium as marked forearm vasoconstriction will attend falling right atrial pressure with no change in arterial mean or pulse pressure or in dp/dt (53). To see if SVR during LBNP is controlled only by high pressure baroreceptors, LBNP was applied in a ramp of -1 mm Hg/min for 40-50 min (Fig. 8) (Johnson, Rowell, Niederberger, and Eisman, in preparation). This caused right atrial mean pressure to fall in a ramp which immediately triggered forearm vasoconstriction without any measurable change in any arterial signal. When LBNP reached approximately -20 mm Hg, a fall in aortic pulse pressure and a rise in heart rate always occurred (correlation between the two was -0.85 to -0.93) presumably indicating the onset of an arterial baroreceptor response. SBF tended to fall by about 15% sometime after forearm vasoconstriction but before heart rate, mean or pulse pressure or dp/dt changed. This suggests that low pressure baroreceptors provide another input to regulation of SVR in conditions where right atrial pressure falls such as in heat stress or hemorrhage. Most of the 40% decrease in SBF occurred after heart rate rose. The splanchnic region appears less sensitive than skin and muscle to this input.

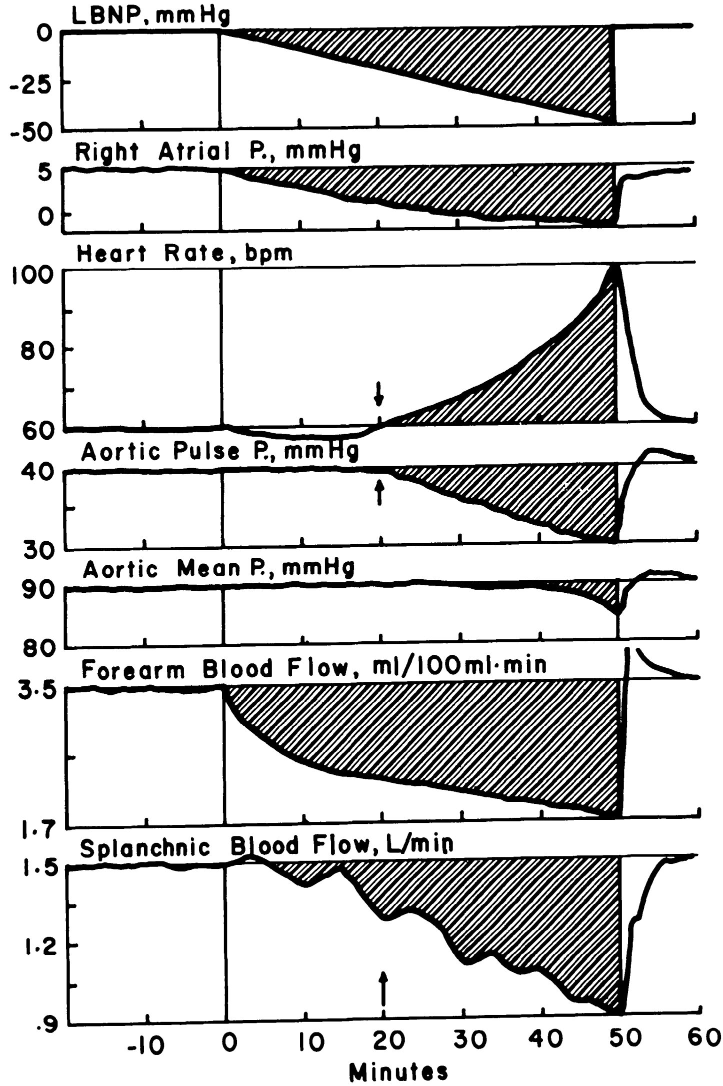


Fig.8. Schematic illustration of cardiovascular responses to a ramp of LBNP applied at a rate of -1 mm Hg/min. Up to -20 mm Hg (indicated on data by arrows) no measurable changes in any parameter of arterial pressure or in heart rate occurred. Note the sudden decrease in forearm blood flow as right atrial pressure begins to decline. SBF began to decrease slowly before -20 mm Hg LBNP, where arterial pressure and heart rate showed the first change. (Johnson, Rowell, Niederberger, and Eisman - unpublished observations.)

V. Overall Predictability of Splanchnic Vasomotor Responses

Figure 9 puts together much of the preceding data. No matter which of these stresses is applied to men having a wide range of cardiovascular capacities, the slopes relating changes in SBF to heart rate are always statistically the same. This is also true for renal blood flow during exercise - other conditions have not been examined in this way. Thus, in man, in contrast to the dog (11, 17, 40, 41, 43, 44), the increase in sympathetic nervous outflow to the heart to increase rate is directly proportional to the increase in sympathetic vasomotor outflow to vasoconstrict visceral organs. The different intercepts for resting and exercise data probably reflect a greater contribution of vagal withdrawal to increase heart rate at low levels of exercise, as compared with the relatively greater sympathetic stimulation attending baroreceptor activity (25).

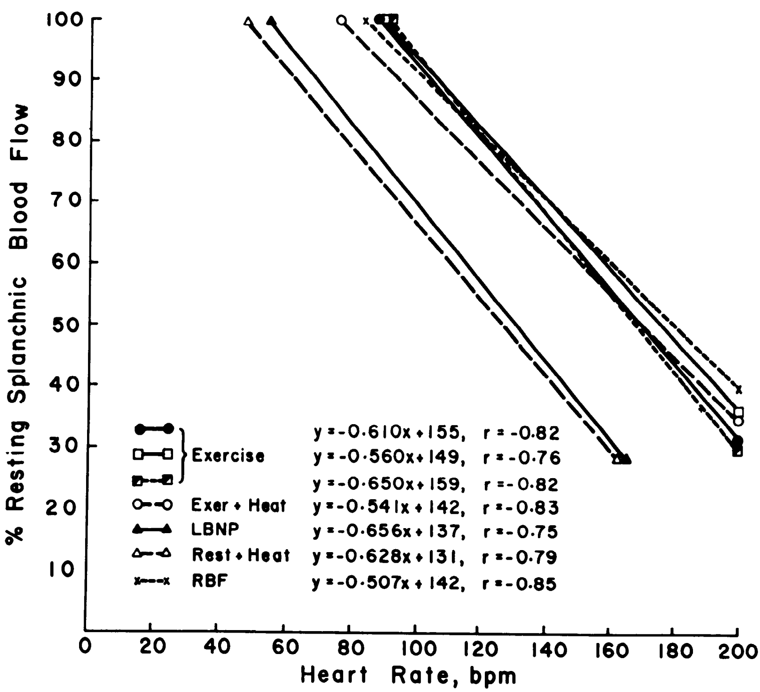


Fig.9. Relationship between SBF as per cent of resting value and heart rate (uncorrected for resting value) during exercise, exercise plus heat, LBNP and heating at rest and also renal blood flow (10) during exercise (adapted from Rowell (28)). Lines ☐ and ◩ show SBF before ☐ and after ◩ physical conditioning (unpublished date of Clausen et al. - by permission).

Thus, under a wide variety of stresses, heart rate reflects the severity of the stress both in terms of relative demands on cardiac output and in terms of the degree of sympathetic vasomotor outflow to visceral organs. Adaptations which are attended by reductions in heart rate at any given level of stress should produce proportional reductions in the degree of splanchnic vasoconstriction. For example, lines □ and ■ in Figure 9 (unpublished date of Clausen, et al. - by permission) show that physical conditioning (line ■) which lowered heart rate at any given $\dot{V}_{O_2}$ did not alter the normal relationship between heart rate and SBF before conditioning (line □).

Do changes in SVR reflect changes in overall sympathetic vasomotor outflow - so that the increase in vasomotor activity to other regions could be predicted from changes in heart rate? Figure 8 suggests that the answer is no, since marked skin and muscle vasoconstriction can precede any change in heart rate. Whether these regional differences can be attributed to different receptors causing the responses, different rates of sympathetic outflow to different regions, or different regional sensitivities to the same stimulus, is unknown. Currently, such investigations must be conducted in animals other than man. Man does, however, provide a means of understanding how some systems function under precisely controlled conditions where input and output variables can be scaled with respect to the system's capacity to respond. The ability to define in man the functional limits of the cardiovascular system provides a powerful scientific base from which to study its regulation.

REFERENCES

1. Beiser, G.D., R. Zelis, S.E. Epstein, D.J. Mason, and E. Braunwald. The role of skin and muscle resistance vessels in reflexes mediated by the baroreceptor system. J. Clin. Invest. 49: 225-231, 1970.
2. Bevegard, B.S., and J.T. Shepherd. Regulation of the circulation during exercise in man. Physiol. Rev. 47: 178-213, 1967.
3. Blackmon, J.R., L.B. Rowell, J.W. Kennedy, R.D. Twiss, and R.D. Conn. Physiological significance of maximal oxygen intake in pure mitral stenosis. Circulation 36: 497-510, 1967.
4. Blair, D.A., W.E. Glover, and I.C. Roddie. Vasomotor responses in the human arm during leg exercise. Circulation Res. 9: 264-274, 1961.
5. Bradley, S.E., F.J. Ingelfinger, G.P. Bradley, and J.J. Curry. The estimation of hepatic blood flow in man. J. Clin. Invest. 24: 890-897, 1945.
6. Brooksby, G.A., and D.E. Donald. Release of blood from the splanchnic circulation in dogs. Circulation Res. 31: 105-118, 1972.
7. Clausen, J.P., and J. Trap-Jensen. Effects of training on the distribution of cardiac output in patients with coronary artery disease. Circulation 42: 611-624, 1970.
8. Delius, W., K.-E. Hagbarth, A. Hongell, and B.G. Wallin. Manoeuvres affecting sympathetic outflow in human skin nerves. Acta Physiol. Scand. 84: 177-186, 1972.

9. Detry, J.-M. R., G. L. Brengelmann, L. B. Rowell, and C. Wyss. Skin and muscle components of forearm blood flow in directly heated resting man. J. Appl. Physiol. 32: 506-511, 1972.
10. Grimby, G. Renal clearances during prolonged supine exercise at different loads. J. Appl. Physiol. 20: 1294-1298, 1965.
11. Herrick, J. F., J. H. Grindley, E. J. Baldes, and F. C. Mann. Effect of exercise on the blood flow in the superior mesenteric, renal and common iliac arteries. Am. J. Physiol. 128: 338-344, 1940.
12. Hník, P., O. Hudlická, J. Kučera, and R. Payne. Activation of muscle afferents by non-proprioceptive stimuli. Am. J. Physiol. 217: 1451-1457, 1969.
13. Holmgren, A. Circulatory changes during muscular work in man: with special reference to arterial and central venous pressures in the systemic circulation. Scand. J. Clin. Lab. Invest. 8, Suppl. 24: 1-97, 1956.
14. Hultman, E. Studies on muscle metabolism of glycogen and active phosphate in man with special reference to exercise and diet. Scand. J. Clin. Lab. Invest. 19, Suppl. 94: 1-63, 1967.
15. Iriki, M., W. Riedel, and E. Simon. Regional differentiation of sympathetic activity during hypothalamic heating and cooling in anesthetized rabbits. Pflugers Arch. Ges. Physiol. 328: 320-331, 1971.
16. Kullmann, R., W. Schonung, and E. Simon. Antagonistic changes of blood flow and sympathetic activity in different vascular beds following central thermal stimulation. I. Blood flow in skin, muscle, and intestine during spinal cord heating and cooling in anesthetized dogs. Pflugers Arch. Ges. Physiol. 318: 146-161, 1970.
17. Lacroix, E., and I. Leusen. Splanchnic hemodynamics during induced muscular exercise in the anesthetized dog. Arch. Intern. Physiol. Biochem. 74: 235-250, 1966.
18. Lind, A. R., and G. W. McNicol. Muscular factors which determine the cardiovascular responses to sustained and rhythmic exercise. Can. Med. Assoc. 69: 706-713, 1967.
19. Marx, H. J., L. B. Rowell, R. D. Conn, R. A. Bruce, and F. Kusumi. Maintenance of aortic pressure and total peripheral resistance during exercise in heat. J. Appl. Physiol. 22: 519-525, 1967.
20. McCloskey, D. I., and J. H. Mitchell. Reflex cardiovascular and respiratory responses originating in exercising muscle. J. Physiol. (London) 224: 173-186, 1972.
21. Mitchell, J. H., D. N. Gupta, and S. E. Barnett. Reflex cardiovascular responses elicited by stimulation of receptor sites with pharmacological agents. Circulation Res. 20: I-192-I-200, 1967.
22. Mitchell, J. H., D. S. Mierzwiak, K. Wildenthal, W. D. Willis, Jr., and A. M. Smith. Effect on left ventricular performance of stimulation of an afferent nerve from muscle. Circulation Res. 22: 507-516, 1968.
23. Perez-Gonzalez, J. F., and J. H. Coote. Activity of muscle afferents and reflex circulatory responses to exercise. Am. J. Physiol. 223: 138-143, 1972.
24. Radigan, L. R., and S. Robinson. Effects of environmental heat stress and exercise on renal blood flow and filtration rate. J. Appl. Physiol. 2: 185-191, 1949.

25. Robinson, B. F., S. E. Epstein, G. D. Beiser, and E. Braunwald. Control of heart rate by the autonomic baroreceptor mechanisms and exercise. Circulation Res. 19: 400-411, 1966.
26. Rowell, L. B. Cardiovascular limitations to work capacity. In: Physiology of Work Capacity and Fatigue, edited by E. Simonson. Springfield, Ill.: Charles C Thomas, 132-169, 1971.
27. Rowell, L. B. Dye techniques for estimating hepatic-splanchnic blood flow in man. In: Dye Curves: Theory and Practice of Non-Diffusible Indicator Dilution, edited by D. Bloomfield. Baltimore: University Park Press, 1973.
28. Rowell, L. B. Splanchnic Circulation. In: Textbook of Physiology and Biophysics, edited by T. C. Ruch and H. D. Patton. Philadelphia: Saunders, 1973, 20th ed., Vol. 2, Chapt. 14. In press.
29. Rowell, L. B., J. R. Blackmon, and R. A. Bruce. Indocyanine green clearance and estimated hepatic blood flow during mild to maximal exercise in upright man. J. Clin. Invest. 43: 1677-1690, 1964.
30. Rowell, L. B., J. R. Blackmon, R. H. Martin, J. A. Mazzarella, and R. A. Bruce. Hepatic clearance of indocyanine green in man under thermal and exercise stresses. J. Appl. Physiol. 20: 384-394, 1965.
31. Rowell, L. B., G. L. Brengelmann, J. R. Blackmon, R. A. Bruce, and J. A. Murray. Disparities between aortic and peripheral pulse pressures induced by upright exercise and vasomotor changes in man. Circulation 37: 954-964, 1968.
32. Rowell, L. B., G. L. Brengelmann, J. R. Blackmon, and J. A. Murray. Redistribution of blood flow during sustained high skin temperature in resting man. J. Appl. Physiol. 28: 415-420, 1970.
33. Rowell, L. B., G. L. Brengelmann, J. R. Blackmon, R. D. Twiss, and F. Kusumi. Splanchnic blood flow and metabolism in heat stressed man. J. Appl. Physiol. 24: 475-484, 1968.
34. Rowell, L. B., G. L. Brengelmann, and J. A. Murray. Cardiovascular responses to sustained high skin temperature in resting man. J. Appl. Physiol. 27: 673-680, 1969.
35. Rowell, L. B., J.-M. R. Detry, J. R. Blackmon, and C. Wyss. Importance of the splanchnic vascular bed in human blood pressure regulation. J. Appl. Physiol. 32: 213-220, 1972.
36. Rowell, L. B., J.-M. R. Detry, G. R. Profant, and C. Wyss. Splanchnic vasoconstriction in hyperthermic man - role of falling blood pressure. J. Appl. Physiol. 31: 864-869, 1971.
37. Rowell, L. B., H. J. Marx, R. A. Bruce, R. D. Conn, and F. Kusumi Reductions in cardiac output, central blood volume, and stroke volume with thermal stress in normal men during exercise. J. Clin. Invest. 45: 1801-1816, 1966.
38. Rowell, L. B., E. J. Masoro, and M. J. Spencer. Splanchnic metabolism in exercising man. J. Appl. Physiol. 20: 1032-1037, 1965.
39. Rowell, L. B., C. R. Wyss, and G. L. Brengelmann. Sustained human skin and muscle vasoconstriction with reduced baroreceptor activity. J. Appl. Physiol. In press, 1973.
40. Rushmer, R. F., D. L. Franklin, R. L. Van Citters, and O. A. Smith. Changes in peripheral blood flow distribution in healthy dogs. Circulation Res. 9: 675-687, 1961.

41. Scher, A.M., W.W. Ohm, K. Bumgarner, R. Boynton, and A.C. Young. Sympathetic and parasympathetic control of heart rate in the dog, baboon and man. Federation Proc. 31: 1219-1225, 1972.
42. Schonung, W., H. Wagner, C. Jessen, and E. Simon. Differentiation of cutaneous and intestinal blood flow during hypothalamic heating and cooling in anesthetized dogs. Pflugers Arch. Ges. Physiol. 328: 145-154, 1971.
43. Vatner, S.F., D. Franklin, R.L. Van Citters, and E. Braunwald. Effect of carotid sinus nerve stimulation on blood flow distribution in conscious dogs at rest and during exercise. Circulation Res. 27: 495-503, 1970.
44. Vatner, S.F., C.B. Higgens, S. White, T. Patrick, and D. Franklin. The peripheral vascular response to severe exercise in untethered dogs before and after complete heart block. J. Clin. Invest. 50: 1950-1960, 1971.
45. Wade, O.L., and J.M. Bishop. Cardiac Output and Regional Blood Flow. Oxford: Blackwell, 1962.
46. Wahren, J., G. Ahlborg, P. Felig, and L. Jorfeldt. Glucose metabolism during exercise in man. In: Advances in Experimental Medicine and Biology. Vol. II: Muscle Metabolism During Exercise, edited by B. Pernow and B. Saltin. New York: Plenum Press, 1971, p. 189-203.
47. Walther, O.-E, M. Iriki, and E. Simon. Antagonistic changes of blood flow and sympathetic activity in different vascular beds following central thermal stimulation. II. Cutaneous and visceral sympathetic activity during spinal cord heating and cooling in anesthetized rabbits and cats. Pflugers Arch. Ges. Physiol. 319: 162-184, 1970.
48. Webb-Peploe, M.M. Effect of changes in central body temperature on capacity elements of limb and spleen. Am. J. Physiol. 216: 643-646, 1969.
49. Webb-Peploe, M.M., D. Brender, and J.T. Shepherd. Vascular responses to stimulation of receptors in muscle by capsaicin. Am. J. Physiol. 222: 189-195, 1972.
50. Wildenthal, K., D.S. Mierzwiak, N.S. Skinner, Jr., and J. H. Mitchell. Potassium-induced cardiovascular and ventilatory reflexes from the dog hind limb. Am. J. Physiol. 215: 542-548, 1968.
51. Wilkins, R.W., J.W. Culbertson, and F.J. Ingelfinger. The effect of splanchnic sympathectomy in hypertensive patients upon estimated HBF in the upright as contrasted with the horizontal position. J. Clin. Invest. 30: 312-317, 1951.
52. Zelis, R., D.T. Mason, and E. Braunwald. Partition of blood flow to the cutaneous and muscular beds of the forearm at rest and during leg exercise in normal subjects and in patients with heart failure. Circulation Res. 24: 799-806, 1969.
53. Zoller, R.P., A.L. Mark, F.M. Abboud, P.G. Schmid, and D.D. Heistad. The role of low pressure baroreceptors in reflex vasoconstriction responses in man. J. Clin. Invest. 51: 2967-2972, 1972.

CEREBRAL CORTICAL CONTROL OF MOVEMENT*

HIROSHI ASANUMA
The Rockefeller University
New York, N.Y.

Introduction:

The purpose of the series of experiments which will be described in this article was to increase our understanding of how the motor cortex controls the movement. It has been a continuing controversy whether the motor cortex controls the contraction of single muscles or rather muscle groups. Hughlings Jackson and his followers, based on the fact that a patient can recover the use of a limb after destruction of that limb area previously defined by stimulation, favored the idea of a widespread overlapping of the representation of muscle groups (cf. Ruch 1965). This view was strongly supported by Sherrington's early experiences (Hering and Sherrington, 1897, Sherrington, 1906) in which stimulation on the surface of the cortex could not produce solitary contraction of a muscle and that the combination of the muscles activated by cortical stimulation was always in a reciprocal fashion, i.e., "cortical stimulation never produced simultaneous contraction of the true antagonists" (Sherrington, 1906). The latter evidence led him to think that the motor cortex controls the coordinated contraction of a group of muscles.

The interpretation that the motor cortex "thinks" in terms of movements, not muscles was so persuasive that more than half a century has passed under the dominance of this theory. In 1947, however, Chang, Ruch and Ward demonstrated evidence that the motor cortex may be able to think in terms of muscles. They stimulated the surface of the monkey cortex, with maximum possible caution, and were able to elicit solitary contraction, although occasionally, of a single muscle. Succeeding experiments by Bernhard and Bohm (1954) demonstrated that a single shock stimulation of the motor cortex activated the fast conducting corticospinal neurons of the pyramidal tract which in turn elicited a monosynaptic response in a forelimb nerve but not in the rest of the nerves. They also showed that the cortical field which produced the monosynaptic response in a certain nerve was more restricted than the fields from which other (polysynaptic) activities in the motoneurons of the same nerve could be evoked. The study about the localization of cortical motor function was further advanced by Landgren, Phillips and Porter (1962). They stimulated the surface of the motor cortex while recording intracellularly from motoneurons and demonstrated the existance of a cluster of neurons which projected monosynaptically to motoneurons and which was confined within a narrow focus of the cortex having a cross section of the order of $1mm^2$. Thus progress in the stimulation experiments of the motor cortex provided evidence that the contraction of individual muscles is represented in small areas of the motor

* Taken from the introductory remarks given at the session on Brain and Motor Activity at the 1973 Federation Meetings.

cortex in a mosaic fashion. This conclusion, however, does not resolve the question of "whether the motor cortex thinks in terms of movements or muscles" because as has been pointed out by Bernhard and Bohm (1954) in their stimulation experiments, a given cortical stimulus which facilitated a monosynaptic reflex, at the same time inhibited the monosynaptic reflex of the antagonist in the absence of peripheral influences.

In the meantime, another line of investigation of the motor cortex developed depending on the rapid progress of the electrical techniques which enabled recording of the electrical signals associated with the activities of neurons in the central nervous system. In 1953, Malis, Pribram and Kruger showed that the motor cortex received afferent inputs from the periphery in the absence of the sensory cortex. This observation raised the question of the functional significance of these afferent inputs converging onto the motor cortex.

The specific purpose of a series of experiments performed in my laboratory has been to further elucidate the details of the localization of the cortical motor function and then to relate the motor function to the afferent inputs, i.e., to study the input-output relationships. The term "motor cortex" is used instead of "motorsensory cortex" because a recent histological study (Hassler and Muhs-Clement, 1964) has shown that the cat's pericruciate cortex corresponds to the motor cortex of the primates.

The Organization of Cortical Efferent System

As stated in the "Introduction" the short latency, low threshold effect of cortical stimulation is mediated, primarily, by the pyramidal tract (Bernhard and Bohm, 1954, Landgren et al. 1962). This tract originates from the pyramidal tract cells (PT cells) which are located in the deep layers of the cortex (layers V and VI) and the majority of them are located in the motor cortex. The motor area is known to bear the thickest (up to 4.5 mm in human) cortex in the whole brain and the thickness of the motor cortex in the monkey is only slightly less than in the human (Harman, 1947) although in the cat, it is considerably less (2.5 to 3.0 mm). To activate the PT cells from the surface, therefore, a stimulating current has to travel a long distance through the brain. This inevitably activates a large number of cortical neurons including the PT cells and obscures the accuracy of measuring the location of the target cells.

This difficulty was overcome by stimulating the depth of the cortex directly with a microelectrode (Asanuma and Sakata 1967). Furthermore by utilizing a closed chamber (Davies, 1956), respiratory and pulsatory movement of the brain could be minimized and the electrode could be positioned into the depth without damaging the tissue. With this method, we found that threshold current for facilitation or inhibition of the monosynaptic reflexes was much lower (less than 1/100) than the threshold from the surface.

Stimulating with weak current through the microelectrode, we found that the sites which produced facilitation or inhibition of given reflexes were confined to a narrow focus within the depth of the cortex. Figure 1 illustrates an example of the results obtained. Among several cortical penetrations six passed through a discrete region where intracortical microstimulation (ICMS) of 6 µa or less facilitated monosynaptic reflexes in n. extensor carpi ulnaris (wrist extensor). The effective area was reconstructed by histological examination and found to extend along the direction of the radial fibers within the gray matter. At the edge of the effective area, the threshold increased sharply. Other trials revealed similar results and the diameter of the effective areas, i.e., the efferent zones, ranged from 0.5 mm to a few mm, the average being 1.0 mm.

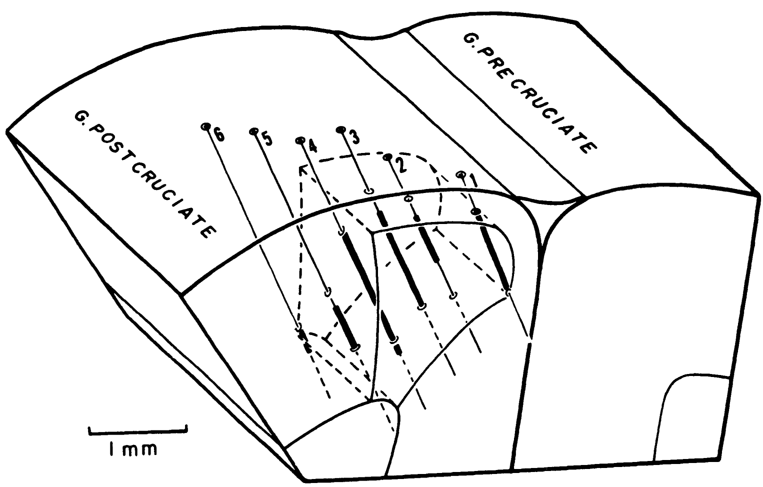


Fig.1. Solid diagram of effective volume for the facilitation of monosynaptic reflexes in n. extensor carpi ulnaris (ECU) within the cat's motor cortex. Numbers indicate positions on the surface where microelectrode was inserted and heavy line show regions where intracortical microstimulation (ICMS) facilitated ECU monosynaptic reflexes. (Asanuma and Sakata, 1967).

At this stage, it became imperative that the effective spread of the stimulating current within the brain be known to quantitatively analyze the results. This was examined (Stoney, Thompson amd Asanuma 1968) by introducing 2 microelectrodes into the cortex, one stationed close to a PT cell and the other, moved through the neighboring tissue. ICMS was delivered at various depths through the moving electrode and the effect was monitored by recording action potentials through the stationary electrode. Figure 2 shows an example of the results. As the stimulating electrode approached the target cell, the threshold decreased to a minimal value and then increased again. Other trials revealed similar results and in all cases, negative currents were far more effective than positive currents and the curves always took the form of parabolas.

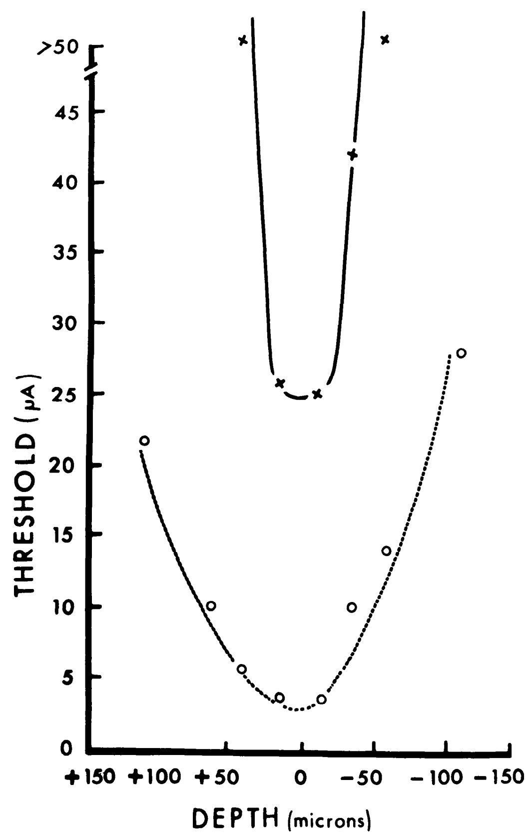


Fig.2. Depth - threshold relationship for direct excitation of a PT cell by intracortical microstimulation (ICMS). Threshold current is plotted against relative depth of the stimulating electrode. Electrode depth is expressed as distance superficial or deep to the point of minimum threshold. Open circles: thresholds for cathodal pulses. Crosses: thresholds for anodal pulses. (Modified from Stoney, Thompson and Asanuma,1968).

For the analysis of the parabola, the following calculations were made (Asanuma and Sakata, 1967): In a volume conductor the voltage (V) of any point is given by the following equation

$$V = \frac{is}{4\pi r}$$

where i is the current, s is the specific resistivity of the conductor and r is the distance from the current source (i.e. stimulating electrode).

The voltage gradient across the cell body ($\Delta V/\Delta r$) is given by the following equation:

$$\frac{\Delta V}{\Delta r} = \frac{dV}{dr} = \frac{-is}{4\pi r^2}$$

It seems reasonable to assume that: 1) the effective current for cell firing is that current which passes through the cell membrane; 2) the current density which passes through the membrane is proportional to the voltage difference (ΔV) across the cell body (Δr). When a cell is in a steady state, the threshold current for exciting the cell is constant, hence the voltage gradient ($\Delta V/\Delta r$) across the cell body is constant. Therefore at the edge of the effective area,

$$i = r^2K$$

Since this equation describes a parabola, we applied this equation to the actual values. At any point during the traverse of the electrode, the distance (r) from the electrode tip to the cell can be resolved into two components (Fig. 3) and

$$i = K(r_1^2 + r_2^2)$$

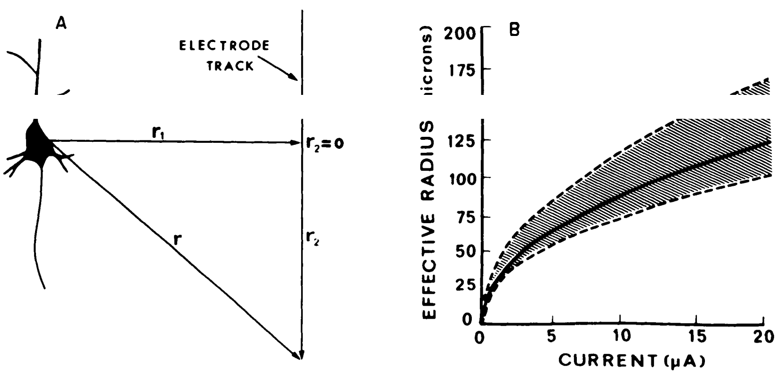


Fig.3. A: Geographical relationship between the electrode track and the target cell. Perpendicular line from the cell to the electrode track (r_1) represents distance from the cell to the minimum threshold point. r_2 represents the distance from the minimum threshold point to the electrode tip. B: relationship between stimulating current and effective radius for direct excitation. Hatched line and shaded area indicates the 95% confidence interval for estimate of the effective current. (Stoney, Thompson and Asanuma, 1968).

The perpendicular line to the electrode track (r_1) remains constant throughout the traverse and the distance along the electrode track (r_2) could be read directly from the micromanipulator. At the point of the closest approach to the cell, $r_2 = 0$, $r_1 = r$, and the threshold current will be minimal:

$$i_{min} = Kr_1^2$$

From these equations, it becomes:

$$i - i_{min} = Kr_2^2$$

Since we know the values for i, i_{min} and r_2 from the experiments, we could estimate the K value which approximated 1300. The relationship between r and i when K = 1300 is shown in Fig. 3, B.

From the above calculations, we could infer that a single cathodal current pulse (0.2 msec duration, 10 µa) activated only those cells located within a sphere of a radius of about 90 µ around the tip of the microelectrode. Since the neuronal population densities for different parts of the cortex in various species are known (Sholl, 1959), an estimate of the numbers of cells activated by ICMS is possible. In the cat, 10 µa current pulse of 0.2 msec duration is calculated to activate 28 neurons if applied at a depth of 1.0 mm (PT cell layer) within the motor cortex (Stoney et al. 1968).

The preceding results, indicated the existence of discrete efferent zones within the depth of the cortex which control contraction of individual muscles. Stimulation on the surface of the cortex, as stated in the introduction, never produced simultaneous contraction of the antagonists. We know, however, from our experiences that agonists and antagonists can contract simultaneously during voluntary movements. Similarily, these muscles undergo co-activation when a cat climbs a tree, hanging

To provide a solution to the question, following experiments were undertaken. Instead of monosynaptic reflexes, contraction of antagonistic muscles, i.e., m. extensor digitorum communis (EDC, wrist flexor) and m. palmaris longus (PAL, wrist extensor) were recorded to determine the effect of ICMS. Figure 4 shows an example of the results. The penetration shown by the inset figurine passed through efferent zones for both EDC and PAL. When ICMS was delivered to the EDC (pos. #1) or PAL zone (pos. #3), the resulting contraction appeared in EDC or PAL, without relaxation in the antagonist as shown in Fig. 4, 1 and 3. This is a striking difference from the surface stimulation. Stimulation of EDC or PAL area on the surface of the cortex under the same experimental set-ups also produced contraction of the target muscle, but in addition, that contraction was very frequently accompanied by the relaxation of the antagonist. When the intermediate zone was stimulated, the feature of the contractions were different from when EDC or PAL zone was stimulated. As shown in Fig. 4-2, both contractions waxed and waned, but it was observed that the contractions were not always mutually exclusive. Successive stimuli with the same intensity sometimes caused simultaneous contraction of both muscles and sometimes elicited contraction of one muscle accompanied by relaxation of the other. Thus when a single cortical efferent zone was stimulated, the resulting effect was a solitary contraction of the target muscle which was not accompanied by the relaxation of the antagonist unless the intermediate zone was stimulated. We know, however, that the

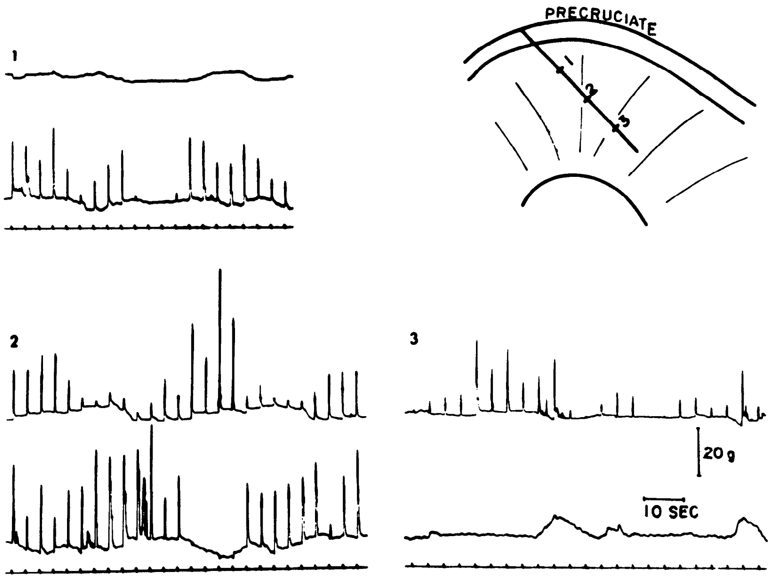


Fig.4. Contractions produced in m. extensor digitorum communis (EDC: upper trace) and m. palmaris longus (PAL: lower trace) by intracortical microstimulation (ICMS). Inset figurine shows electrode track and the foci stimulated. Stimulation at pos. 2 produced simultaneous as well as reciprocal contraction of the 2 antagonistic muscles. The third line of each set of traces indicates ICMS. (Asanuma and Ward, 1971).

surface stimulation always produced contraction of the muscles in a reciprocal fashion (Sherrington, 1909). To solve the problem, two microelectrodes instead of one were inserted into the motor cortex, one into the EDC zone and the other into the PAL zone, and the interaction between the two stimuli were examined. In an example shown in Fig. 5, one electrode was positioned at an area where stimulation produced sustained contraction of EDC for the duration (1 sec.) of the stimulus train. The effect of stimulation of PAL zone on EDC contraction was examined by delivering the second ICMS through the second electrode. Three penetrations were made in this trial and the effect of the second stimulation was checked at 0.5 mm intervals along each penetration. It was found that an area which produced contraction of PAL was located approximately 1.5 mm from the EDC point. Out of 3 sites which produced PAL contraction, only one site produced inhibition of EDC contraction. The other 2 sites produces contraction of PAL independently of EDC contraction. Furthermore, it was found that inhibition of EDC contraction was produced by stimulation of an adjacent area which did not produce contraction of PAL. In addition, in other experiment which is not shown here, stimulation which produced contraction of EDC facilitated contraction of PAL. The results demonstrated that the area which produces contraction of a muscle is not necessarily co-extensive with the area which inhibits contraction of the antagonist. The results suggested that the corticofugal pathway which is responsible for the contraction of a muscle is different from the pathway for the inhibition of the antagonist. In other words, corticofugal fibers which activate inhibitory interneurons for a particular motoneuron pool or pools are not always the branches of the fibers which excite the motoneuron pool of the antagonist. This interpretation is also supported by the observation that the cervical interneurons which were activated by ICMS of the motor cortex were different from the interneurons activated by stimulation of group I afferent fibers (Asanuma, Stoney and Thompson, 1971). Taken together, it is suggested that the inhibitory - excitatory interaction between different motoneuron pools taking place during cortically induced movements is different from the interaction occuring during the spinal reflexes which is reciprocal in character.

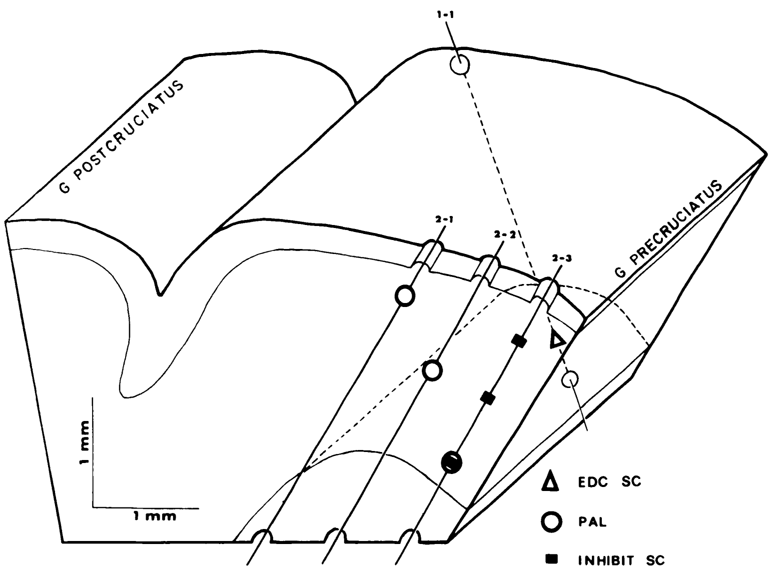


Fig.5. Differentiation of excitatory area for m. pal. long.(PAL) and inhibitory area for m. ext. dig. com. (EDC). Triangle represents the point which produced sustained contraction of EDC. Circles represent points which produced contraction of PAL. Stimulation of points represented by filled squares inhibited sustained contraction of EDC. Note circles and filled squares did not overlap except at one point.(Asanuma and Ward, 1971).

The difficulty in producing simultaneous contraction of agonist and antagonist by surface stimulation may be explained by the following considerations. Although there is discrete spatial differentiation between the excitatory area for a given muscle and the inhibitory area for the antagonist, these areas are located close to one another. In addition, these two areas are often located near the excitatory area for the antagonist. Hence, current pulses applied to the surface indiscriminately activate all the regions and reveal only the predominant effects.

The columnar cortical efferent zones found in the cat's motor cortex were also found to exist in the motor cortex of the monkey(Asanuma and Rosén, 1972). An example of the results is shown in Fig. 6 in which ICMS could produce all of four thumb movements, i.e., extension, flexion, abduction and adduction. Each efferent zone had a sharp boundary and the efferent zones controlling the various movements of a joint were located close together. Each efferent zone extended along the direction of radial fibers in the gray matter, as shown by the extension area in Fig. 6. In addition, although not shown, it was found, by using the electromyograms as indicators, that the edge of a given efferent zone very frequently overlapped with the edge of another efferent zone which projected to the antagonist. This frequent overlap is a marked difference from the cat's in which simultaneous contraction of the antagonists such as shown in Fig. 4 occurred only occasionally. The difference may indicate the difference of the characteristics of the movements between these two species; the motor cortex of the monkey, especially the forelimb area may be organized in such a way that can fix a joint by simultaneously contracting the antagonists to exert a force to the outside of the body whereas in the cat, it may be organized to support the body weight against the gravity (Asanuma and Rosén, 1972).

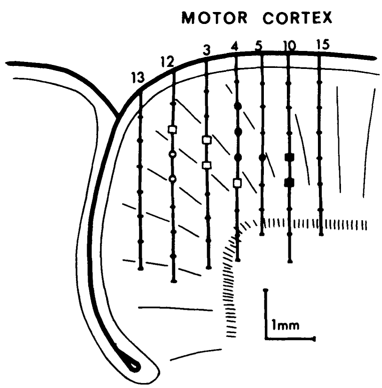


Fig.6. Distribution of effective spots within the depth of the monkey motor cortex with intracortical microstimulation (ICMS) of 5 μa. Crosses on the penetrations are the spots where ICMS did not produce any movement. O : thumb flexion, □: thumb extension, ●: thumb adduction, ■: thumb abduction. (Asanuma and Rosén, 1972).

Afferent Inputs to Cortical Efferent Zones; Input-Output Relationships

In the preceding section, it was shown that there are discrete efferent zones within the depth of the motor cortex in the cats and monkeys. A natural question then is what information do these efferent zones receive from the periphery since it is known that both the monkeys' (Malis et al., 1953) and cats' (Brooks Rudomin and Slayman, 1961, a, b. Buser and Imbert, 1961) motor cortices receive inputs from the periphery.

Before getting into the experiments, however, some technical problems had to be solved. The basic method we used consisted in, first recording the unitary activities of neurons in the motor cortex to delineate their receptive fields, then stimulating the same area through the same micro-electrode to define the motor effects. By repeating this procedure, the relationship between afferent input to and motor outflow from a given area of the cortex could be studied. The input-output relationships identified in this way, however, would be invalidated if the spread of the stimulating current was wider than the extent of the area from where the electrode could record the activities of the neurons. This problem was again resolved by inserting two electrodes into the brain, one for recording unitary spikes from a PT cell and the other for delivering ICMS. Threshold current for exciting the target PT cell was determined first by monitoring the action potentials of the target cell through the recording electrode. The stimulating electrode was then used as a recording electrode and the antidromic spike of the same PT cell was recorded through the same electrode. With this method, the relationship between current needed to excite a given cell from a given site and the size of the antidromic spike of the same cell recorded at the same site could be examined. Figure 7 shows the result. When the threshold grew higher, the spike amplitude became smaller. The majority of the neurons excited by ICMS of 10 μa or less were located close enough to the electrode so that the activities of the same cells could be recorded by the same microelectrode. When 5 μa was used, the action potentials of all the cells excited could be recorded by the same electrode.

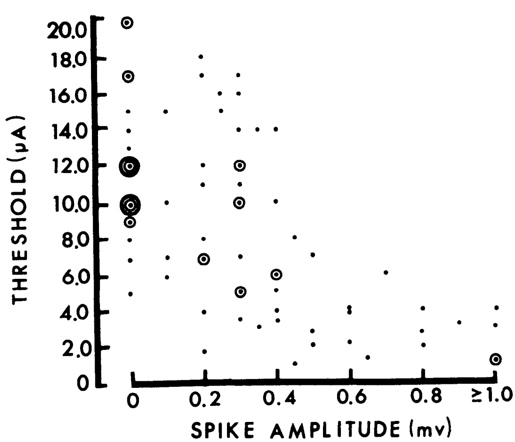


Fig.7. Relationship between the threshold currents for direct excitation of PT cells delivered through a tungsten microelectrode and the amplitude of the antidromic spikes of the same cells recorded by the same microelectrode. Circled points indicate overlap of values. (Stoney, Thompson and Asanuma, 1968).

Input-output relationships of discrete motor colonies were first examined in the cat by Asanuma, Stoney and Abzug (1968) and Sakata and Miyamoto (1968) and then in the monkey by Rosén and Asanuma (1972). In this section, the details about the monkey experiments will be described because the results from both species were essentially similar, but the monkey experiments revealed greater details of the relationships.

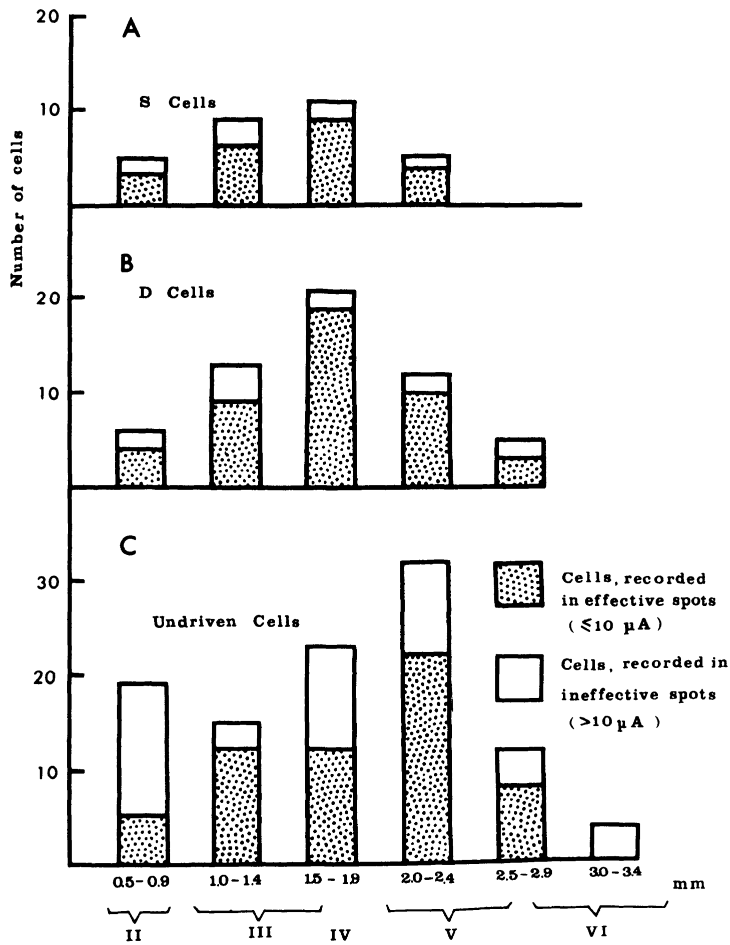


Fig.8. Depth distribution of all S-cells (A), D-cells (B) and undriven cells (C) in the monkey motor cortex. The depth values were calculated along the direction of radial fibers using histology preparations. Dotted areas show the distribution of cells found within cortical efferent zones (ICMS threshold ≤ 10 µa). Clear areas show the distribution of cells found outside of efferent zones. The approximate extent of each cortical layer is shown on the abscissa superimposed upon the depth values given in mm. (Rosén and Asanuma, 1972).

We will start with the nature of the afferent inputs to the motor cortex. Neurons recorded during this series of experiments were classified into 3 types and their distributions within the depth of the cortex are shown in Fig. 8. S-cells refers to neurons which responded to hair bending, light touch or light pressure of somewhere on the contralateral body surface. D-cells are those neurons which responded to passive joint movements and/or pressure to deep structures. There was no difference in the depth distribution between neurons driven by superficial and deep receptors but there was a marked difference between driven cells and undriven cells. Undriven cells were found more in the deep layers. Furthermore, cells found in the low threshold areas received more peripheral inputs than cells located in the high threshold areas. The overall feature of the distribution of driven cells suggests that the afferent inputs from the periphery arrive in the superficial layers of the cortex and then impulses descend synaptically to the deep layers. The fact that there were more undriven cells in the deep layers indicated that these transsynaptic impulses were not powerful enough to activate all the corticofugal neurons located in the deep layers.

An example of the distribution of S- and D- cells within a given efferent zone is shown in Fig. 9. In this experiment, the electrode was inserted into the brain and whenever unitary activities of neurons were recorded, their receptive fields were examined and then ICMS of 5 µa was delivered. In addition, the effect of ICMS was examined at 0.5 mm intervals irrespective of the existence of the spikes. As is shown, the electrode passed through the areas which produced flexion, extension, adduction and abduction of the thumb. The cells driven by skin stimulation showed the characteristic localization of their receptive fields in relation to the motor effects. Two cells found in the "thumb flexion column" were both activated from the ventral aspect of the thumb. The cells found in the columns for thumb extension, adduction and abduction were activated from the distal tip, the medial aspect and the lateral aspect of the thumb respectively. The other cells found in this area were activated by passive thumb movements or thenar pressure although some of the cells could not be driven by natural peripheral stimulation.

Other trials revealed similar results which could be summarized as follows: cells driven by peripheral stimulation were sparsely scattered in radial columns within the hand area of the monkey motor cortex and received afferent input from superficial as well as from deep receptors located in restricted parts of the distal forelimb. This columnar arrangement coincided with the columnar organization of cortical efferent zones so that each efferent column received sensory information from a portion of the limb in close anatomical relation to the muscle to which it projected. In the following section, further details about the afferent inputs will be described.

Out of 192 cells isolated from the monkey motor cortex, 37 (19%) were activated by tactile stimulation. All the receptive fields except eight were confined to non-hairy parts of the monkey's hand. The majority of the cells adapted rapidly to maintained mechanical stimulation. Fig. 10 shows the receptive fields of all driven cells found in identified thumb areas. The receptive fields of all six S- cells found in thumb flexion zones were located on the ventral aspects of the thumb (Fig. 10A). Similarly, all four cells located in thumb adduction zones were activated from the medial aspect of the thumb (Fig. 10B). Similar results were obtained for other fingers and showed that each of the efferent zones received tactile inputs almost exclusively from that side of the finger or hand which was in the direction of the movement produced by ICMS of the same zone.

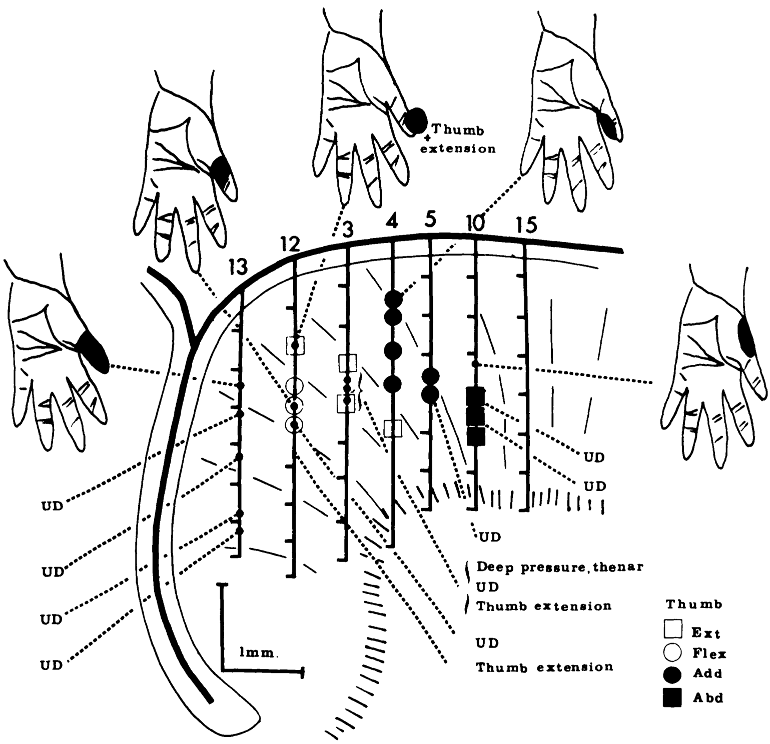


Fig.9. Reconstruction of electrode tracks and cell locations within the monkey motor cortex. Electrode penetrations (solid lines, identified by numbers) passed through efferent zones projecting to various thumb muscles. The peripheral motor effects produced by ICMS ($\leq$ 5 μa) are indicated by symbols explained in the figure. Cortical spots where 5 μa ICMS did not produce motor effects are shown by small solid lines perpendicular to the tracks. Positions of cells encountered are connected by dotted lines to figurines and descriptions which explain receptive fields and adequate stimuli. Spontaneously active cells not driven by peripheral stimulation are indicated as UD. (Rosen and Asanuma, 1972).

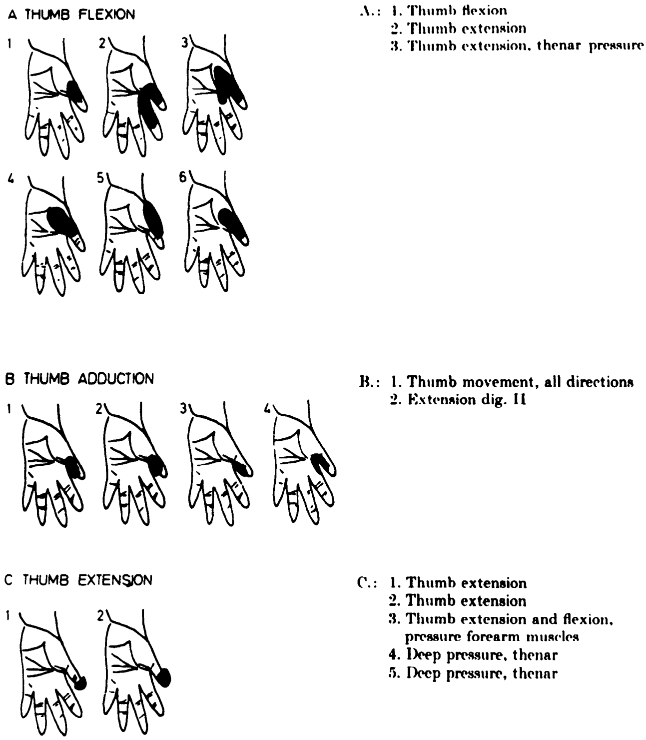


Fig.10. Summary of receptive fields and adequate stimuli of all driven cells encountered within efferent zones where ICMS ($\leq$10 μa) produced thumb extension (A), thumb adduction (B) or thumb extension (C). The receptive fields of cells activated by tactile stimuli (S-cells) are shown in figurines on the left. The type and location of the adequate stimulus for activation of cells driven by deep receptors (D-cells) are listed on the right. (Rosén and Asanuma, 1972).

Inputs from deep receptors to efferent zones are summarized in Table 1. A total of 56 cells responded to stimulation of the deep structures (D-cells). Of these, 42 responded to passive joint movement and the remainder to pressure applied to deep structures. All the cells listed in the table were found at sites where muscle contraction could be produced with ICMS of 10 μa or less. Of the 42 cells activated by passive joint movement, the majority (38 cells) were driven from the joint involved in the movement produced by ICMS. In the analysis shown in Table 1, the following assumptions were made. Cells activated by manipulation of a joint and uninfluenced by pressure applied to the bellies of the muscles stretched by the effective joint movement were considered to be activated by joint receptors (Table 1a, b). Cells driven by passive joint movement and also by pressure of the muscle stretched by the effective joint movement were considered to be activated by inputs from the receptors located in these muscles (Table 1c). This discrimination was difficult for thumb and finger movements, but could be done easily for cells driven by wrist movements because of the good anatomical separation between the joint and the forearm muscle bellies. Thirteen cells were found in zones projecting to wrist muscles and were driven by passive joint movements. Of these, 6 were activated by receptors in the wrist joint. In all these cases, the direction of joint movement adequate for activating the cells was the same as that produced by ICMS. Five cells activated by a movement opposite to the direction of ICMS induced movement were activated from muscle receptors. Two cells were driven by passive movement of the elbow. Thus the cells located in zones projecting to the wrist muscles received information from the receptors in the wrist joint as well as the receptors in the wrist muscle to which the cortical zone projected. Cells located in the thumb and finger zones could be driven by a passive movement opposite to that induced by ICMS as shown in Table 1b, but it is possible that they were activated by afferent impulses from receptors situated in the intrinsic hand muscles. The muscle receptors responsible for the corticipetal impulses are unlikely to be the annulospiral endings because group I afferent fibers have not been found to project to the motor cortex)Oscarson and Rosén, 1963, Phillips, Powell and Wiesendanger, 1971).

Table 1.
Adequate Stimuli of D-Cells Recorded in Efferent Zones

Peripheral stimulus	Thumb	Finger	Wrist
PASSIVE JOINT MOVEMENT			
a) Joint receptor, Same direction as ICMS-effect-	6	4	6
b) Joint receptor, Opposite direction to ICMS-effect-	2	5	0
c) Muscle receptor, Opposite direction to ICMS-effect-	2	4	5
d) Joint, different from that engaged in ICMS-effect -	1	1	2
Deep pressure ----------------------------------	2	4	2
Total number of cells ----------------------------	13	18	15

In summary, cells in a given cortical efferent zone receive information about the contraction of the target muscle as well as about the movement of the target joint. In addition, they receive inputs from the skin area most likely to be excited by the movement elicited by the contraction of the target muscle during the course of a manipulatory sequence. In short, the afferent inputs converge into an efferent zone as a sequence of the contraction of the target muscle. What would be the functional significance of these inputs in the performance of movements? The pattern of somatic sensory inputs which were found to reach the motor cortex appears to be more suited to a role as feedback information, of possible use for modulating the output from individual cortical columns during the movements, rather than being involved in the initiation of motor activity. The tactile placing reaction (Bard, 1938) is a reflex type movement known to be mediated by the motor cortex. Ablation of the sensory cortex abolishes the placing reaction whereas it does not abolish the evoked potential in the motor cortex (Malis, Pribram and Kruger, 1953). Automatic grasping reaction can be elicited by tactile stimulation of the hand of monkeys and humans (Denny-Brown, 1960). This reaction does not disappear after removal of the sensory cortex but is abolished by ablation of the motor cortex or by section of the pyramidal tract. The input-output columns described in this article may serve as the neuronal basis for this reaction although it is known that some type of grasping reaction (e.g. instinctive grasping reaction) involves sequential contraction of many muscles in a specific pattern which makes it difficult to be explained by the input-output relationships described here.

Synaptic Connections Within the Cortical Efferent Zone

The existence of a columnar organization within the motor cortex in the cats and monkeys was based on the observation that stimulation within a given column produced contraction of the same muscle. The existence of vertically connected neuronal aggregates within the cortical gray substance has long been proposed by Lorente de Nó (1949). The first physiological evidence which indicated the existence of vertical arrangement of neurons was provided by Mountcastle (1957) who examined the receptive fields of neurons in the sensory cortex of the cats. He found that the neurons of similar receptive fields were arranged in a vertical direction along the radial fibers. Further insight about the columnar organization was presented by Hubel and Wiesel (1962) who studied the details of information processing within the cat's visual cortex. Except for the histological studies (Colonnier, 1966: Lorente de Nó, 1949), the evidence for the existence of a columnar organization was indirect to the extent that it was inferred from similarities of the receptive fields of neurons or from similarities of the effects of stimulation within a column. On the other hand, the histological studies have shown the existence directly, but could not elucidate on the details of the organization.

To provide another evidence which will give further insight of the columnar organization, we have undertaken the following electroanatomical experiments (Asanuma and Rosén, 1973). Two electrodes were inserted into the motor cortex, a micropipette electrode for intracellular recordings and a tungsten electrode, for ICMS. Weak ICMS of 4 μa was delivered through the tungsten electrode and postsynaptic potentials (PSPs) were recorded through the other electrode. Two independent manipulators were used for insertions and they were aligned in such a way that the distance between the tips of the electrodes could be calculated simply from the scales on the manipulators. Whenever a successful intracellular recording was made, a current (20 μa, 5 sec.) was passed through the tungsten electrode and a lesion was made and the location was identified by the later histological examination. By this method, we could identify the site of stimulation and also the location of the cell from which the intracellular recording was made.

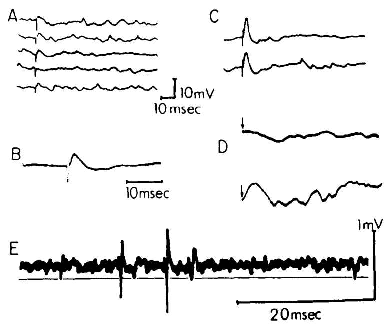


Fig.11. Postsynaptic potentials obtained from a cortical neuron. A: unitary EPSPs in response to threshold ICMS (2 μa). EPSP appeared in second, third and fifth lines. B: unitary EPSP averaged by a computer. C: EPSPs in response to stronger stimulation (4 μa). D: EPSPs which are related to discharge of other neurons. Upper line - lack of summed EPSP when averaging computer was triggered by large spikes shown in E. Lower line - summated EPSP when the computer was triggered by small spikes. E: extracellular spikes recorded by tungsten electrode simultaneously with the intracellular recordings. Line underneath the record indicates the level of spike discriminator when summed EPSP shown in D was obtained.(Asanuma and Rosén, 1973).

Figure 11 shows an example of the results. In this example, ICMS of 4 μa produced a large EPSP as shown in C. The intensity of stimulus was then decreased and at threshold strength, the response appeared in all or none fashion as shown in Fig. 11A. Note that when the response appeared, the size and time course of the EPSP were similar to those of small synaptic potentials which occured spontaneously, suggesting that the response to threshold ICMS was unitary in character. The likely interpretation is that although threshold stimulation excited several cells around the stimulating electrode, only one of these cells had synaptic contact with the penetrated cell. This hypothesis was tested in the following way. Without changing its position, the tungsten electrode used for ICMS was then used to record the spontaneous activities of neurons around the electrode (Fig. 11E). These unitary spikes were used to trigger an averaging computer and the unitary EPSPs which followed the spikes could be summed (Mendell and Henneman, 1968). When the computer was triggered by large or medium size spikes, summation of EPSPs did not occur as shown in the first line of Fig. 11D. By lowering the gate of the discriminator and triggering the computer with small spikes, a response shown in the second line of Fig. 11, D suddenly appeared. The results indicate that the summed response was produced by the discharges of one or a few of the neurons represented by small spikes in Fig. 11 E. The correlation between the spikes and the PSPs was examined, in this series of experiments, whenever a stable intracellular recording was made, but summed PSPs appeared only in a group of cells which will be described in the following.

Latency distribution of PSPs in relation to the distance between stimulating and recording electrodes is shown in Fig. 12. The minimum latency observed was 0.8 msec, which may give an impression that this could have been di-synaptic PSP. This seemingly long latency could be accounted for if we think of the factors such as utilization time (0.2 msec: stimulus pulse duration), delay time for the initiation of the spike after local response (unknown), conduction time along the fibers (unknown) plus synaptic delay of 0.3-0.5 msec (Eccles, 1964). For di-synaptic PSPs, additional factors such as delay time for initiation of spikes after initiation of EPSP, conduction time along the fibers, and another synaptic delay have to be added. From these reasons, a group of PSPs, which had a peak latency at 1.0 msec (Fig. 12, right) and marked with open circles (Fig. 12 left) are classified as monosynaptic PSPs. Without exception, all the correlated PSPs observed by using the method shown in Fig. 11 appeared in these cells which produced monosynaptic PSPs. From these it is proposed that "whenever a summated PSP which is related to spontaneous discharges of a given cell appears then these two neurons are connected monosynaptically." This hypothesis seems to be reasonable because a given unitary PSP is unlikely to elicit a discharge of the cell to produce a secondary PSP in a third cell which is still time locked with the original spike.

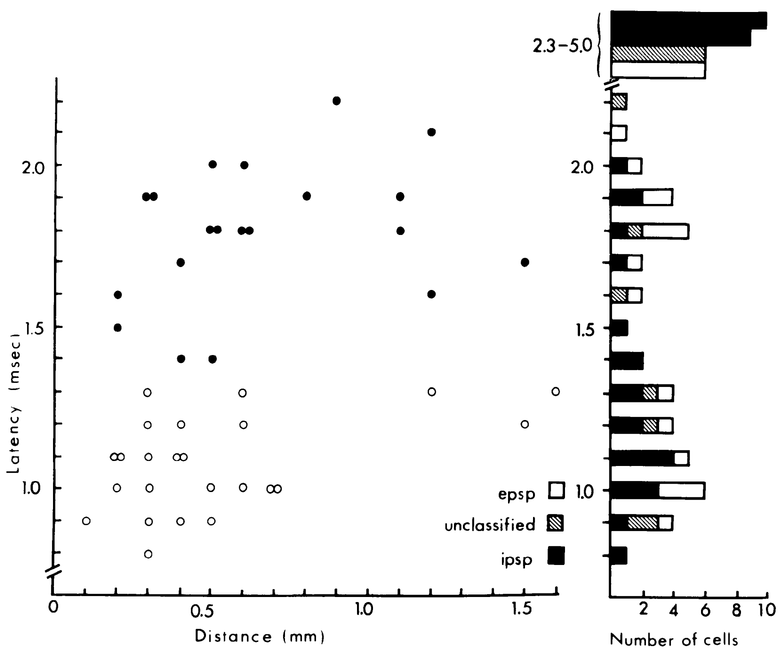


Fig.12. Latency distribution of postsynaptic potentials to ICMS of 4 μa. Left: Latency distribution against distance between stimulating and recording electrodes. Open circles indicate monosynaptic PSPs. Right: latency histogram of PSPs appeared within 5.0 msec after stimulation. Hatched bars which are labelled as unclassified indicate depolarizing PSPs recorded by KCl electrodes. The rest of PSPs were recorded by K-Cit. electrodes. (Asanuma and Rosén, 1973).

Altogether 24 cells which received monosynaptic PSPs by ICMS delivered to the neighboring tissue within the motor cortex could be isolated. Table 2 shows the type of PSPs recorded from these 24 cells in relation to the stimulating sites. The result suggests that although there are distinct laminas within the gray matter of the cortex, each lamina contains a mixture of inhibitory and excitatory interneurons. We could not find an aggregation of neurons which was located in a particular region (or depth) having a monolithic function (excitatory or inhibitory).

Table 2.
Classification of monosynaptic PSP's in reference to stimulating sites.

	Layers					
Effects	II	III	IV	V	VI	Total
EPSP	0	3	2	2	1	8
IPSP	1	3	1	5	2	12
untyped*	0	3	1	0	0	4

* untyped PSPs were obtained by KCl electrode.

The next question was how far does each neuron send its axon within the cortex. Figure 13 shows the result. Since there was no particular layer which had a simple function and since the number of the samples was small, the sites of stimulation were grouped into three, i.e., superficial (layers II and upper III), intermediate (lower III and IV) and deep (V and VI layers). The intensity of ICMS used was 4 μa which presumably excited about 10 neurons around the electrode (Stoney et al. 1968). Stimulation with this intensity, however, did not produce any observable monosynaptic PSPs in the majority of cells around the electrode (Fig. 13A). Among the cells located near the stimulating electrode, only one-third revealed observable PSPs, indicating that neurons in the cortex did not send axons diffusely to the neighboring cells. Since we know that the averaging computer was able to detect even the unitary PSPs, the chances of our missing the electrically meaningful PSPs in these two-thirds of the cells were very small. The result indicated that an average of one out of 30 neighboring neurons had a monosynaptic connection with a given cortical neuron. The extent of monosynaptic connections from superficial and intermediate layers was limited in the horizontal as well as in the vertical direction. The maximum horizontal spread was 0.45 mm and ICMS in the superficial layers did not produce monosynaptic PSPs in the neurons located in the deep layers. However, when the deep layers were stimulated, the spread of the effect was far more extensive and monosynaptic PSPs were recorded even in the superficial layers although the horizontal spread was still restricted within 0.6 mm. The spread of polysynaptic connections was wider than that of monosynaptic connections as shown in Fig. 13 B. There seems to be a general trend that the inhibitory effects from the superficial and intermediate layers spread wider than the excitatory effects.

The result revealed that there was a virtual lack of monosynaptic connections from neurons in the superficial layers to neurons in the deep layers where the large corticofugal neurons are located. This

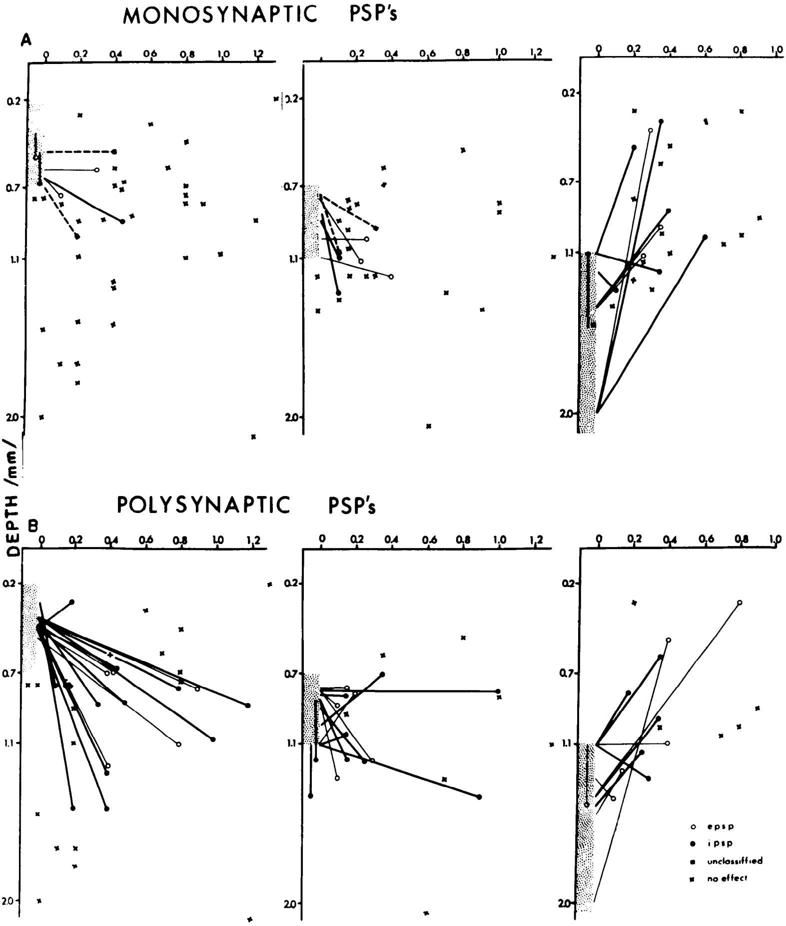


Fig.13. Spread of mono- and polysynaptic connections within the cortex. Sites of stimulation are grouped into superficial, intermediate and deep layers and are marked with stipples. Each line (heavy, light and hatched) connects sites where ICMS was delivered and PSP was recorded. Ordinate: depth along the radial fibers. Abscissa: horizontal distance from the stimulating electrode. Unclassified PSPs were recorded by KCl electrodes. Crosses indicate positions where intracellular recordings were made, but ICMS did not produce PSPs. (Asanuma and Rosén, 1973).

led us to conclude that impulses arriving at the motor cortex through specific and non-specific as well as association fibers activate cortical interneurons in the superficial and intermediate layers. These interneurons, in turn inhibit or excite the next order neurons not in a diffuse fashion but in a specific way according to their selective connections within the cortex. In view of the short horizontal spread of their monosynaptic connections, these interneuronal networks, as a whole, fit into a columnar pattern which extends along the direction of the radial fibers. When the impulses finally reach the deep layers, corticofugal impulses are initiated and at the same time, the impulses are sent back to the neurons in the superficial and intermediate layers constituting a feedback loop within the motor cortex. The wider spread of polysynaptic excitatory and inhibitory effects in the superficial and intermediate layers may be correlated with mutual facilitatory and inhibitory interactions between adjacent columns in the motor cortex which has been described previously (Asanuma and Ward, 1971).

Final Comments

One of the questions imposed on this series of experiments was "whether the motor cortex thinks in terms of movements or muscles?" The answer obtained was "the motor cortex thinks in terms of muscles." It has been shown that each muscle is represented by a small volume of the cortex which has a discrete boundary and is located within the depth of the motor cortex i.e., the cortical efferent zone. Stimulation within a given efferent zone produced contraction of a given muscle, but did not necessarily inhibit the antagonist, instead sometimes facilitated contraction of the antagonist. Studies about the afferent inputs to cortical efferent zones revealed that each efferent zone received peripheral inputs specifically related to the contraction of the muscle to which the efferent zone projected. These afferent pathways constituted ascending link of a loop circuit which connects the motor cortex and the periphery. A schematic diagram of this closed loop is shown in Fig. 14.

This loop circuit by itself, however, does not explain how the movement is initiated and also how it is organized in a purposeful way. The afferent inputs involved in this loop are topographically organized and in many cases, specific in a particular modality. These inputs are most likely to have been transferred through the dorsal column - medial lemniscus -n. ventralis posterolateralis system as had already been inferred (cf. Brooks and Stoney, 1971). The motor cortex, however, is known to receive most powerful inputs from the n. ventralis lateralis which does not receive inputs from the dorsal column - medial lemniscal system. Neurons in VL are shown to receive non-specific inputs from the periphery in parallel to the inputs from the cerebellum (Massion and Albe-Fessard, 1965, a, b). Stimulation of VL is known to produce powerful mono- and polysynaptic activation of PT cells (Amassian and Weiner, 1966). Furthermore, it has been shown that the projection fibers from VL to the motor cortex branch somewhere in the white matter and reach different parts of the motor cortex (Massion and Rispal-Padel, 1973). Obviously, the VL - Cx system has a different characteristic from the lemniscal - Cx system suggesting that the functional significance of this system is different from the loop system that we have studied. Investigation about this system has just been started in our laboratory to further increase our understanding of how the motor cortex controls the movement.

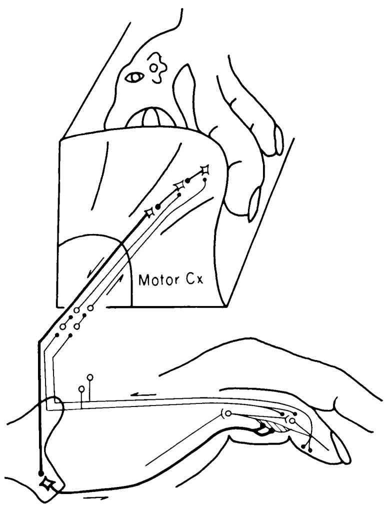


Fig.14. Schematic diagram indicating a closed loop between the motor cortex and the periphery. Activation of a cortical efferent zone pro-

lated to the muscle contraction and send impulses back to the original cortical efferent zone.

Acknowledgements

This series of works has been supported continuously by the grants from the National Institute of Neurological Diseases and Stroke and also from the Health Research Council of the City of New York. The author would like to express his gratitude to Miss K. Alexieva for her technical assistance during the experiments and also to Dr. C. Ghez for his helpful criticism in preparing the manuscript.

REFERENCES

Amassian, V.E., and H. Weiner: Monosynaptic and polysynaptic activation of pyramidal tract neurons by thalamic stimulation. In: The Thalamus, edited by D.P. Purpura and M.D. Yahr. New York: Columbia University Press, 255-282, 1966.

Asanuma, H., and I. Rosén: Topographical organization of cortical efferent zones projecting to distal forelimb muscles in the monkey. Exptl. Brain Res. 14: 243-256, 1972.

Asanuma, H., and I. Rosén: Spread of mono- and polysynaptic connections within cat's motor cortex. Exptl. Brain Res. 16: 507-520, 1973.

Asanuma, H., and H. Sakata: Functional organization of a cortical efferent system examined with focal depth stimulation in cats.

J. Neurophysiol. 30: 35-54, 1967.
Asanuma, H., S.D. Stoney, Jr., and C. Abzug: Relationship between afferent input and motor outflow in cat motosensory cortex. J. Neurophysiol. 31: 670-681, 1968.
Asanuma, H., S.D. Stoney, Jr., and W.D. Thompson: Characteristics of cervical interneurones which mediate cortical motor outflow to distal forelimb muscles of cats. Brain Res. 27: 79-95, 1971.
Asanuma, H., J.E. Ward: Patterns of contraction of distal forelimb muscles produced by intracortical stimulation in cats. Brain Res. 27: 97-109, 1971.
Bard, P.: Studies on the cortical representation of somatic sensibility. Bull. New York Acad. Med. 14: 585-607, 1938.
Bernhard, C.G., and E. Bohm: Cortical representation and functional significance of the corticomotoneuronal system. Arch. Neurol. and Psychiat. 72: 473-502, 1954.
Brooks, V.B., P. Rudomin, and C.L. Slayman: Sensory activation of neurons in the cat's cerebral cortex. J. Neurophysiol. 24: 286-301, 1961.
Brooks, V.B., P. Rudomin, and C.L. Slayman: Peripheral receptive fields of neurons in the cat's cerebral cortex. J. Neurophysiol. 24: 302-325, 1961.
Brooks, V.B., and S.D. Stoney, Jr.: Motor mechanisms: the role of the pyramidal system in motor control. Ann. Rev. Physiol. 33: 337-392, 1971.
Buser, P., and M. Imbert: Sensory projections to the motor cortex in cats. In: Sensory Communications, edited by W.A. Rosenblith. New York: Wiley , 607-626, 1961.
Chang, H-T, T.C. Ruch, and A.A. Ward: Topographical representation of muscles in motor cortex of monkeys. J. Neurophysiol. 10: 39-56, 1947.
Colonnier, M.L.: The structural design of the neocortex. In: Brain and Conscious Experience, edited by J.C. Eccles. New York: Springer-Verlag, 1-23, 1966.
Davies, P.W.: Chamber for microelectrode studies in the cerebral cortex. Science 124: 179-180, 1956.
Denny-Brown, D.: Motor mechanisms - Introduction: the general principles of motor integration. In: Handbook of Physiology. Am. Physiol. Soc. 2: 781-796, 1960.
Eccles, J.C.: The Physiology of Synapses. Berlin: Springer-Verlag, 1964.
Harman, P.J.: On the significance of fissuration of the isocortex. J. Comp. Neurol. 87: 161-168, 1947.
Hassler, R., and K. Muhs-Clement: Architektonisher Aufbau der sensomotorischen und parietalen Cortex der Katze. J. Hirnforsch. 6: 377-420, 1964.
Hering, H.E., and C.G. Sherrington: Ueber Hemmung der Contraction Willkürlicher Muskeln bei elektrisher Reizung. Pflüg. Arch. ges. Physiol. 68: 222-228, 1897.
Hubel, D.H., and T.N. Wiesel: Receptive fields, binocular interaction and functional architecture in the cat's visual cortex. J. Neurophysiol. 160: 106-154, 1962.
Landgren, S., C.G. Phillips, and R. Porter: Cortical fields of origin of the monosynaptic pyramidal pathways to some alpha motoneurones of the baboon's hand and forearm. J. Physiol. London. 161: 112-125, 1962.

Lorente de Nó, R.: Cerebral cortex: architecture, intercortical connections, motor projections. In: Physiology of the Nervous System by J.F. Fulton. Chapt. 15, 3rd Ed. New York-London: Oxford University Press, 1949.

Malis, L.I., K.H. Pribram, and L. Kruger: Action potentials in motor cortex evoked by peripheral nerve stimulation. J. Neurophysiol. 16: 161-167, 1953.

Massion, J., and P.A. Albe-Fessard: Activities evoquees chez le chat dans la region du nucleus ventralis lateralis par diverses stimulations sensorielles. I. etude macrophysiologique. Electroenceph. clin. Neurophysiol. 19: 433-451, 1965.

Massion, J., and P.A. Albe-Fessard: Activities evoquees chez le chat dans la region du nucleus ventralis lateralis par diverses stimulations sensorielles. II. etude microphysiologique. Electroenceph. clin. Neurophysiol. 19: 452-469, 1965.

Massion, J., and L. Rispal-Padel: Differential control of motor cortex and sensory areas on ventrolateral nucleus of the thalamus. In: Corticothalamic Projections and Sensorimotor Activities, edited by T.L. Frigyesi, E. Rinvic, and M.D. Yahr. New York: Raven Press. In press, 1973.

Mendell, L.M., and E. Henneman: Terminal of single Ia fibers: Distribution within a pool of 300 homonymous motor neurons. Science 160: 96-98, 1968.

Mountcastle, V.B.: Modality and topographic properties of single neurons of cat's somatic sensory cortex. J. Neurophysiol. 20: 408-434, 1957.

Oscarsson, O., and I. Rosén: Projection to cerebral cortex of large muscle-spindle afferents in forelimb nerves of the cat. 169: 924-945, 1963.

Phillips, C.G., T.P.S. Powell, and M. Wiesendanger: Projection from low-threshold muscle afferents of hand and forearm to Area 3a of baboon's cortex. J. Physiol. London. 217: 419-446, 1971.

Rosén, I., and H. Asanuma: Peripheral afferent inputs to the forelimb area of the cat monkey motor cortex: Input-output relations. Exptl. Brain Res. 14: 257-273, 1972.

Ruch, T.C.: The cerebral cortex: Its structure and motor function. In: Physiology and Biophysics, edited by T.C. Ruch and H.D. Patton. Philadelphia: Saunders, 252-273, 1965.

Sakata, H., and J. Miyamoto: Topographic relationship between the receptive fields of neurons in the motor cortex and the movements elicited by focal stimulation in freely moving cats. Japan. J. Physiol. 18: 489-507, 1968.

Sherrington, C.: The integrative action of the nervous system. New York: Scribner. (Reprinted 1947, Cambridge University Press).

Sholl, D.A.: A comparative study of the neuronal packing density in the cerebral cortex. J. Anat. 93: 143-158, 1959.

Stoney, S.D., Jr., W.D. Thompson, and H. Asanuma: Excitation of pyramidal tract cells by intracortical microstimulation: Effective extent of stimulating current. J. Neurophysiol. 31: 659-669, 1968.

MUSCLE-NERVE TRANSPLANTS

Experimental Models to Study Influences on Differentiation*

ETHEL COSMOS
Institute for Muscle Disease, Inc.
New York City

An interdependence of nerve and muscle has been recognized by scientists for over a century and yet many factors underlying this coexistence still remain theoretical. The established alterations of muscle which result from neurectomy, tenotomy, immobilization, injury, chemical nerve blocks, and many other techniques used to inhibit the passage of trophic effects from the nerve to its specific muscle partner concede the necessity of an intact nerve for the maintenance of the integrity of the mature muscle (as a review, Gutmann, 1962; Gutmann and Hník, 1963; Guth, 1968).

In tissue culture the early formation of myotubes occurs in the absence of added neural tissue (as a review, Mauro, Shafiq, and Milhorat, 1970; Banker, Przybylski, Van der Meulen and Victor, 1972). But as shown more recently (Peterson and Crain, 1972), the addition of fetal spinal cord to culture media is essential to the maturation and to the maintenance of specific cell cultures. Certainly in vivo experiments designed to block the nerve transmitter substance (Drachman, 1964) during embryonic development or to neurectomize neonatal muscle establish the inability of muscle to complete its ontogenetic period without adequate innervation (Cosmos, 1966a; Engel and Karpati, 1968).

Evidence for the multiple role of neurons during the period of differentiation has been furnished by nerve cross-union studies (Buller, Eccles and Eccles, 1960a). In these experiments the normal physiological characteristics of muscles were determined by the type of innervation imposed upon them. The concept of a "neurotrophic influence" was again under investigation as a specific substance of unknown definition that was important to the physiological behavior of fast and slow muscles**. A period of intense investigation ensued to establish the biochemical and histochemical changes associated with the alteration of the physiological behavior of muscle after nerve cross-union (as a review, Milhorat, 1967; Romanul and Van Der Meulen, 1967; Bárány and Close, 1971). Many important observations resulted from these investigations; one of which was a reemphasis of the heterogeneous nature of muscle (Padykula, 1952).

---

* Taken from the introductory remarks given at the session on Skeletal Muscle I at the 1973 Federation Meetings. This investigation was supported by a grant from the Muscular Dystrophy Associations of America, Inc., and by a USPHS Award NS-06942-06.

** A conference on the Trophic Function of the Neuron organized by Drs. Daniel B. Drachman and Alfred A. Smith and sponsored by the New York Academy of Sciences was held in New York City on March 5 to 7,1973. The Proceedings (available within the year) will review the most recent progress in this very complicated area of nerve-muscle relationships.

Muscle is not completely fast or slow, or white or red; instead, it is composed of degrees of mixtures of fiber types. These muscles show specific trends in ontogeny (Buller, Eccles and Eccles, 1960b; Cosmos, Butler and Scott, 1965; Cosmos, 1966b; Cosmos and Butler, 1967) as do the nerves that innervate them (Nyström, 1968).

As a result of these endeavors there has emerged a stronger union between the disciplines of physiology and histochemistry at the level of neuron-muscle fiber interaction. Thus, recent studies are focused on the identification of fibers within specific motor units. The stimulation of individual motoneurons has shown that a motor unit encompasses a homogeneous population of muscle fiber types (Edström and Kugelberg, 1968). In fact, three types of motor units have been classified according to a correlation of their physiological and histochemical properties (Burke, Levine, and Zajac, 1971).

It is important that the nerve cross-union experiments of Buller, Eccles and Eccles (1960a), which initiated intense investigations into nerve-muscle interrelationships during the last decade, indicate a more complete reversal of fast or white muscle than of slow or red muscle. White muscle, which develops its adult characteristics late in ontogeny (Buller, Eccles and Eccles, 1960b; Cosmos, Butler and Scott, 1965; Cosmos, 1966b; Bass, Lusch and Pette, 1970; Copper, Cassens, Kastenschmidt and Briskey, 1971), submits more readily not only to experimental alterations of laboratory origin but also to pathological derangements of genetic origin. Thus, an analysis of the ontogeny of muscles from birds with hereditary muscular dystrophy reveals an impairment in the maturation of white muscle (Cosmos, 1965, 1966b, 1970a); in this species red muscle seems unaffected (Cosmos and Butler, 1967). This abnormality is expressed as an arrest in the differentiation of white muscle (pectoralis) characteristics; instead, the immature pattern of a mixture of fiber types is retained. Whereas the normal pectoralis differentiates rapidly ex ovo to a nearly homogeneous white muscle, that of the dystrophic bird differentiaties to a heterogeneous, haphazard mixture of fibers. This haphazard development is attributed to the loss of mechanisms which normally control the organized process of muscle differentiation. Thus, the genetically abnormal muscle presents an interesting experimental tissue characterized by chaotic metabolic and morphogenic development resulting from an unleashing of the controls. Our challenge then was to identify or at the most to research these controls.

Since a specific fiber type is selected as a target for the dystrophic abnormality, the implication of a neuronal control seemed reasonable or at least fashionable for the sixties. Our original strategy was to study denervation effects and then to superimpose on these nerve cross-union studies. However, this approach was abandoned for two reasons: 1) The neurectomized dystrophic muscle succumbed rapidly to denervation influences compared to the more gradual effects noted with the aneural normal tissue (Cosmos, 1966a). 2) The location of the afflicted pectoralis in the avian species made cross-union of motoneurons impossible. Such experiments have been achieved with the avian latissimus dorsi (Jirmanová, Hník and Zelená, 1971) but not with the pectoral muscles.

However, the alternative approach of cross-muscle experiments seemed to offer a solution: Instead of bringing a foreign nerve to a muscle, we could transplant a muscle to a foreign nerve.

To our knowledge the most successful technique of muscle transplantation is that introduced by Professor Studitsky and his co-workers. My first exposure to this method was in the summer of 1959 at an International Union of Physiological Sciences held in London where I was a post-doctoral fellow at University College. I unexpectedly attended a session on the autotransplantation of minced rat muscle by Dr. A. N. Studitsky, a scientist from the U. S. S. R. During his presentation he showed films of the intact rat gastrocnemius, the excised and finely minced muscle, and then the muscle which had regenerated from the fragments. By the end of the first week, nerve fibers began to enter the graft and, by the end of three weeks, the regenerate responded to indirect stimuli. Furthermore, if a nerve was not allowed to innervate the graft, it commenced to atrophy after about 10 days of regeneration. This established that neurons play an important role both in the regeneration and in the maintenance of the graft. I recall that at that time I felt it was a novel but impossible technique. Since most of Professor Studitsky's early experiments were reported in Russian, I refer you to a recent monograph on muscle transplantations in which all of the work of Studitsky's group is reviewed (Carlson, 1972).

Our strategy was to test the extramyogenic influences of normal hosts on the growth and differentiation of transplanted dystrophic muscle. In turn, the extirpated normal muscle could be exposed to the dystrophic influences of the abnormal host. Since our interests focused on developmental patterns, our operational techniques were performed with the immature muscle of newly hatched chicks instead of with the mature muscle reported by the Studitsky group. In order to avoid problems of incompatibility between two different strains of birds, we first attempted the crosses between chicks hatched from an embryonic parabiotic union of normal and dystrophic eggs, 9 to 12 days in ovo (Lazzarini, 1960). This technique was abandoned primarily because of the poor survival of successful parabiotics. However, it was of interest that studies on some of the successful parabiotics indicated no change in the expression of dystrophy as a result of the embryonic partnership (Cosmos, unpublished observations).

The viability of heterotransplants was excellent. During the first month the minces became innervated and vascularized and they assumed the outline of the pectoral muscle. However, histochemical examination of the regenerates identified characteristics of the donor muscle. Thus, the regenerated minces were not influenced by host factors during the period of their differentiation. As a result of this experimental model, we concluded that the dystrophic abnormality in this species is inherent in the cell (Cosmos, 1970b; Cosmos and Butler, 1971a, b, 1972). To eliminate the possibility that a neuronal influence was preestablished during embryogenesis, we transplanted both pectoral muscles from 12 day embryos to newly hatched chicks. Again the host could not alter the characteristics of the regenerates.

Even though the technique of heterotransplantation of avian muscle has not been tested by other investigators, a similar model has been employed for the investigation of murine dystrophy (Laird and Timmer, 1965, 1966). Although these investigators crossed only portions of muscle between normal mice and mice with hereditary muscular dystrophy, the results reported were similar to those of the avian transplants, i.e., the retention of donor characteristics in foreign hosts. More recently the cross-transplantation of entire muscle minces of sexually mature mice was accomplished by Salafsky (1971) with the conclusion that the neurons of normal hosts were effective in imposing normal physiological behavior on dystrophic regenerates at the end of 77 days of transplantation. In our cross-transplantation studies of the gastrocnemius of 6 week old normal and dystrophic littermates (129/ReJ Bar Harbor strain of mice with hereditary muscular dystrophy), a histochemical analysis of the dystrophic regenerate revealed abnormalities in this tissue (Cosmos, Butler and Milhorat, 1973). From this observation we could not conclude a normalizing influence by the host even up to 6 months of transplantation.

To equate our experiments on the avian and murine dystrophies, we felt that it was necessary to perform the operational procedures on immature mice. We were limited in the immature period selected for these experiments since the clinical signs of dystrophy are not detected until about 10 to 18 days after birth. At this period, both normal and dystrophic muscles have not attained their adult profile of distribution of fiber types; in addition, the dystrophic tissue lags behind that of normal in its degree of differentiation. A disbalance in speed of development is not limited to the individual muscles but it extends to the animals themselves. The normal mouse is a healthy and actively growing animal; the dystrophic mouse is a deteriorating one. The former presents a physiologically sound environment for its mince; the latter surrounds the regenerate with muscles failing both structurally and physiologically (Sandow and Brust, 1958; Brust, 1966; Douglas and Baskin, (1971).

For the experiments with the sexually immature mice we transplanted the tibialis anterior (TA) as a mince between two littermates, normal (N) and dystrophic (D). The normals from common litters are of mixed genetic background; some are homozygous normals and others, heterozygous. A second series of similar experiments was completed with homozygous normal and dystrophic mice (non-littermates).

The experimental plan was as follows:

N heteromince	-	normal muscle transplanted as a mince to a dystrophic host.
D heteromince	-	dystrophic muscle transplanted as a mince to a normal host.
N automince	-	normal muscle removed, minced, and returned to original site (N host).
D automince	-	dystrophic muscle removed, minced and returned to original site (D host).

In the series done with the immature littermates, analysis of the regenerates between 3 to 26 weeks of transplantation revealed that all viable regenerates assumed the position and outline of the TA (Fig. 1) but none were successful in reduplicating the fiber type distribution characteristic of this muscle (Fig.2), i.e., a crown predominant in anaerobic fibers and a core composed mainly of aerobic fibers. Instead, a variety in the pattern of distribution of fiber types was noted between the regenerates. Of 12 dystrophic heteromінces done, 2 failed to regenerate, 5 regenerated poorly in that at least one half of the tissue was replaced by lipid, and the remaining 5 were full tissues. In the latter there was no correlation between the age of the transplant and the degree of improvement. At 3 weeks postoperatively the D heteromince histochemically resembled a 2 week dystrophic muscle (at time of transplant) in its stage of differentiation; from 9 to 26 weeks it revealed a mixture of all fiber types in a variety of patterns. Nerve endings (cholinesterase reaction) either were restricted to a central zone as in the normal tissue (cf Figs. 3 and 4) or were diffuse especially in areas of deterioration (Fig. 5). A comparison of the structure of a D heteromince after five months of transplantation (Fig. 6) reveals few similarities to the normal TA of the unoperated leg (Fig. 2). There seems to be a tendency for the accumulation of some anaerobic fibers in the upper crown area of the section; however, sections further into the muscle demonstrate a deterioration of this area (Fig. 7). A deterioration of fibers with anaerobic enzymic activities is noted during the wasting period of a dystrophic muscle in its natural environment (Cosmos, Butler and Milhorat, 1973).

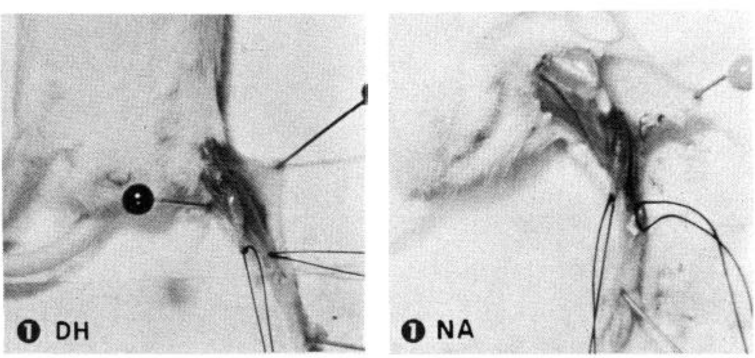


Fig.1. Photographs of regenerates in normal hosts 6 months postoperatively. The underneath muscle is the extensor digitorum longus. DH is the dystrophic heteromince and NA is the normal automince.

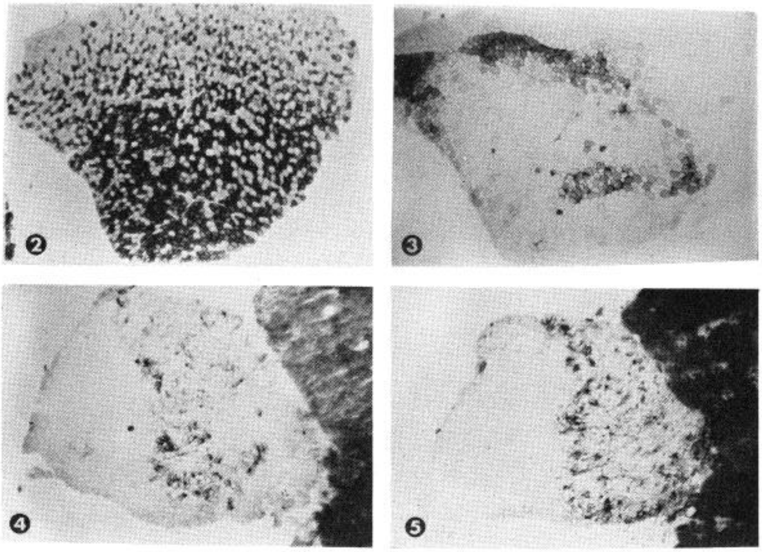


Fig.2. Photomicrograph of the mature TA from a normal mouse. Frozen section incubated for succinic dehydrogenase (SDH), the mitochondrial enzyme characteristically high in aerobic fibers. For method see Cosmos and Butler (1967).

Figs. 3,4,5. Photomicrographs of frozen sections of the normal TA and the regenerated D heteromince (19 wk postoperatively) stained for cholinesterase (CHE) activity to demonstrate nerve endings. Reaction in the normal muscle (3) is restricted to the area between the white crown and the red core. In one section of the regenerate (4), the localization of nerve endings is similar to that of the normal (cf 3 and 4). However, other areas of the D heteromince show a more diffuse distribution of CHE activity associated with deterioration (5).

An ontogenetic analysis of the TA of the dystrophic mouse reveals an unusual ability of this muscle to differentiate towards a normal pattern at about 4 to 7 weeks after birth. Following this period, the muscle loses mass and fibers with weak anaerobic enzymic activities disappear. Even though the ability of the dystrophic muscle to mimic the topography of normal tissue is expressed maximally for only a short period during its ontogeny, it is conceivable that in the functional environment of a normal host, this natural potential of a dystrophic tissue could be expressed and maintained for a prolonged period. However, even in such an environment the wasting characteristics of the abnormal muscle should be expressed eventually. Such an interpretation is quite suitable to describe the development and the deterioration of dystrophic muscle regenerating in a normal host. The entire process of dystrophy in this environment seems to be extensively prolonged.

In contrast to the D heterominces, the N autominces differentiated a distribution of fibers more closely resembling that of normal muscle.

Normal tissue placed in the dystrophic host (N heteromince) was viable up to the 26 weeks of transplantation studied. This was in sharp contrast to the failure of the dystrophic muscle to regenerate when returned to a dystrophic host. The fact that some D heterominces fail to regenerate and that some normal minces in either host regenerated poorly could be attributed to the variable genetic background of the normal animal as either donor or host.

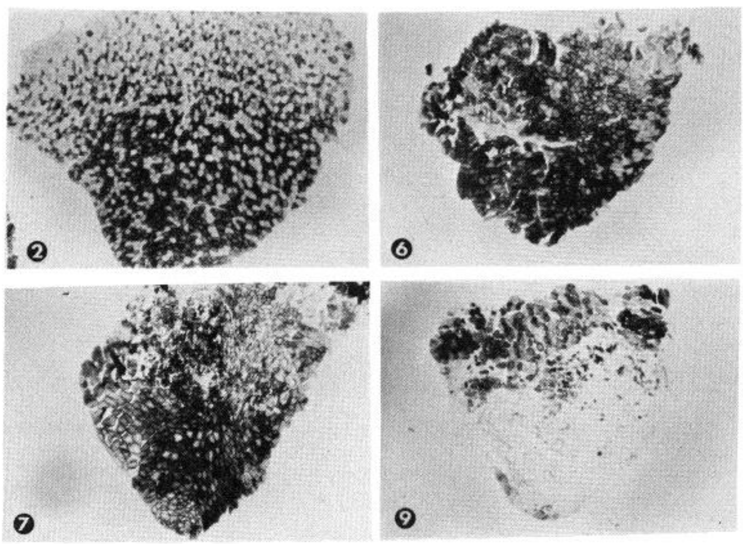


Fig.6. Photomicrograph of a D regenerate in a N host (D heteromince) 19 wk after transplantation. This preparation represents the optimal differentiation of fiber types (SDH reaction) noted in the immature series of transplants with the dystrophic muscle. A photomicrograph of a normal TA (2) is placed next to it as a comparison. The section shown in Fig. 6 resembles many preparations we have of 4 to 7 week dystrophic muscles of our ontogenetic series in its microscopic structure and fiber type distribution.

Fig.7. Photomicrograph of a section of the same muscle shown in Fig.6 but taken from a lower part of the regenerate. Note the deterioration of the upper crown area in this section. SDH reaction.

Fig.9. Photomicrograph of a section of a regenerate of a dystrophic muscle transplanted as a mature tissue to a homozygous normal host (26 wk after transplantation). The non-reactive portion (light area) represents lipid; the remaining fibers can be identified as specific types (SDH reaction). Figure 9 is typical of the majority of D heterominces in this series.

In experiments using homozygous normal mice as hosts or donors, all minces were viable (Fig. 8). Note that all low points (under 4 mg) on the graph correspond to regenerate weights of the littermate series (O,●). Since these are matched as cross transplants, we can relate them to the heterozygous normals. Thus, a combination of heterozygous normals and homozygous dystrophics either as hosts or donors limits the regenerative ability of minces.

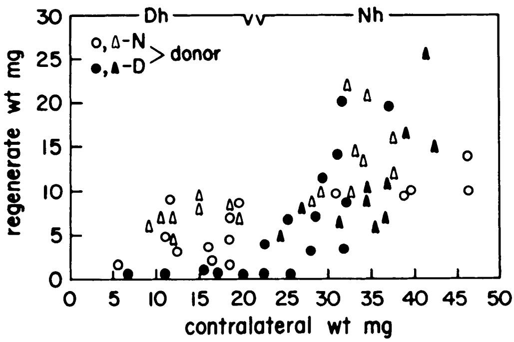


Fig.8. The weight of the regenerate is related to the weight of the unoperated, contralateral TA of the host. All open symbols (OΔ) represent minces from N donors and all closed symbols (●▲), from D. donors. The series of experiments done with immature littermates (O●) give weights similar to those done with the older series of homozygous N and D animals (Δ▲) with the exception of those weights under 4 mg. These low points are related to regenerates of heterozygous normal mice, host or donor (see text). In the D host, D autominces (●) failed to regenerate.

Unfortunately, the series of experiments involving homozygous normal and dystrophic mice were not done with immature animals. Only normal mice 5 to 6 weeks old and dystrophic ones 7 to 8 weeks of age were available. At this time differentiation of fibers seems to be optimal in both animals; however, many of the dystrophic muscles studied at this age show signs of wasting. A glance at Figure 8 gives the impression that the D heterominces(▲)have regenerated well; the external appearance of these was also impressive. However, a microscopic examination of these transplants indicated that in 8 out of 11 experiments examined up to 9 months postoperatively, lipid composed two thirds to four fifths of the weight of the regenerate (Fig. 9); intact cells could be identified easily as to fiber types. The remaining (3) D heterominces (21 wk and 36 wk) demonstrated wasting to a lesser degree.

All the regenerates in this series (homozygous normal and dystrophic) showed the presence of all fiber types in various distribution patterns. Innervation (cholinesterase reaction) was diffuse and seemingly random; the normal distribution of motor endplates was not recaptured. Muscle spindles were either rare or absent as shown by others in reinnervation of adult tissue (Zelená and Sobotková, 1971). In some areas of the muscle, disorientated fibers were noted but on the whole most muscles showed good orientation of fibers. Outstanding in this series was the progressive improvement of the N autominces with time of regeneration contrasted to the extensive wasting of the D heterominces as mentioned above. Further, all N heterominces were viable. None showed the extensive wasting which characterized the dystrophic regenerate residing in a normal host. The normal regenerate maintained for 36 weeks in a dystrophic environment was striking in its fullness of tissue. This was in strong contrast to the negative response of all dystrophic minces in this host. However, it must be stressed that with increased time of transplantation, the N heteromince was composed of abnormal cells. This regenerate on the whole did not seem to be as deteriorated as the muscle of the unoperated leg. Thus, we attributed the abnormal appearance of this regenerate to the failing environment of the host animal.

We have presented a technique of exchanging muscles between two different animal strains as an experimental model to study neuronal influences on the differentiation of normal and abnormal muscles. Regenerates of both the avian and the murine series were subjected to a rigorous analysis of histochemical identification of fiber types. Due to the nearly homogeneous nature of the pectoralis, identification of normal or dystrophic characteristics in the avian regenerates is relatively straightforward. However, the mammalian tissue presents a more complicated problem. The pattern of a heterogenous arrangement of anaerobic and aerobic fibers typical of the tibialis anterior cannot be reduplicated in a regenerate; the newly formed mixtures compound the problem of interpretation. However, if the operational techniques are performed on undifferentiated tissue, the growth of the transplants seems to follow patterns of the ontogeny of normal or dystrophic muscle. In contrast, the transplantation of differentiated muscle from mature mice yields regenerates which are slower in differentiation as in N autominces or which accentuate the characteristic wasting typical of dystrophy as in the D heteromince. This observation is substantiated by the physiological properties of some of these regenerates done in collaboration with Dr. Ryine Hsieh of the Division of Physiology at the Institute for Muscle Disease (Hsieh, Butler, Zeman and Cosmos, 1973).

ACKNOWLEDGEMENTS

I wish to thank my collaborator, Jane Butler, who has participated both in the performance and in the analyses of these experiments. I also wish to acknowledge the capable assistance of Dr. N.V. Vallyathan and Richard J. Zeman in some of the histochemical analyses and Jan Koniarek for his expert maintenance of the mouse colonies.

REFERENCES

Banker, B.Q., R.J. Przybylski, J.P. Van Der Meulen, and M. Victor. (Editors), 1972: Research in Muscle Development and the Muscle Spindle. Excerpta Medica, Amsterdam, Holland.

Bárány, M., and R. I. Close, 1971: The transformation of myosin in cross-innervated rat muscles. J. Physiol. 213: 455.

Bass, A., G. Lusch, and D. Pette, 1970: Postnatal differentiation of the enzyme activity pattern of energy-supplying metabolism in slow (red) and fast (white) muscles of chicken. Eur. J. Biochem. 13:289.

Brust, M., 1966: Relative resistance to dystrophy of slow skeletal muscle of the mouse. Am. J. Physiol. 210:445.

Buller, A. J., J. C. Eccles, and R. M. Eccles, 1960a: Interactions between motoneurones and muscles in respect of the characteristic speeds of their responses. J. Physiol. (London) 150:417.

Buller, A. J., J. C. Eccles, and R. M. Eccles, 1960b: Differentiation of fast and slow muscles in the cat hind limb. J. Physiol. (London) 150:399.

Burke, R. E., D. N. Levine, and F. E. Zajac, 1971: Mammalian motor units: Physiological-histochemical correlation in three types in cat gastrocnemius. Science 174:709.

Carlson, B. M., 1972: The Regeneration of Minced Muscles. Karger, Basel, Switzerland.

Cooper, C. C., R. G. Cassens, L. L. Kastenschmidt, and E. J. Briskey, 1971: Activity of some enzymes in developing muscle of the pig. Pediat. Res. 5:281

Cosmos, E., 1965: A study of phosphorylase activity in muscle of normal and dystrophic chickens. J. Histochem. Cytochem. 13:704.

Cosmos, E., 1966a: Differentiation of muscle fibers after denervation. J. Histochem. Cytochem. 14:819.

Cosmos, E., 1966b: Enzymatic activity of differentiating muscle fibers. I. Development of phosphorylase in muscles of the domestic fowl. Develop. Biol. 13:163.

Cosmos, E., 1970a: Ontogeny of red and white muscle: The enzymic profile and lipid distribution of immature and mature muscles of normal and dystrophic chickens, pp. 193-207. In: The Physiology and Biochemistry of Muscle as a Food, 2. Editors: E. J. Briskey, R. G. Cassens and B. B. Marsh. The Univ. of Wis. Press, Madison, Wis.

Cosmos, E., 1970b: Proc. Symp. Myogenesis and the Muscle Spindle, Cleveland.

Cosmos, E., and J. Butler, 1967: Differentiation of fiber types in muscle of normal and dystrophic chickens. A quantitative and histochemical study of the ontogeny of muscle enzymes, pp. 197-204. In: Exploratory Concepts in Muscular Dystrophy and Related Disorders. Editor: A. T. Milhorat. Excerpta Medica, Amsterdam, Holland.

Cosmos, E., and J. Butler, 1971a: Muscle transplants in normal and dystrophic hosts. Proc. Internat. Union of Physiol. Sci. 9:121.

Cosmos, E., and J. Butler, 1971b: The survival and differentiation of transplanted muscle, p. 10. In: II Internat. Congress on Muscle Diseases. Editor: B. A. Kakulas. Excerpta Medica, Amsterdam, Holland.

Cosmos, E., and J. Butler, 1972: Differentiation of muscle transplanted between normal and dystrophic chickens, pp. 149-162. In: Research in Muscle Development and the Muscle Spindle. Editors: B. Q. Banker, R. J. Przybylski, J. P. Van Der Meulen, and M. Victor. Excerpta Medica, Amsterdam, Holland.

Cosmos, E., J. Butler, and A. T. Milhorat, 1973: Hereditary muscular dystrophy: A possible myogenic defect in the differentiation of muscle, pp. 459-467. In: Proc. of Second Internat. Congr. on Muscle Diseases. Editor: B. A. Kakulas. Excerpta Medica, Amsterdam, Holland.

Cosmos, E., J. Butler, and R. Scott, 1965: Phosphorylase activity in differentiating muscle fibers of the domestic fowl. J. Histochem. Cytochem. 13:719.
Douglas, W.B., and R.J. Baskin, 1971: Contractile properties of developing mouse dystrophic muscle. Am. J. Physiol. 220:1344.
Drachman, D.B., 1964: Atrophy of skeletal muscle in chick embryos treated with botulinum toxin. Science 145:719.
Edström, L., and E. Kugelberg, 1968: Histochemical composition, distribution of fibres and fatiguability of single motor units. Anterior tibial muscle of the rat. J. Neurol. Neurosurg. Psychiat. 31:424.
Engel, W.K., and Karpati, G., 1968: Impaired skeletal muscle maturation following neonatal neurectomy. Develop. Biol. 17:713.
Guth, L., 1968: "Trophic" influences of nerve on muscle. Physiol. Rev. 48:645.
Gutmann, E. (Editor), 1962: The Denervated Muscle. Czechoslovak Academy of Sciences, Prague, Czechoslovakia.
Gutmann, E., and P. Hník (Editors), 1963: The Effect of Use and Disuse on Neuromuscular Functions. Czechoslovak Academy of Sciences, Prague, Czechoslovakia.
Hsieh, R.T., J. Butler, R.J. Zeman, and E. Cosmos, 1973: Regenerated minces of muscle from normal and dystrophic mice. Federation Proc. 32:359.
Jirmanová, I., P. Hník, and J. Zelená, 1971: Implantation of "fast" nerve into slow muscle in young chickens. Physiol. Bohemoslov. 20:199.
Laird, J.L., and R.F. Timmer, 1965: Homotransplantation of dystrophic and normal muscle. Arch. Pathol. 80:442.
Laird, J.L., and R.F. Timmer, 1966: Transplantation of skeletal muscle into a host with muscular dystrophy. Tex. Rep. Biol. Med. 24:169.
Lazzarini, A.A., 1960: Immunological effects of multiple experimental embryonal parabiosis in birds. Ann. N.Y. Acad. Sci. 87:133.
Mauro, A., S.A. Shafiq, and A.T. Milhorat, (Editors), 1970: Regenerattion of Striated Muscle and Myogenesis. Excerpta Medica, Amsterdam, Holland.
Milhorat, A.T., Editor, 1967: Exploratory Concepts in Muscular Dystrophy and Related Disorders. Excerpta Medica, Amsterdam, Holland.
Nyström, B., 1968: Fibre diameter increase in nerves to "slow-red" and "fast-white" cat muscles during postnatal development. Acta Neurol. Scand. 44:265.
Padykula, H., 1952: The localization of succinic dehydrogenase in tissue sections of the rat. Am. J. Anat. 91:107.
Peterson, E.R., and S.M. Crain, 1972: Regeneration and innervation in cultures of adult mammalian skeletal muscle coupled with fetal rodent spinal cord. Exptl. Neurol. 36:136.
Romanul, F.C.A., and J.P. Van Der Meulen, 1967: Slow and fast muscles after cross innervation. Enzymatic and physiological changes. Arch. Neurol. (Chic.) 17:387.
Salafsky, B., 1971: Functional studies of regenerated muscles from normal and dystrophic mice. Nature 229:270.
Sandow, A., and M. Brust, 1958: Contractility of dystrophic mouse muscle. Am. J. Physiol. 194:557.
Zelená, J., and M. Sobotková, 1971: Absence of muscle spindles in regenerated muscles of the rat. Physiol. Bohemoslov. 20:433.

THE PHYSIOLOGY OF WEIGHTLESSNESS

The Symposium published on the following pages was presented on Friday April 14, 1972 as a part of the American Physiological Society program in conjunction with the meetings of the Federation of American Societies for Experimental Biology.

Its publication in this issue is most timely in that it goes to press coincident with the launching of Skylab, the first long-term manned orbital laboratory of the United States National Aeronautics and Space Administration. This will constitute the first opportunity to gain insight into the physiological effects of weightlessness on man by a program of planned experimentation.

The papers presented herein represent a summary of physiological knowledge and speculation developed in the pre-Skylab era. They may provide a useful background for the interpretation of the Slylab results.

THE PHYSIOLOGY OF WEIGHTLESSNESS -

Chairman's Introduction

W. R. ADEY
Space Biology Laboratory
Brain Research Institute
University of California, Los Angeles

This symposium is historic as the first formal presentation of data from biological and biomedical experiments in U.S. space flights before member societies of FASEB. The data were gathered in the Biosatellite Program of the NASA office of Space Science and Applications, and from certain studies on astronauts in the manned space-flight program.

Studies of the weightless state originated in research on effects of acceleration and buoyant states. The buoyant condition has been offered as a substitute for weightlessness, most frequently and vocally by physical scientists not acquainted with compartmental complexities of living tissues, nor with the equally complex and dynamic kinetic organization of organ systems. In fact, we are unable to simulate on the ground the phenomenon of weightlessness as it is seen in space flight or free fall.

Early space flight training for man included parabolic aircraft flights. The aircraft followed a Keplerian trajectory that produced a condition of free fall for 25 to 50 sec (10). The flights were too brief as a training exercise in complex motor tasks, and did not realistically simulate conditions in extravehicular activity (EVA), which were better mimicked by underwater training.

1. The Biosatellite Program

Studies of the effects of weightlessness on living organisms became the objective of the NASA Biosatellite program in 1964. Six flights were planned, using Thor Delta launch vehicles and a highly sophisticated spacecraft constructed by the General Electric Company. These flights were planned to fulfill two missions; they would acquire fundamental knowledge about the weightless state, and they would build bridges to the manned spaceflight program by providing information related to biomedical problems.

The subsequent history of biological and medical research has been disappointingly slow. Manned flights have been predicated on testing and proving engineering systems, and biomedical data acquisition has been primarily in "survival parameters" of cardiovascular and respiratory functions. A report of the President's Science Advisory Committee (13) states: "Pressures for early and reasonably certain success led to placing primary emphasis initially on validations of the capability to construct, orbit and recover manned spacecraft, with long-range scientific goals in the biomedical field set aside as potentially interfering with flight objectives. Scientific requirements were thus deemphasized at the very time

3. The Nature of a Flight Experiment in Space Biology

Space flight experiments demand extreme dedication on the part of investigators and their entire teams. Lead times from experiment formulation to flight are inevitably long, up to five years or more. Simulations are many and tedious, for the experiments must function automatically with high reliability. This concept of a "hands off" relationship with one's experiments is a salutary and even frustrating experience for the biologist, accustomed to handling contingencies by personal intervention, and even to changing his protocol in the middle of an experiment. The figure of the engineer looms ever larger between the experimenter and his experiment, as he emphasizes endlessly the growing interfaces between the experiment and spacecraft systems that will sustain the fragile living organisms, and the biotelemetry systems that must not fail if years of experiment preparation are to succeed.

These logistic problems of flight preparations were exemplified in the primate flight of Biosatellite III*, which combined a series of central nervous, psychophysiological, cardiovascular, metabolic and radiobiological studies. They involved the coordinated contributions of investigators from the University of California, Los Angeles; the University of Southern California; the University of California, Berkeley; Texas Woman's University; the Jet Propulsion Laboratory; and NASA personnel from Ames Research Center, Kennedy Space Center, and Goddard Space Flight Center.

No account of biological and medical studies in space and the efforts in bioinstrumentation necessary for their accomplishment would be complete without reference to the substantive and continuing "spinoff" that has contributed importantly to terrestrial medical research and practice. For example, the urological surgical procedures developed by Dr. A.T. K. Cockett (4) at the Harbor General Hospital, Los Angeles, for use in the flight monkey have been effective in his management of congenital abnormalities of the urinary tract in the newborn; the radiotelemetry systems essential in all space missions have been adapted to clinical needs in intensive hospital care and in environmental medicine, as well as for research. The Biosatellite Program expended approximately $160 million. This figure has been criticized in terms of the possible

---

* Logistic plan of academic institutions and organizations contributing to the primate flight of Biosatellite III. Monitoring of brain states and behavioral performance was by University of California, Los Angeles (UCLA); cardiovascular studies by University of Southern California (USC); metabolic and radiation studies by University of California, Berkeley (UCB), and Jet Propulsion Laboratory (JPL); bone densitometry by Texas Woman's University (TWU); urological surgical procedures and reproductive physiology by Harbor General Hospital, Los Angeles, (HGH). Experiment coordination was the responsibility of UCLA in close liaison with NASA Ames Research Center. Flight coordination by NASA Office of Space Science and Applications culminated in launch preparations at Kennedy Space Center (NASA-ULO). Spacecraft construction was the responsibility of the General Electric Company Reentry Systems Division (GE-RSD). World-wide data acquisition was accomplished through NASA Goddard Spaceflight Center (GSFC).

when development of basic scientific knowledge and a cadre of scientific talent should have been begun.... Early manned programs were designed to avoid biomedical obstacles whereever possible."

Biosatellite flights were effectively limited to two. Biosatellite I failed to reenter on command. Data from Biosatellite II are presented here by Dr. A. Brown and Dr. F. de Serres. The flight studied effects of weightlessness on simple organisms. Biosatellite III involved a single primate for nine days. Our fundamental information is thus limited. Although assessment of the scientific significance of Soviet experiments in space biology is not always easy, it should be pointed out that the USSR has conducted a continuing series of experiments with both simple life forms and higher vertebrates, including mammals.

2. The Significance of Research in Space Biology and Medicine

We must have ever before us the essential importance of gravity and the organism. The position has been succintly stated in the PSAC document cited above: "In all terrestrial biology, the force of gravity is a subtle and everpresent factor. In research such as on the growth of seedlings, the functions of the inner ear, and the control of blood pressure, it is a recognized but almost non-eradicable factor. The opportunity to use the space environment advances such studies by a giant step. Now the possibility of dissecting away gravity as a fundamental biologic stimulus is present. It is conceivable, for example, that studies on the blood pressure controlling mechanisms may be the key to unlock a more complete understanding of basic physiological mechanisms on a broad basis, rather than being useful solely as a test of an astronaut's reactions to space flight.... The Biosatellite Programs have been developed specifically to consider these problems from simple living forms to subhuman primates."

In manned space flight, metabolic, cardiovascular and neurological changes have occurred (2, 3). Weight loss, including loss of muscle tissue, has been reported in U. S. astronauts, and involves altered electrolyte metabolism, with excretion of as much as 15 percent of the exchangeable potassium. Little is yet known about associated changes in steroid metabolism. Decreased bone density has been reported in man and monkey (11). Vestibular disturbances have become troublesome as freedom of movement has increased in larger spacecraft. Misperception of body position and reports of illusory movement have been frequent. Cosmonaut E. V. Khrunov (9) has succintly described some of the changes in psychological states in weightlessness. "As it was many times reported in the press, the realization of intention proper is delayed under conditions of weightlessness. Cosmonaut G. T. Beregovoy called this phenomenon 'delay in intention.' Prior to taking a camera, for example, you must think how to do this." This striking account of modified formulation of intention has its counterpart in the progressive decline in body and eye movements in the Biosatellite III monkey (7).

An encouraging recent development in NASA policy is the establishment of an Office of Life Sciences, combining all biological and biomedical research under a single administration for the first time.

value of comparable expenditures in urgent terrestrial research. The pressing urgency of some of the latter cannot be denied, but perhaps we should evaluate the costs of these first uncertain and even painful steps for the biologist in space against the continuing expenditures in unmanned space missions. The latter, conducted almost exclusively for scientific purposes, are now budgeted at approximately $700 million annually. It is not clear that the goals of the biologist in space are any less worthy as national objectives than those of his physical scientist colleagues. Yet there are currently no significant U. S. programs of research on the fundamental biological effects of space on terrestrial organisms.

4. Bioscience Research in Space in Retrospect and Prospect

When man first set foot on the moon, it was justly remarked that this small step for man was a giant leap for mankind. This was surely a worthy appraisal of such an historic achievement. Is it not logical then to ask what effects the weightless environment, encountered in all man's journeys through space, may have on his biological functions, and indeed on all terrestrial organisms that have evolved across a billion years in the continuous influence of earth's gravity?

As is often the case with simple questions, this inquiry has raised emotional tensions amongst biological and physical scientists to unexpected levels; so that substantive problems are clouded over and objective appraisal of scientific goals are lost in unrelated issues. Association with the space program carries with it the chimera that one will enjoy scientific riches without end, and that the scientific advantage so enjoyed by the privileged few will carry them to elyssian realms beyond the reach of those in mundane fields of terrestrial biology and medicine. Man was ever greedy of his fellow man, and the scientist is not without avarice.

Nevertheless, it is disappointing and discouraging to find misinformation permeating even a committee of the U. S. National Academy of Sciences which recently reviewed NASA programs of life science research in space (5). It concluded about Biosatellite III that "considered solely as a contribution to fundamental physiological knowledge, the information to be obtained was not shown to be new and unpredictable, nor to require environmental conditions that were unique to space flight that could not be adequately simulated on the ground." Important new unpredictable findings from this flight are presented here and elsewhere (1,4, 6, 7, 8, 11, 12, 14, and 15). More importantly, we might invite the committee to show us what new ways they have devised to effectively simulate weightlessness in the mammal in terrestrial conditions.

It is in the interests of correcting such misinformation that this Symposium was organized. In the philosophy of our astronaut counterparts, we have labored over these experiments in space in the name of all biology, not for personal aggrandisement, but rather in the humble awareness of the privilege, the honor and the responsibility inherent in these studies. For just as no man may enter the void of space by his own unaided efforts, neither can the space biologist perform a successful experiment without a quite extraordinary team effort.

REFERENCES

1. Adey, W. R., and P. M. Hahn. Aerospace Med. 42: 273, 1971.
2. Berry, C. A. Aerospace Med. 40: 762, 1969.
3. Berry, C. A. Council on Space Research, (COSPAR) Madrid, Proceedings, p. 263, 1972.
4. Cockett, A. T. K., A. P. Roberts, and W. R. Adey. J. Oklahoma State Med. Assoc. 182, 1972.
5. Glass, H. B., editor. Life Sciences in Space, Natl. Acad. Sci., Washington, D. C., 1970.
6. Hahn, P. M., T. Hoshizaki, and W. R. Adey. Aerospace Med. 42: 295, 1971.
7. Hanley, J., and W. R. Adey. Aerospace Med. 42: 304, 1971.
8. Hoshizaki, T., R. Durham, and W. R. Adey. Aerospace Med. 42: 288, 1971.
9. Khrunov, E. V. Council on Space Research (COSPAR), Madrid, Proceedings, p. 264, 1972.
10. Machell, R. G., editor. Summary of Gemini Extravehicular Activity. Natl. Aeronautics and Space Admin., Manned Spacecraft Ctr., Houston, Texas. NASA Document MSC-G-R-67-2. June, 1967.
11. Mack, P. B. Aerospace Med. 42: 828, 1971.
12. Meehan, J. P., and R. D. Rader. Aerospace Med. 42: 322, 1971.
13. President's Science Advisory Committee, Space Science and Technology Panel. The Biomedical Foundations of Manned Space Flight. U. S. Govt. Printing Office, Washington, D. C., Nov. 1969.
14. Tejada, R. I., P. M. Hahn, and W. R. Adey. Aerospace Med. 42: 281, 1971.
15. Walter, D. O., J. I. Berkhout, R. Buchness, E. Kram, L. Rovner, and W. R. Adey. Aerospace Med. 42: 314, 1971.

CARDIOVASCULAR OBSERVATIONS IN THE MACACA NEMESTRINA MONKEY IN BIOSATELLITE III

JOHN P. MEEHAN and ROLAND D. RADER
Department of Physiology
University of Southern California, Los Angeles

ABSTRACT

An electrocardiogram, an impedance pneumogram, the arterial, and central venous pressures (CVP) were recorded continuously seven days prior to and during the entire orbital flight of the Macaca nemistrina monkey in Biosatellite III. On reaching orbital flight, CVP rose between one and two cm. water above preflight values, indicating a central shift of blood volume. Heart rate, respiratory rate and arterial pressure were relatively high at the beginning of the flight but declined steadily until recovery was effected 8 days after launch. The monkey went into negative fluid balance due, in part, to the operation of the Henry-Gauer reflex. Multiple factors operated to bring about the unexpected physiological deterioration and death of the monkey.

The first effort to measure intravascular pressures in orbital space flight took place in connection with the flight of the chimpanzee Enos, in Project Mercury (4). It was anticipated then that arterial pressure would not be directly affected by the physical environment. The central venous pressure, however, was expected to exhibit an absolute increase in the weightless condition consequent to a central shifting of the blood volume. The arterial pressure behaved as expected. The catheter for obtaining central venous pressure located in the right atrium found its way into and through the pulmonary artery before lift-off, thus providing pulmonary artery pressure instead of the desired central venous pressure.

The opportunity to once again directly study vascular pressures in the absence of gravity was provided in the Biosatellite III experiment. The task required the development of equipment and techniques of a high degree of reliability. The general approach used in Project Mercury employing intravascular catheterizations was followed. Catheters were introduced in each anterior tibial artery and advanced to the descending aorta. Similarly, two catheters were placed in the inferior vena cava near the heart. A single channel electrocardiogram and an impedance pneumogram were also obtained.

Five potential flight subjects were completely instrumented. One of the five, #470, was selected as the optimum flight subject. The remaining four animals served as ground-based controls. Launch occurred on June 28, 1969, at 2310 EDT. The active portion of the experiment was terminated by the death of the animal on July 8, 1969 at approximately 2400 Hawaiian Standard Time.

Cardiovascular data was obtained from seven days preceding the launch until the monkey's death. The animal exhibited a marked reduction in heart rate, arterial and venous pressures and body temperature (UCLA data) during flight. He was dehydrated when recovered and failed to respond to remedial measures.

The monkey faced the direction of acceleration with the long axis of the body perpendicular to the direction of acceleration. The increase in heart rate several seconds before ignition to the initial lift-off was apparently a reaction to vehicle motion and noise. After the main engine cutoff (lift-off +223.5 seconds) both the heart rate and respiration rate declined until the second engine cutoff, at which time the heart rate increased (Fig. 1.).

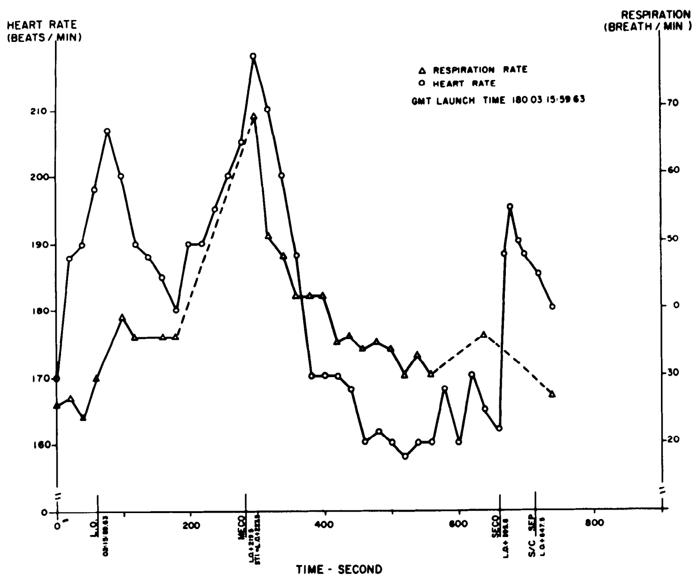


Fig.1. Heart and respiration rate changes during lift-off sequence.

Initial orbital values of central venous pressure showed a marked increase relative to the ground levels. This was predicted on the basis of a reduction in gravitational effects on the long axis of the body and a consequent decreased pooling of blood in the extremities. The upper curve in Figure 2 shows the pressure measured near the right heart and the lower curve the pressure measured essentially in the right atrium. The pressure difference between the two catheters of approximately 2 mm Hg is reasonable. The dynamic response of each tracing substantiates their placement. The increase in pressure of approximately 2 mm Hg upon achieving orbit is on the same order of magnitude as that produced by changing position from day to night on the ground-test animal. Figure 3 illustrates the venous pressure response obtained when the position of the flight animal was altered according to prescribed schedules before launch. The pressure level is approximately 2 mm Hg higher in the night position than the level in the day position. These pressure levels agree with the concept that blood pools in the extremeties when the subject is in a more upright position, causing a lowering of pressure in the chest region.

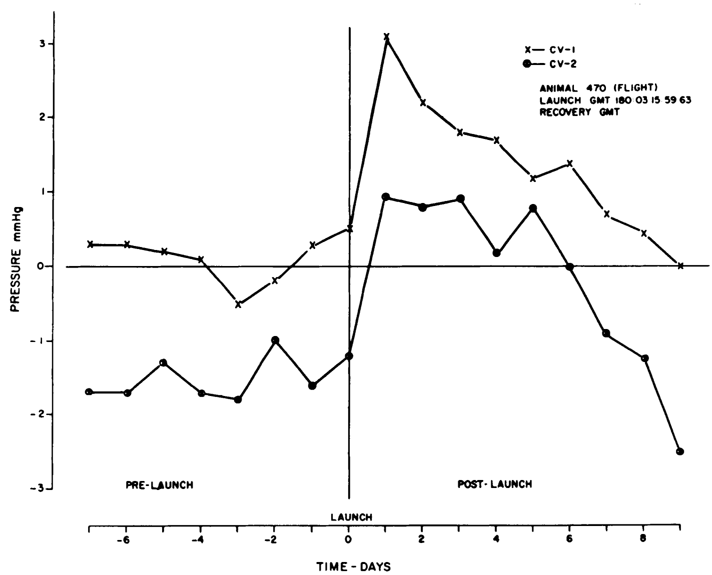


Fig.2. Venous pressure data from the two venous catheters.

Samples of data received at the Goddard Space Flight Center during the flight are shown in Figure 4. The upper channel on each chart is respiration; the second is electrocardiogram; the third and fourth are central venous pressure; and the fifth, sixth, seventh and eighth are arterial pressures. Channels 6 and 8 are samples at slower rates, producing the rather blocked waveform. The pulse appearing on all pressure measurements results from heparin infusion. The quality of the data received throughout the flight remained very good. The heart rate in Figure 4 (D) is considerably slower than in Figure 4(A), thus permitting a better inscription of the arterial pressure curves.

Figure 5 records the cardiovascular data for the flight animal plus the four that were instrumented and held as ground controls. Both the respiratory rate and the heart rate of the flight monkey showed progressive shifting of the 24 hour rhythm when compared with the data for the ground-control animals.

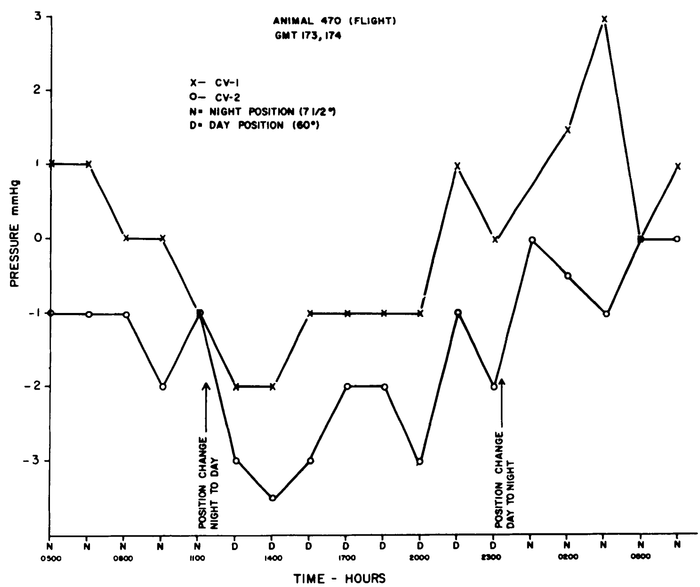


Fig.3. Cyclic variation in central venous pressure induced by position.

Figure 6 relates the heart rate, arterial pressure and central venous pressure before and during the flight. The heart rate fell steadily throughout the flight, however, the arterial blood pressure was maintained at physiological levels until after the eighth day of flight. The average venous pressure fell steadily after the fifth day but did not reach preflight values until the eighth day.

DISCUSSION

The rapid physiological deterioration of the flight animal was not expected, especially in view of the history of successful manned flights for as long as 14 days. There are, however, many differences between the manned flights and the flight of the monkey, so that the sum total of stress factors operating on the monkey were much higher than for the astronauts. Thus it was necessary to have the monkey in close restraint because of the various catheters and other instrumentation; and even though the animal subjects were conditioned to the type of restraint required, the experience frustrated their normal drives.

The astronauts were confined also, but they did have some freedom of movement in the early flights and indeed considerable movement during the later flights in larger spacecraft. Furthermore, the astronauts in addition to being highly experienced pilots, had a very clear understanding and appreciation of their mission: the picture of restraint, then, is clearly a different matter for the astronaut.

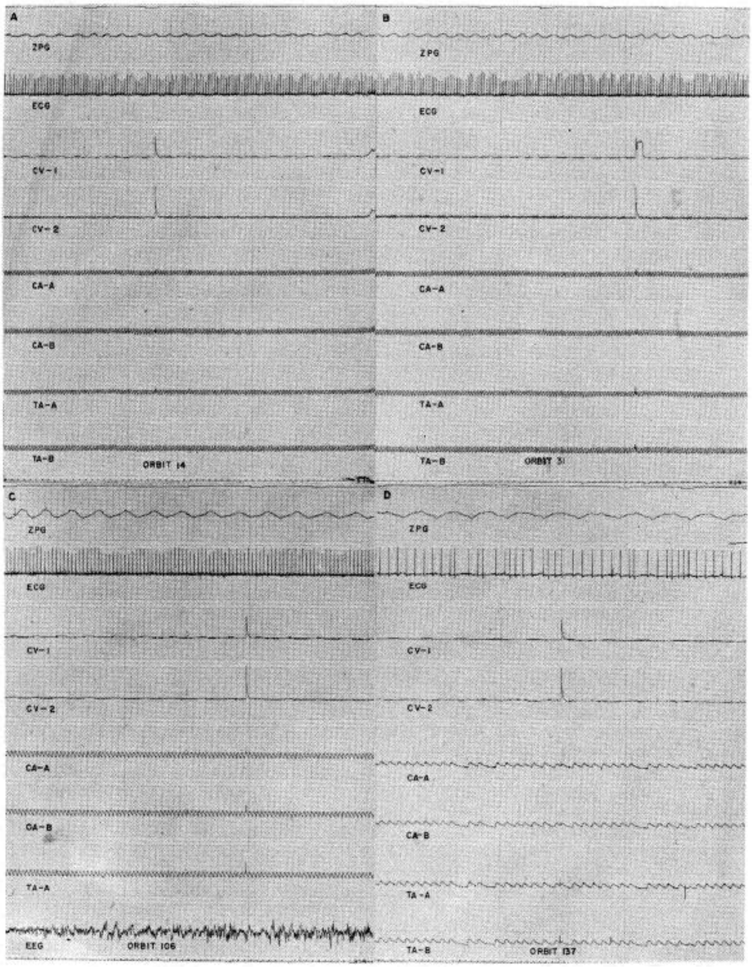


Fig.4. Samples of cardiovascular data obtained throughout the flight.

A continuing drop in the animal's body temperature was observed during the flight, yet the spacecraft temperatures of 68^{o} to 72^{o}F were as planned. However, since there was a considerable velocity of air movement over the animal, there is the possibility that significant body cooling may have resulted from this air movement, especially if moisture was being evaporated from the surface of the animal. Thus the matter of restraint and isolation as contributing factors to the hypothermia must also be considered. It is a well known fact that some animals exhibit the physiological processes of temperature regulation accomplished by the hypothalamus, and, as a consequence, body temperature falls. This is usually a limited process however, and body temperature is restored after a few hours. This it is entirely possible that the central mechanisms responsible for this phenomenon were operating in the case of the monkey. There was very little evidence of shivering as judged by examination of all of the electrophysiologic data collected, suggesting suppression of this thermogenic mechanism.

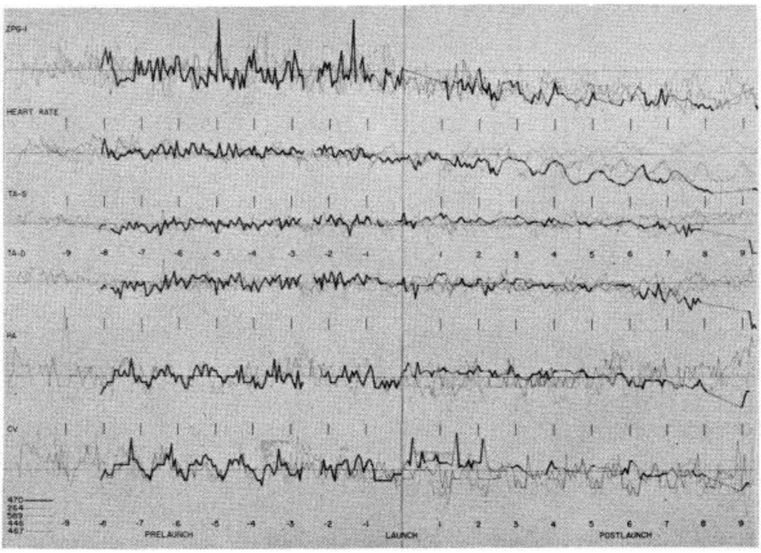


Fig.5. Compiled cardiovascular data. The data is normalized over the prelaunch period such that the data in the post launch period indicates deviations from the prelaunch data. Traces from top to bottom are as follows:

ZPG-1:	Respiration Rate
Heart Rate:	
TA-S:	Systolic Arterial Pressure
TA-D:	Diastolic Arterial Pressure
PA:	Central Venous Pressure
CV:	Central Venous Pressure

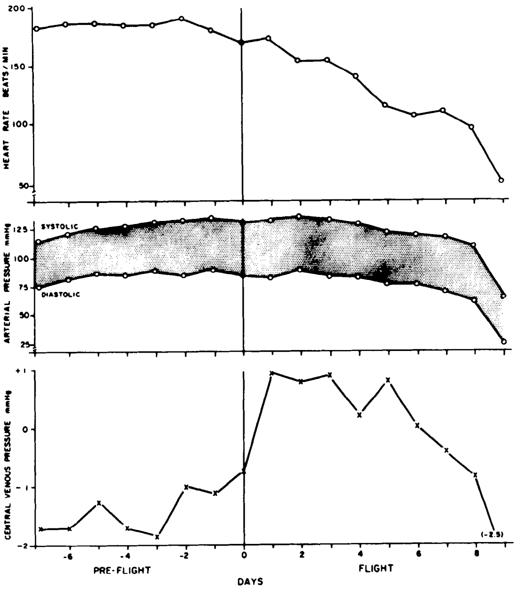


Fig.6. Heart rate, blood pressure and central venous pressure prior to and during the flight.

The weightless state is associated with abnormal vestibular stimuli, and symptoms of motion sickness were experienced by five of the six crew members in Apollo 8 and 9 (1). The monkey did initially work the VM task which was designed to further stimulate the vestibular apparatus, since the animal moved his head in a circular path when tracking the target on the co-rotating disks. It may be relevant that this task was abandoned by the animal after two days, even though the on-board camera revealed him to be alert into the eighth flight day. Hence the abnormal vestibular inputs which were undoubtedly experienced by the monkey were another stress factor, and an associated autonomic disturbance of the sweat glands may have played a role in stimulating the excessive evaporative fluid loss.

The voluntary water intake of the flight animal as well as that of the ground controls was quite variable and did not bear any particular relationship to the physical environment. It was usual to observe a marked increase in water consumption at times when the animals were handled or manipulated as, for example, following implantation of catheters. The urine volume is correspondingly high and the specific gravity low under such circumstances. Although this excessive water intake certainly has a psychogenic component, it does require specific physiologic adjustments of kidney function.

It is generally assumed that the recumbent individual or the individual in the weightless environment experiences a shift of blood volume toward the heart. The rise in central venous pressure in the monkey indicated that this indeed does happen. The observed increase in atrial pressure of 2-3 cm H_2O was of an order of magnitude sufficient to provide a stimulus for the loss of body fluid as described by Gauer and Henry (2).

As seen in Figure 6, this pressure remained above preflight levels until the eighth day of flight. The hypothermia experienced by the animal would further enhance the shift of blood volume centrally and perhaps help to maintain the observed increase in central venous pressure.

An unexpected dividend to the biologists from the accurate observation of humidity and water absorbed, which was feasible in the flight capsule, is the useful data which was available concerning the evaporative water loss during the flight; this was not available for the ground control animals during their simulated flight in their mock-ups for these were not closed systems. Figure 7 clearly shows that the animal realized close to the maximum fluid deficit after 3 to 4 days of flight. The relatively high urine volume in the face of a progressively increasing loss of body fluids strongly suggests that the animal encountered serious electrolyte problems. As shown by water immersion studies, the fluid loss will be hypotonic in the well hydrated subject. However, when hydration is limited, the increased volume elimination is accomplished by an increase in osmolar clearance only (3, 5), and the experiments of Gauer, Henry and Behn (3), show that excessive sodium loss can actually occur. It was their impression that this loss was more marked in subjects who are anxious. It seems, then, that there is reasonable evidence to support the hypothesis that the monkey was considerably disturbed by his environment. In fact, the irrevocable physiologic derangements probably occurred early in the flight; thereafter adaptation may not have been possible in view of the multifaceted stress factors affecting fluid and electrolyte metabolism.

Such was probably not the case with the astronauts. The striking observations of Lutwak, et al. (6), of a decrease rather than an expected increase in the urinary secretion of 17-hydroxycorticoids is compatible with the view that astronauts Borman and Lovell were, in fact, quite at ease during the 14-day Gemini 7 flight. Their verbal reports further support this contention.

The length of time required for the cardiovascular changes to weightlessness to approximate their full effect is probably longer than 3 or 4 days. If the blood volume data of the Gemini flights is any indicator it would appear that perhaps as long as 14 days or longer are required. Neither the command pilot nor the pilot of the 14-day Gemini 7 flight had decreased blood volumes; such was not the case in flights of a shorter duration. It is possible that, in time, the venous tone is reduced - probably as a consequence of the absence of gravitational loading. As this occurs the venous system becomes more distensible thus permitting a return of the blood volume to its original more peripheral distribution. As this redistribution takes place, the central venous pressure should fall toward preflight values. One may speculate that in normal circumstances, as the venous pressure falls, the receptor drive from the atria will be reduced, thus allowing the regulatory mechanisms affecting the kidneys to return toward more usual levels of activity. In the case of the monkey, the central venous pressure remained elevated until almost the end of the flight when the rapid fall of systemic arterial pressure confirmed that he was in serious trouble.

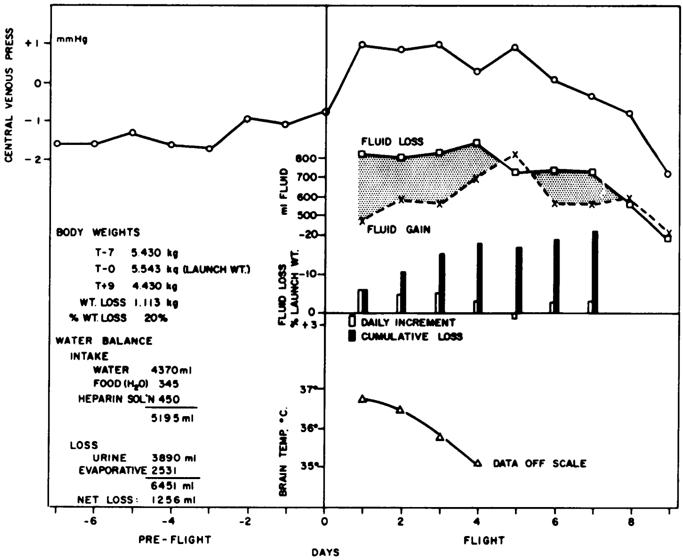


Fig.7. Summary of fluid balance, body weight changes and brain temperature during the flight.

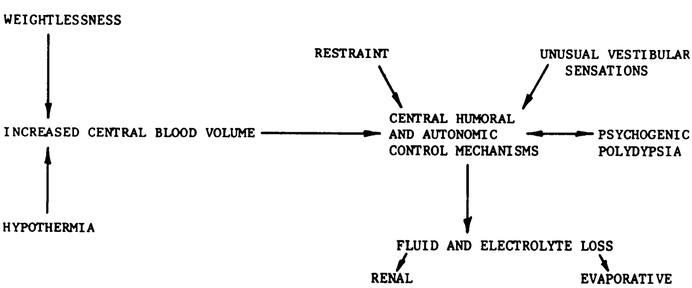


Fig.8. Summary diagram of stress factors operating in the Biosatellite III flight.

Figure 8 summarizes the various factors and mechanisms operating in the flight of the monkey. Weightlessness and hypothermia acted to shift blood volume centrally: this provided a strong drive for the reduction of blood volume. Restraint, unusual vestibular sensations and the continuing polydipsia, all acted to disturb the central mechanisms which might have restored normal control and regulation of salt and water metabolism. It is highly probable that the function of the kidney was significantly affected and that an excessive amount of salt was lost. We can speculate that a serious electrolyte disturbance was superimposed on the growing dehydration. Unpleasant vestibular sensations may have contributed to the high evaporative loss by autonomic disturbances - the whole problem being compounded and reinforced by the unnatural restraint to which the monkey was subjected.

Thus, there were a number of factors all operating in concert which may have prevented the effective adaptation of the monkey to the environment. For the first time, the astronauts have been subjected to a similar series of profound stresses during the recently completed Apollo 13 flight. It will indeed be of great interest to study the data from that flight when they become available.

REFERENCES

1. Berry, C.: Journal of Aerospace Med. 41: 500-519 (May) 1970.
2. Gauer, O.H., and J. P. Henry: Physiological Reviews 43: (3) 423-481, (July) 1963.
3. Gauer, O.H., J. P. Henry, and C. Behn. Annual Review of Physiology, 32: 547-595, 1970.
4. Henry, J.P., and J. D. Mosely, editors. Results of the Project Mercury Ballistic and Orbital Chimpanzee Flights, NASA SP-39, Office of Scientific and Technical Information, Natl. Aeronautics and Space Admin., Washington, D.C., 1963.
5. Johnson, J.A., W. W. Moore, and W.E. Segar. American Journal of Physiology. 217: 210-14, 1969.
6. Lutwak, L., et al. Journal of Clinical Endocrinology and Metabolism. 29: 1140-56, 1969.

THE ROLE OF CARDIAC RECEPTORS IN FLUID BALANCE

L. W. CHAPMAN and J. P. HENRY
Department of Physiology
University of Southern California, Los Angeles

Negative fluid balance has been a significant problem in man's attempt to conquer the weightless environment. All available evidence suggests that the escape from gravitational forces results in an increase in thoracic blood volume (1). Gauer and Henry initiated studies 25 years ago to determine the effect on fluid balance of shifts in circulating blood volume. They demonstrated that increasing thoracic blood volume by negative pressure breathing (NPB) at the expense of extrathoracic volume resulted in an increase in urine flow (Fig. 1) (2). These studies directed the attention of the researchers to the role of the cardiac stretch receptors on salt and water excretion.

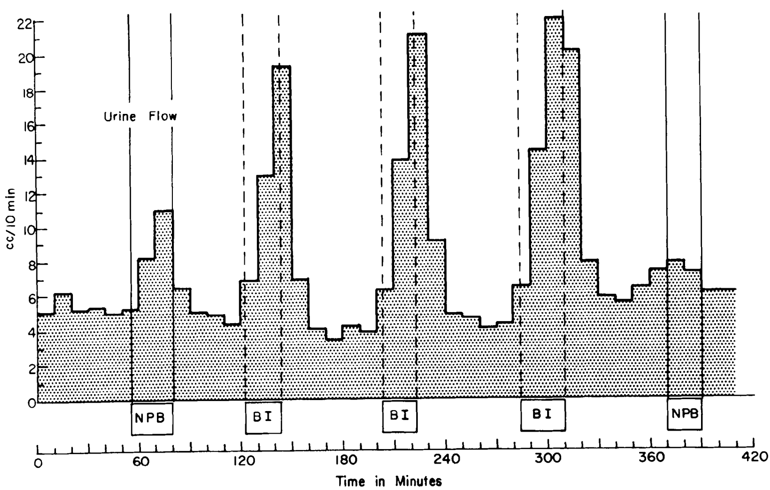


Fig. 1. The diuretic effects of negative pressure breathing and balloon inflation in the left atrium in the dog. (From Gauer, O.H. and J.P. Henry. Klin. Wchnschr. 34: 356, 1956).

Increasing left atrial stretch by intermittent obstruction of the mitral orifice with a small balloon produced an increase in urine flow similar to that found with NPB (Fig. 1). Since the increase in urine flow was predominantly an increase in water excretion, Gauer and Henry suggested that the renal response was due to a decrease in antidiuretic hormone (ADH) secretion. The reflex nature of the response was established when it was demonstrated that vagal cooling abolished the urinary response to left atrial distension (Fig. 2) (3).

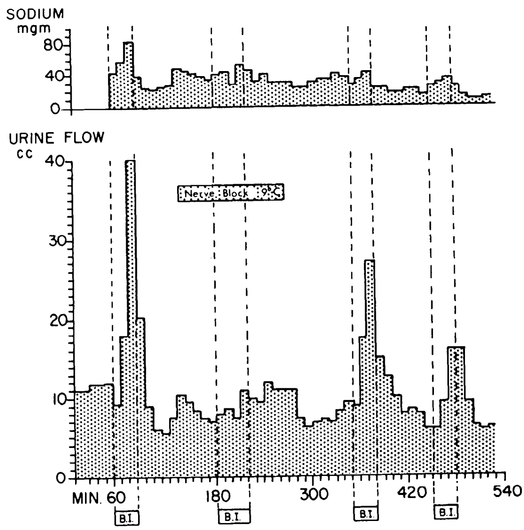


Fig.2. The effect of balloon inflation on sodium excretion and the blocking of the diuresis by bilateral cooling to 9°C. (From Wright Air Development Center Technical Report 478).

The Gauer-Henry reflex received a severe setback when a number of investigators could not reverse the balloon increase in urine flow with exogenous ADH (Fig. 3) (4, 5). It was only after a sufficiently sensitive assay for ADH had been developed that the existence of such a reflex was established (Fig. 4) (6). The influence of the left atrial receptors on ADH secretion has been further confirmed and extended by Johnston, Moore and Segar (7), who have shown that neither these receptors nor osmotic stimuli are dominant in the control of ADH secretion, and thus water excretion (8).

As more research has been directed toward establishing the physiologic effects of atrial stretch, it is only now that some suggestion can be made as to why exogenous ADH could not entirely abolish the renal response to negative pressure breathing or balloon inflation. It is now clear that a change in atrial stretch in the absence of significant changes in arterial baroreceptor reflex mechanisms can alter sympathetic activity to the heart and viscera.

Hakumaki has found an inverse relation between postganglionic sympathetic discharge to the heart and the ratio of B type receptor discharge to A receptor discharge in the cat (9). Further, Arndt working with cats has suggested that the discharge patterns from the two atrial receptor types can in combination be a measure of cardiac output (10). Oberg and White have indicated that the atrial receptors are predominantly responsible for the adjustments of the visceral circulation due to changes in cardiac output (11, 12). The effects of these interrelationships needs further confirmation in the dog which has relatively few A type fibers.

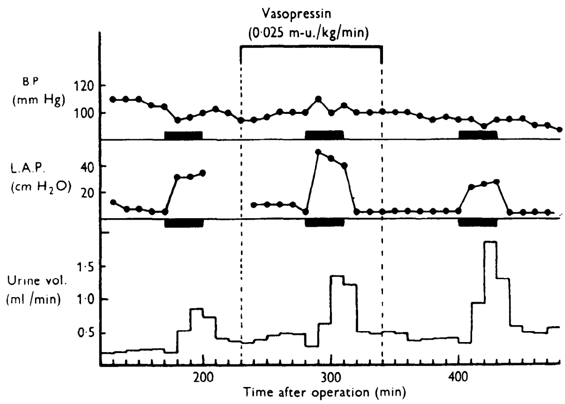


Fig.3. The response of mean blood pressure (B.P.), left atrial pressure (L.A.P.) and urine volume to balloon inflation in the left atrium with and without exogenous antidiuretic hormone. (From Ledsome, J.R. and R.J. Linden, J. Physiol. 170: 456, 1964).

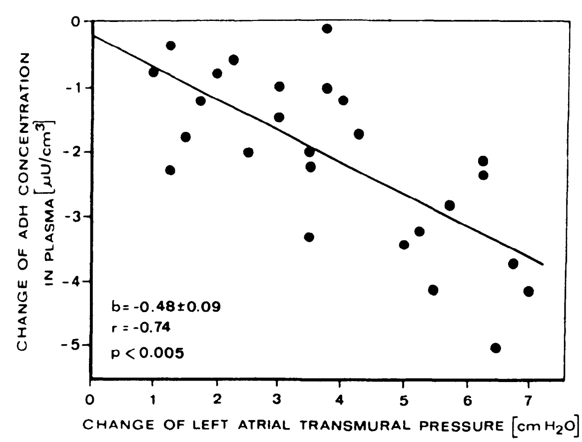


Fig.4. Relation between the changes in left atrial pressure produced by balloon inflation and the change in plasma antidiuretic hormone titers. (From J. A. Johnson, Am. J. Physiol. 217: 210, 1969. Redrawn by O. H. Gauer, Federation Proc. 27: 1132, 1968).

The contradictory findings in the dog of the cardiac responses to pulmonary atrial junction distension by Daly and co-workers (Bradycardia) and Ledsome and Linden (Tachycardia) has been resolved by Edis and Shepherd (13-15). They have shown that the heart rate response to balloon inflation is dependent on the initial cardiac rhythm (Fig. 5). Renal sympathetic nerve activity has also been shown to be depressed with left atrial balloon inflation (16). Thus it now seems clear that part of the renal response to the increased thoracic blood volume of weightlessness can be accounted for on a basis of a decrease in renal sympathetic nerve activity as well as a decrease in ADH.

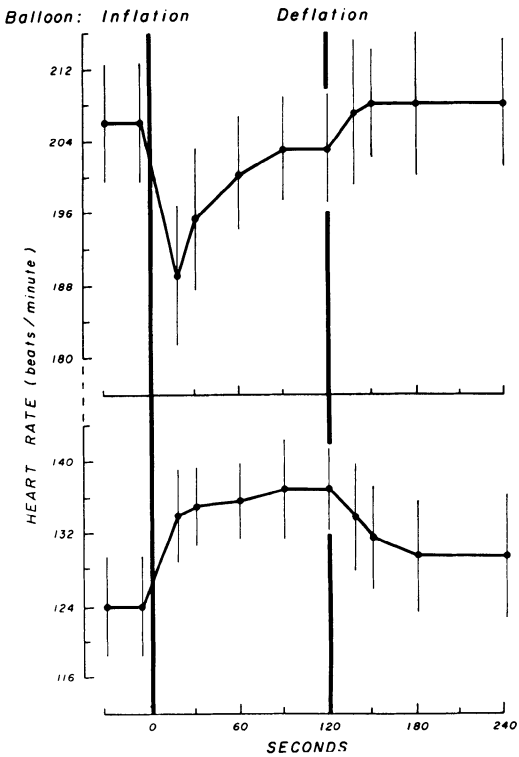


Fig.5. The effect of left atrial balloon inflation on heart rate.(From Edis, A.J., D.E. Donald, and J.T. Shephard.Circulation Res. 27: 1091, 1970).

The contribution of the cardiac receptors to the control of sodium excretion has been less precisely defined than that of water. Since the original search of Mills and de Wardener for factors that contribute to the control of sodium excretion, a number of studies have used selective denervation of the heart to determine the contribution of the "volume" receptors (17, 18). The consensus of these findings is that cardiac receptors do not play a major role in the control sodium excretion, a conclusion to which we do not subscribe. In a majority of the studies a great number of variables which affect renal function were also affected, incidental to changes in atrial receptor activity. Arndt, et al., demonstrated that increases in left atrial stretch resulted in an increase in sodium excretion primarily as a result of renal vasodilation (19). Goetz and co-workers observed a decrease in sodium excretion when atrial stretch was decreased by atrial tamponade in the absence of changes in cardiac output or aortic blood pressure in volume loaded dogs (Fig. 6) (20). In a model that primarily affects atrial stretch in the absence of changes in either aortic pulse or mean pressure or blood gas concentrations, we have demonstrated that sodium excretion in saline volume expanded dogs can be decreased and increased by decreasing or increasing atrial stretch. Further, the immediate renal response to a decrease in atrial stretch appears to be due to an increase in renal sympathetic nerve activity (unpublished observations). Other factors, yet unidentified, also appear to be involved. The exact mechanisms by which the atrial stretch affects renal sodium output are still being sought.

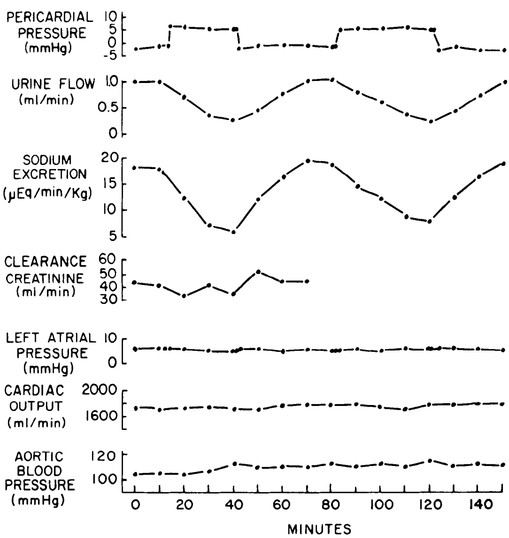


Fig.6. The decrease in urine flow and sodium excretion resulting from the atrial tamponade in the absence of changes in creatinine clearance, left atrial pressure, cardiac output or aortic blood pressure. (From Goetz, K.L., A.S. Hermreck, G.L. Slock, and H.S. Starke. Am. J. Physiol. 219: 1417, 1970).

The increased cardiac receptor activity that occurs with increased thoracic blood volume in weightlessness produces an increased loss of body fluid via the kidneys, but this alone cannot account for the cellular dehydration noted in the monkey in Biosatellite III, or in the returning astronauts. It has long been known that those conditions which promote fluid output reciprocally depress thirst mechanisms. Fitzsimmons in a recent review has clearly pointed out that the cardiac receptors affect the thirst centers probably by acting directly through neural connections and indirectly through the renin-angiotensin system (Fig. 7) (21). In the case of weightlessness the code of the cardiac receptors is serving to inform the hypothalamic thirst centers of an "overfilled" state. The result will be a reduced fluid intake.

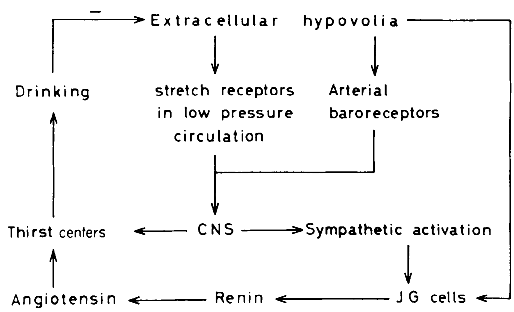


Fig.7. The contribution of the cardiovascular stretch receptors to fluid intake. (From Fitzsimmons, J.T. In: Progress in Physiological Psychology, edited by E. Steller and J.M. Sprague. New York: Academic Press, 4: 119, 1971).

Summary

(Fig. 8). The cardiac receptors affect multiple efferent neural and hormonal pathways, each of which is separately capable of affecting salt and water excretion by the kidney. In the weightless state it is quite probable that the shift of blood volume from the periphery to the thoracic vessels has the behavioral effect of depressing fluid intake as well as increasing salt and water output.

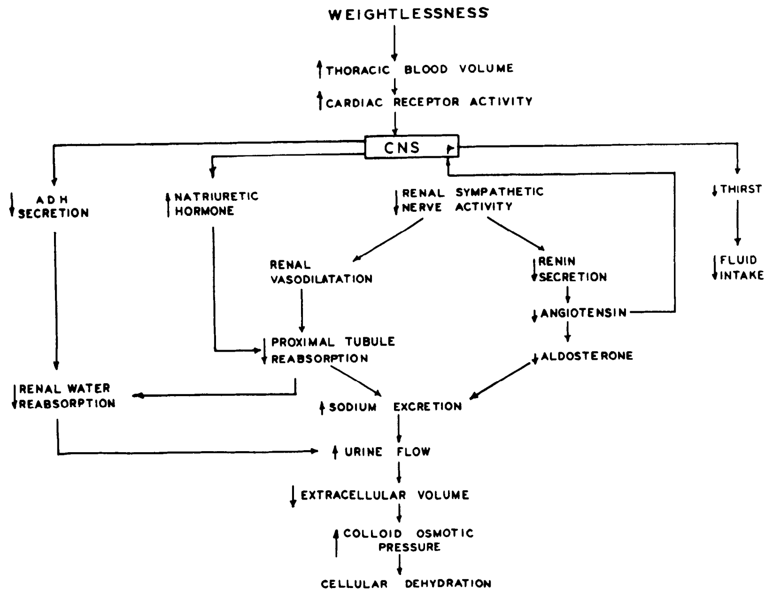


Fig.8. The multiple pathways by which weightlessness and cardiac receptors may lead to cellular dehydration.

REFERENCES

1. McCally, M., and C.C. Wunder. In: Hypogravic and Hypodynamic Environments. French Lick Symposia (Murray, R.H., and M. McCally, Ed., NASA Technical Report SP-269).
2. Gauer, O.H., J.P. Henry, H.O. Sieker, and W.E. Wendt. J. Clin. Invest. 33: 287, 1954.
3. Henry, J.P., O.H. Gauer, and J.L. Reeves. Circulation Res. 4: 85, 1956.
4. Baisset, A., P. Montastruc. Path-Biol., 16: 805, 1968.
5. Ledsome, J.R., R.J. Linden, and W.J. O'Connor. J. Physiol. 159: 87, 1961.
6. Share, L. Am. J. Physiol. 208: 219, 1965.
7. Johnson, J.A., W.W. Moore, and W.E. Segar. Am. J. Physiol. 217: 210, 1969.
8. Johnson, J.A., J.E. Zehr, and W.W. Moore. Am. J. Physiol. 218: 1273, 1970.
9. Hakumaki, M.O.K. Acta Physiol. Scand. (Suppl.) 344, 1970.
10. Arndt, J.O., P. Brambring, K. Hinderof, and M. Rohnett. Pflugers Arch. 326: 300, 1971.
11. Oberg, B., and W. White. Acta Physiol. Scand. 80: 383, 1970.
12. Oberg, B., and W. White. Acta Physiol. Scand. 80: 395, 1970.
13. Daley, I. de B., and E.B. Verney. J. Physiol. 62: 330, 1927.
14. Ledsome, J.R., and R.J. Linden. J. Physiol. 170: 456, 1964.

15. Edis, A.J., D.E. Donald, and J.T. Shephard. Circulation Res. 27: 1091, 1970.
16. Karim, E., C. Kidd, C.W. Malpus, and P.E. Penna. J. Physiol. 213: 38P-39P, 1971.
17. de Wardener, H.E., I.H. Mills, W.F. Chapman, and C.J. Hayter. Clin. Sci. 21: 249, 1961.
18. Mills, I.H., H.E. de Wardener, C.J. Hayter, and W.R. Chapman. Clin. Sci. 21: 259, 1961.
19. Arndt, J.O., H. Reineck, and O.H. Gauer. Arch. Ges. Physiol. 277: 1, 1963.
20. Goetz, K.L., A.S. Hermreck, G.L. Slock, and H.S. Starke. Am. J. Physiol. 219: 1417, 1970.
21. Fitzsimmons, J.T. In: Progress in Physiological Psychology. Ed. by E. Steller and J.M. Sprague. New York: Academic Press, Vol. 4: 119, 1971.

CIRCADIAN RHYTHMS AND SLEEP-WAKE ACTIVITY IN THE BIOSATELLITE MONKEY

T. HOSHIZAKI, P. M. HAHN,
and W. R. ADEY
Space Biology Laboratory
Brain Research Institute
University of California, Los Angeles

Physiologists for years have varied one environmental factor or another to test their significance on the response and the well being of organisms. As one example limiting the atmosphere with a bell-jar led to the discovery of oxygen. The significance of its role in respiratory and metabolic processes is well known. On the other hand, gravity was one factor that could not be removed. All metabolic and physiologic reactions studied so far, occurred under the influence of gravity. With the advent of the space age however, the force of gravity could be eliminated and it became feasible to examine the effects of gravity or more precisely the lack of it (weightlessness) on various organisms. The NASA Biosatellite program (4) thus presented an opportunity to investigate the possible effect of long term weightlessness on the responses of organisms. This paper is concerned with the effects of weightlessness on the circadian rhythms of the *Macaca nemestrina* monkey "Bonny" during the flight of the Biosatellite III spacecraft.

The preliminary ground experiments (6), the preparation and training of the flight animal and the preparation and operation of the Biosatellite III spacecraft (1) have been previously described. Of biorhythm interest, the capsule temperature was maintained at $21 \pm 0.5^{\circ}C$. The internal total pressure drifted from 750 mm of Hg at the beginning to 730 mm of Hg on the 9th day of flight and the relative humidity drifted downward from 55 percent to 45 percent. All of these measures were aperiodic as far as could be determined. On the other hand, the magnetic field experienced by the spacecraft did vary periodically. The period lengths were 1.6, 23.5, and 70.4 hours with the flux density varying from 0.2 to 0.5 gauss. These periodicities were due to the movement of the spacecraft around the earth. However the various physiological responses measured were apparently not synchronized nor driven by these magnetic flux changes (5).

The prelaunch protocol required a daily schedule identical to that of the flight schedule. A strict 24 hour daily schedule was maintained during flight. Light and dark periods were each 12 hours in length. Tasks were presented at the same time each day. Water was presented every hour on the hour during the light period and every three hours in the 12 hour dark period. On days 4 and 5 of the flight extra water was dispensed during the night. Food in the form of pellets was available as a reward for successful completion of the tasks and *ad libitum* during the 2 hours before the end of the light period. Thus the daily schedule presented a strong 24 hour Zeitgeber to the subject (1).

Data for the sleep-wake activity study were obtained by timelapse cinema-photography. One frame was exposed every 20 minutes and the state of the animal recorded for a particular frame was then scored for the 20 minute interval (7). The methods for the acquisition of the cardiovascular data (9) and the urine data (10) have been described. Since the flight was terminated after 8.8 days, analytical methods had to be devised which might clearly show any circadian rhythm changes that may have occurred in spite of the reduced number of daily cycles. The method developed has been called the 4-day averaging technique. The values of 4 consecutive days are pooled, averaged and then compared with the values of a second 4 consecutive days. Using this technique, analysis of the temperature rhythm as measured in the body and brain of the flight subject indicate a period length longer than 24 hours (Fig. 1). The respiration rhythm which was derived from the partial pressure of the carbon dioxide (pCO_2) in the spacecraft also was found to be longer than 24 hours (Fig. 2.). On the other hand, the length of the sleep-wake activity rhythm as recorded by the time-lapse camera was 24 hours (Fig. 3.). When a daily schedule is imposed on subjects, their sleep-wake and temperature rhythms are synchronized (8). However, in Bonny, the body temperature rhythm was desynchronized from the sleep-wake activity and was apparently free-running.

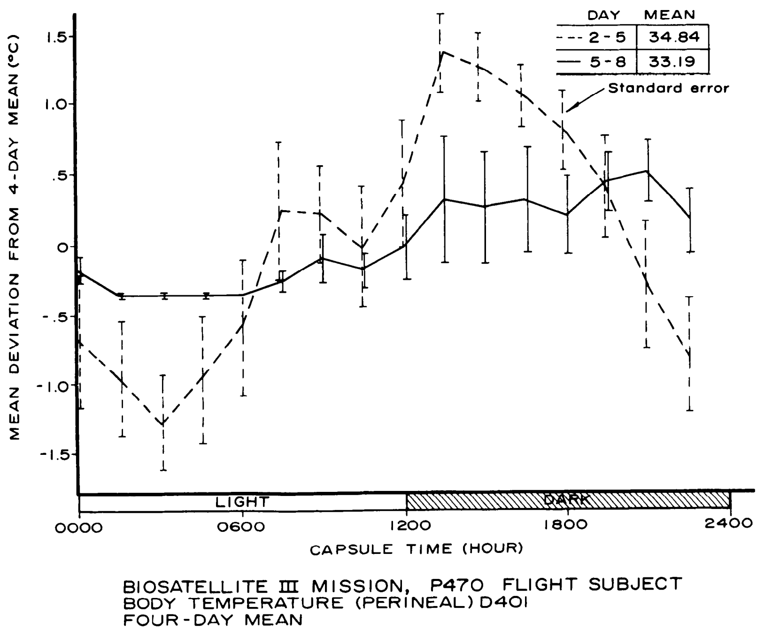
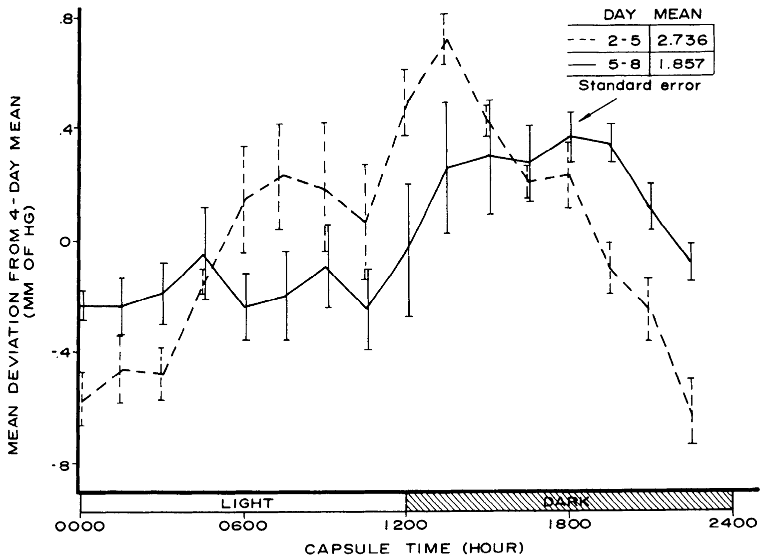


Fig.1. Biosatellite III Mission, P.470 Flight Subject. Body Temperature (Perineal) D401. Four-Day Mean. Day averaging was used for these curves. The solid line (Day 5-8) is shifted to the right of the dotted line (Day 2-5) indicating a period greater than 24 hours between the two sets of days. The zero standard error between 0130 and 0600 capsule time in the solid line is due to the inability to indicate temperature below 33°C (5). Similar data were obtained from the brain.



BIOSATELLITE III MISSION, P470 FLIGHT SUBJECT
ENVIRONMENT, CARBON DIOXIDE PARTIAL PRESSURE D54
FOUR-DAY MEAN

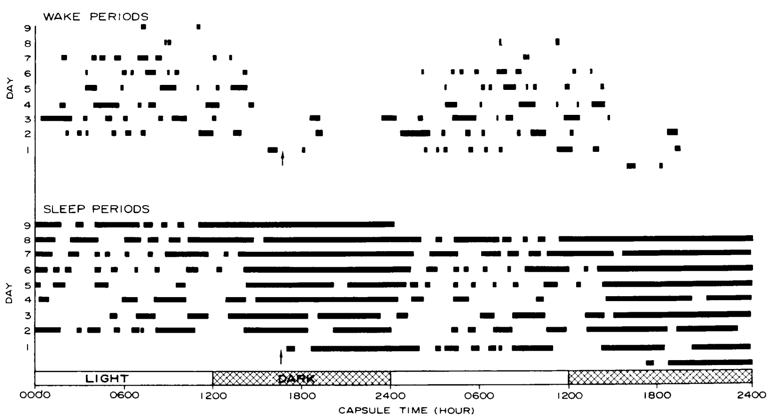
Fig.2. Biosatellite III Mission, P470 Flight Subject. Environment, Carbon Dioxide Partial Pressure D54, Four-Day Mean. The partial pressure of carbon dioxide reflects metabolism of the animal. The gas management system which circulated the air in the spacecraft only removed 10% of the CO_2 during each air change and one may, using the constants of the gas management system, calculate the CO_2 production of the animal(5).

The circadian rhythm of the heart rate was found to have a period length greater than 24 hours (Fig. 4.). The blood pressure on the other hand had a 24 hour rhythm (Fig. 5) (5). Thus, there is evidence that desynchrony occurred between these two cardiovascular measures.

In the urine measures, the calcium excretion rhythm as calculated from the data of Pace, et al. (10) had a period length greater than 24 hours, while urine volume and creatinine excretion rhythms had a 24 hour period. Thus, desynchrony was detected in a third major physiological function of the flight subject.

Desynchrony, as such, was never detected in the cardiovascular measures and brain temperature of the 4 ground-control subjects (Fig. 6) (5), nor in the cardiovascular and EEG measures, metabolic responses and sleep-wake activity, of previous experimental subjects (2, 3, 6) when they were exposed to similar daily regimen in earth gravity.

In summary the flight subject during weightlessness showed simultaneously circadian rhythms longer than 24 hours and rhythms of 24 hours (Table I). It seems quite clear now, that weightlessness in some way affected the circadian rhythms of the flight subject even though a strict 24 hour environment was imposed. It may be of some relevance to note that urine volume rhythm became arrythmic in men who followed a strict 24-hour routine but were exposed to continuous light (8). It is tempting therefore to speculate since several of the flight subject's rhythms uncoupled from the imposed schedule that perhaps gravity or weightlessness may play just as important a role in the synchronization of biorhythms as does light.



BIOSATELLITE III MISSION, P-470 FLIGHT SUBJECT
APPARENT SLEEP/WAKE PERIODS

Fig.3. Biosatellite III Mission, P470 Flight Subject. Apparent Sleep/Wake Periods. Sleep-wake activities of the Biosatellite Monkey, Macaca nemestrina, P-470, as recorded by time-lapse photography. Pictures were taken every 20 min at 0,20, and 40 min. after the hour. Each frame was considered to represent the animal's state for that 20 min period. The sleep-wake states were scored as eyes closed--sleep, eyes open--awake, and eyes not discernible--no data. The data have been plotted to aid visual analysis, i.e., the data is replotted on the right side with a 1 day shift, to connect the data of consecutive days. The periods when the subject awoke briefly and drank water are not indicated in their records. He was generally awake between 0200 and 1400 and appeared to have a 24 hr activity rhythm. Wake periods fell dramatically on Day 8 and 9. Flight began on Day 1 at 1616 (arrow). Capsule time of 0000 or 2400 is 0700 EDT and is the beginning of the 12 hr light period with light intensity of 6.0 foot candles. Light intensity during the dark period was calculated to be around 0.06 footcandles (7).

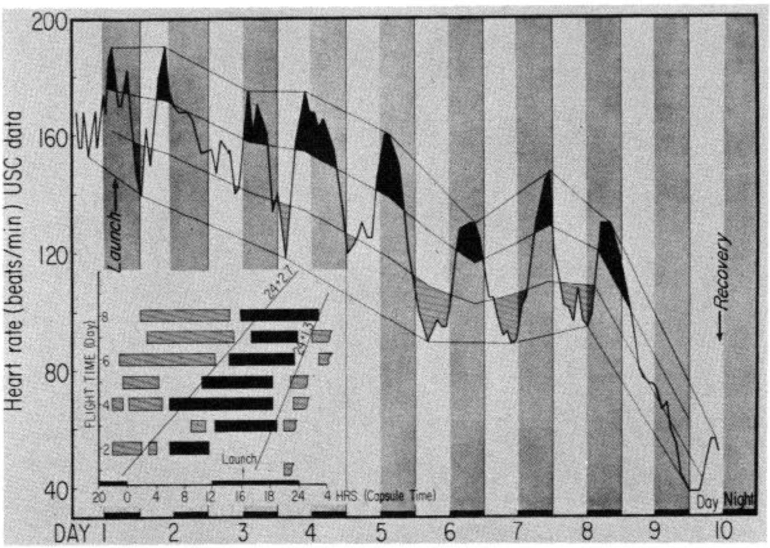
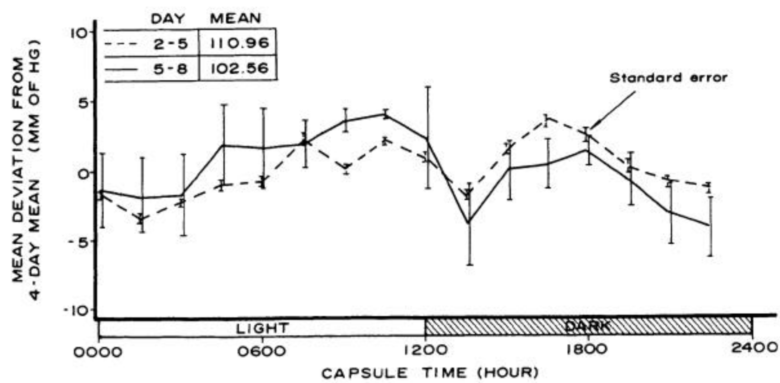


Fig.4. Heart rate of the Biosatellite III monkey, P-470. The inset at the lower left indicates the heart rate peaking later every succeeding day. The two regression lines indicate a daily period of greater than 24 hrs.(5).



BIOSATELLITE III MISSION, P470 FLIGHT SUBJECT
BLOOD PRESSURE, ARTERIAL MEAN (ABDOMINAL) D403
FOUR-DAY MEAN

Fig.5. Biosatellite III Mission, P470 Flight Subject. Blood Pressure, Arterial Mean (Abdominal) D403 Four-Day Mean. The two curves show no displacement from each other (cf Fig.1) indicating a 24 hour period (5).

Table I. Period lengths of the circadian rhythms in the Biosatellite monkey as determined from data acquired at 1.5 hour intervals.

Rhythms	Length in hours	Reference
Sleep-wake	24*	6
Mean arterial pressure	24	5
Urine volume	24	10
Urine creatinine	24	10
Respiration (pCO_2)	25½	5
Heart rate	26	5
Body temperature	26½	5
Brain temperature	26½	5
Urine calcium	30**	10

* Data acquired at 20 minute intervals
** Data pooled into 6 hour intervals

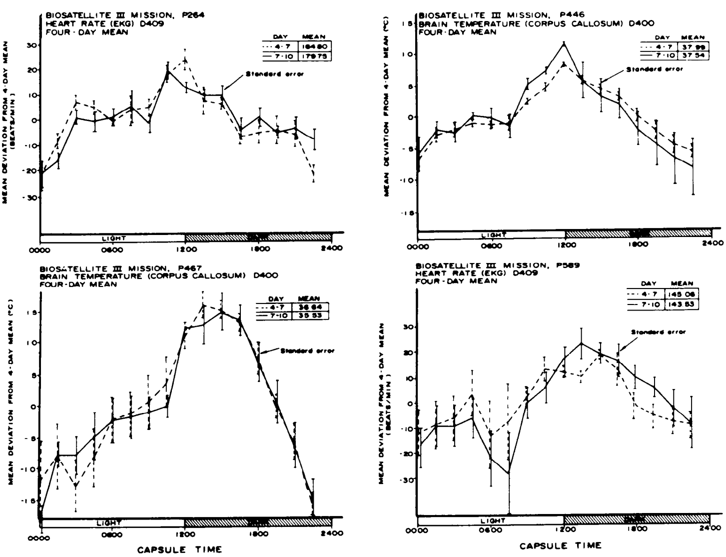


Fig.6. Day averaging technique for these measures in the ground control subjects confirm the 24 hour period. The large standard error at 0600 and 0730 capsule time of P-589 is due to the administration of drugs on Days 7 and 10 (5).

REFERENCES

1. Adey, W. R., and P. M. Hahn. Introduction - Biosatellite III results. Aerospace Med. 42: 273-280, 1971.
2. Anonymous. Biosatellite 3, Flight evaluation report. Contract No. NAS-2-1900. Report from General Electric, Re-entry and Environmental Systems Div., Philadelphia, under NASA-ARC Contract NAS 2-1900, 1969.
3. Anonymous. Project Biosatellite primate mission, UCLA No. 602 test report. Report from Space Biol. Lab., Brain Res. Inst., Univ. Calif., L. A. under NASA-ARC contract NAS 2-2503, 1969.
4. Hahn, P. M. Biosatellite project. Brit. Interplane. Soc. 21: 136-147, 1968.
5. Hahn, P. M., T. Hoshizaki, and W. R. Adey. Circadian rhythm of the Macaca nemestrina monkey in Biosatellite III. Aerospace Med. 42: 295-304, 1971.
6. Hoshizaki, T., W. R. Adey, J. P. Meehan, D. O. Walter, J. Berkhout, and E. Campeau. Central nervous, cardiovascular and metabolic data of a Macaca nemestrina during a 30-day experiment. Biblio. Primatol. 9: 8-38, 1968.
7. Hoshizaki, T., R. Durham, and W. R. Adey. Sleep/wake activity patterns of a Macaca nemestrina monkey during nine days of weightlessness. Aerospace Med. 42: 288-295, 1971.
8. Lobban, M. C. Dissociation in human rhythmic functions. In: Aschoff, J. Circadian Clocks, Amsterdam: North-Holland Publ. Co., 1965, pp. 219-227.
9. Meehan, J. P., and R. D. Rader. Cardiovascular observations of the Macaca nemestrina monkey in Biosatellite III. Aerospace Med. 42: 322-336, 1971.
10. Pace, N., B. W. Grunbaum, D. W. Kiepert, D. F. Rahlman, and G. D. Smith with J. H. Rho, and E. A. Spaeth. Urine excretion rates of calcium, creatine and creatinine in the test monkeys and flight monkey used for NASA Biosatellite III. Report EPL 71-1 from the Environmental Physiology Laboratory, Univ. of Calif., Berkeley under NASA-ARC contract NAS 2-4231, 1971.

WAKE AND SLEEP CYCLES IN THE BIOSATELLITE III PRIMATE IN EARTH ORBITAL FLIGHT

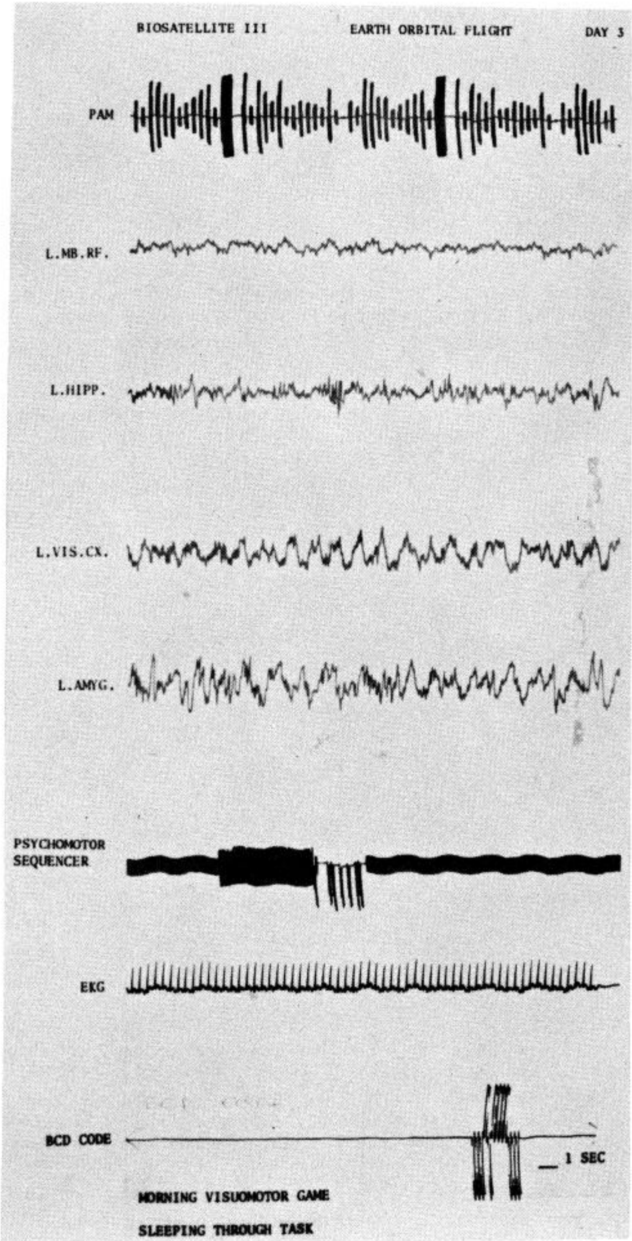
J. HANLEY
Space Biology Laboratory
Brain Research Institute
University of California, Los Angeles

The Biosatellite III experiment offered a unique opportunity to study a higher mammal under zero gravity conditions. The monkey was instrumented in ways impossible to achieve in man. While sleep has been studied extensively in man in the last 15 years, it has been investigated virtually entirely under terrestrial conditions. The one exception in the U.S. Space Program was Astronaut Frank Borman on the Gemini GT VII flight. Approximately 50 hr of recording were taken from three electrode sites in posterior scalp regions.

Telemetered data from the Biosatellite III monkey have indicated that the weightless state induced substantially altered cerebral functions. There was fragmentation of the sleep state and complete loss of the normal 70-90 min cycle displayed by the flight primate during many hours of recording under terrestrial conditions. Spacecraft orbital requirements limited telemetry data capture to approximately 5-7 min per revolution; these data have been supplemented for postflight analysis by data stored on the on-board tape recorder. Though as yet incompletely analyzed, there is so far no evidence that the telemetry data were in any way misleading. It gave true assessment of the general state of consciousness of the primate. Moreover, since the on-board recorder stored abundant data gained during behavioral tasks, it has been possible to confirm the general increase in drowsiness to frank sleep at times when the primate would normally be alertly responding to the behavioral task presentations.

The Biosatellite III experiments had sensors for 33 channels of physiological data. These included 10 EEG, 2 EOG, and 2 EMG channels. Data of a consistently high quality were telemetered to earth and also stored on the on-board tape recorder. Agreement was very high and justified confidence in the two systems.

The Biosatellite III primate never attained its normal sleep-wake cycle throughout the 8.8 days of earth orbital flight. Its sleep was characterized by brevity of state, unusual transitions from one state to another, sleeping well into the day including the periods of behavioral task presentation (2). Figure 1, from the on-board recorder demonstrates brief sleep during daytime task presentation. Rapid eye-movement (REM) sleep, subjectively associated with visual dream experience in man, was confirmed in space flight for the first time, but was much reduced in quantity compared to the amount in normal terrestrial sleep. Stage IV sleep, subjectively associated with refreshing sleep, was also much reduced. On-board data also confirmed the earlier finding that the primate had steadily decreasing eye movements with eventual development of fixed gaze in the final orbits of the flight.


BIOSATELLITE III
EARTH ORBITAL FLIGHT
DAY 3
PAM
L.MB.RF.
L.HIPP.
L.VIS.CX.
L.AMYG.
PSYCHOMOTOR SEQUENCER
EKG
BCD CODE
1 SEC
MORNING VISUOMOTOR GAME
SLEEPING THROUGH TASK

Many states are known to perturb the normal sleep cycle: new and strange environments for the sleeper; drugs of various kinds; change in sleep schedules. The zero-gravity environment may now be added to that list, and if long missions are to be planned for man in space, its disruptive effect on the normal sleep cycle must be taken into account. Astronauts have frequently complained of poor sleep and of making errors attributable to this problem. It is well known that inadequate sleep in terrestrial conditions has an effect on motivation and performance. On the theory that the weightless state would be at least partially simulated in man with high cervical cord transection, Adey, et al. (1) have performed such studies. Their data indicate a situation similar to that seen with the Biosatellite III primate: fragmentation of state and considerably reduced State IV and REM sleep. The sleep of these quadriplegics and the sudden transitions of state seen in Astronaut Borman closely resemble the sleep of the Biosatellite III primate in earth-orbital flight. The serious implications of prolonged disturbance in sleep functions emphasize the value of further investigations into its occurrence and causes in subhuman primates before man is exposed to long-duration space missions.

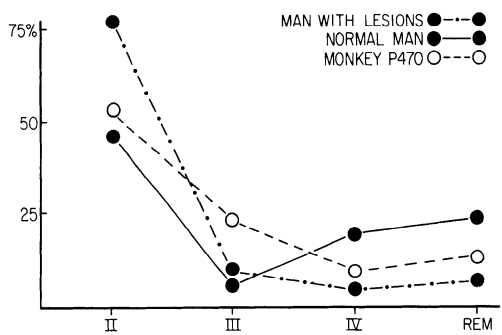


Fig.2. Comparison of amount of sleep spent in each stage between biosatellite monkey, normal man and man with high cervical transection. (Aerospace Med. 42(3): Fig. 14, p.311, 1971).

REFERENCES

1. Hanley, J., and W. R. Adey. Aerospace Med. 42: 304, 1972.
2. Adey, W. R., E. Bors, and R. W. Porter. Arch. Neurol. 19:377, 1968.

Fig.1. The primate's sleep cycle was so perturbed that he sometimes slept through presentation of the behavioral task. The montage is as follows: PAM = pulse amplitude modulation slow scan commutator, LMBRF = left midbrain reticular formation, L. Hipp = left hippocampus, L. Vis Cx = left visual cortex, L. AMYG = left amygdala, EKG = electrocardiogram, BCD CODE = binary coded decimal time code. The EEG is that of slow-wave sleep. The psychomotor sequence has scheduled the visuomotor task.

ELECTROLYTE AND METABOLIC PROBLEMS OF WEIGHTLESSNESS

NELLO PACE
Environmental Physiology Laboratory
University of California, Berkeley

The flight of Apollo 16 marks the 50th since the historic orbital flight of the Russian dog Laika in Sputnik 2 in November 1957, in which man or other mammals have been passengers and have been subjected to the state of weightlessness for periods up to 24 days. Of these 50, the USA has launched 24 manned flights, one chimpanzee flight and one monkey flight, while the USSR has flown 18 manned flights and 6 dog flights.

The longest USA flight to date has been the Gemini 7 flight of Borman and Lovell, which lasted 13.8 days. The USSR flew 2 men for 17.7 days in Soyuz 9 and 2 dogs in Cosmos 110 for 22.0 days, with successful recovery. They also flew the ill-fated Soyuz 11 last June, in which 3 cosmonauts lost their lives due to spacecraft depressurization during reentry, after having spent 23.8 apparently uneventful days in Earth orbit. Thus it seems clear that the mammalian organism can survive at least 3 weeks of weightlessness, and preparations are well along in the USA to send 3 astronauts into Earth orbit next year for 28 days as part of the Skylab Project.

Although these, and the many other, space flight activities of the past 15 years represent remarkable engineering achievements which have resulted in significant expansion of our knowledge in the astrophysical and geological sciences, in the expansion of man's philosophical outlook, and even in his political evolution, the physiological information accrued has been disappointingly little. The reasons for this are manifold and not the subject of discussion here, but chief among them is the fact that space flight still entails exceedingly complex technological constraints which make the design of valid physiological experiments difficult indeed.

At the same time, there have been 4 space flights which had as their primary mission the gathering of in-flight biomedical data, and from which useful physiological information has come. These are the Biosatellite 3 and Gemini 7 flights, the Cosmos 110 flight and the Soyuz 9 flight. Also, the Skylab flight of next year will include a large component of biomedical measurements on the 3 astronauts. However, it must be said that as of now, one of the major electrolyte and metabolic problems of weightlessness is the paucity of existing information and the lack of opportunity for the physiologist to conduct appropriately designed experiments in weightlessness.

Nonetheless, it is now evident that the human organism undergoes physiological changes as a result of exposure to weightlessness. It is not known whether all of these are adaptive and reversible, or if some of them will prove to be progressive as a function of longer exposure periods to the point of adaptive failure. Even if the latter is not the case, there is no question of the importance of achieving full understanding of the physiological processes involved in adaptation to the weightless state.

In general, the results to date, obtained principally from pre- and post-flight measurements, demonstrate important changes in cardiovascular function, neuromuscular function, vestibular function, endocrine function and electrolyte and fluid balance. It is to these last two areas that I will address myself.

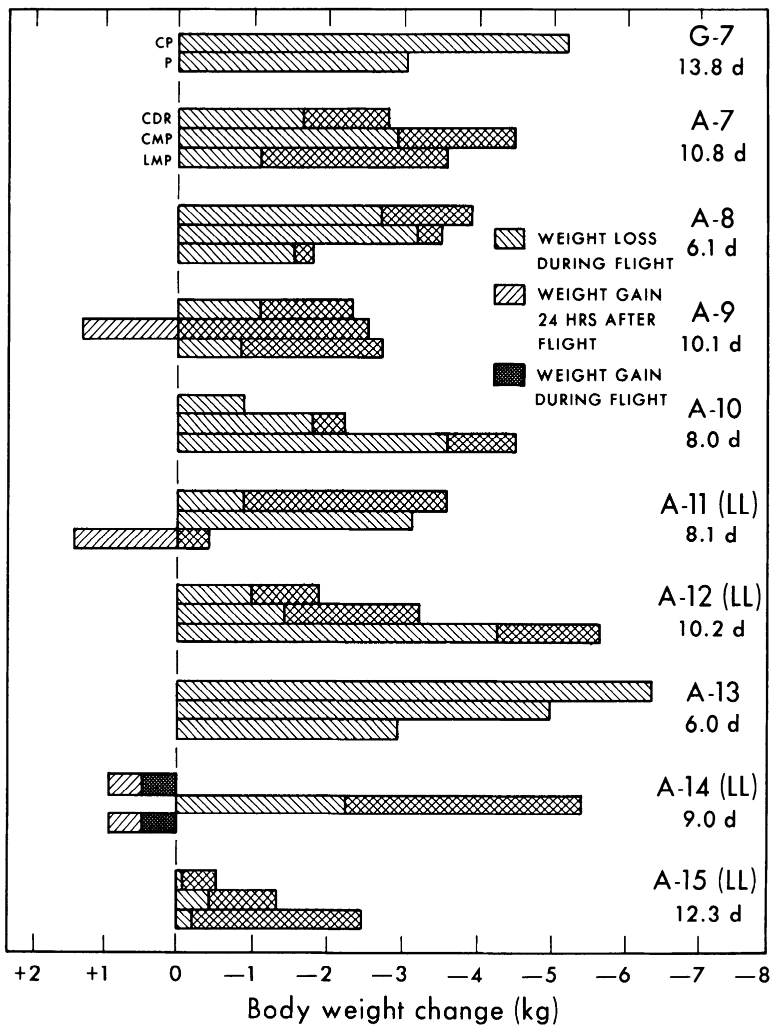


Fig.1. Body weight changes in the Gemini 7 and Apollo 7 through Apollo 15 astronauts.

One of the most consistent findings in both the astronauts and cosmonauts has been a loss of body weight during flight despite special efforts to provide good fluid and caloric intake. Figure 1 summarizes the weight changes reported by Berry (2) in the Apollo 7 through 15 astronauts. Also included are the data from the two Gemini 7 astronauts. It may be seen that all but 2 Apollo 14 astronauts lost weight, the average being about 3 kg. It may also be seen that only about half the loss was replaced within 24 hours after return to Earth.

Caloric balance may be examined in a general way from data published for the early Apollo flights. Berry (1) cites the average daily caloric intake of the 15 astronauts involved in the Apollo 7 through 11 missions as being 1, 680 kcal, with a range of 1, 311 to 2, 278 kcal. Samonski and Tucker (11) have recently reported total oxygen usage for each of these missions and give figures for spacecraft leakage rate, so that astronaut oxygen consumption rates can be estimated. When this is done, it appears that the average O_2 consumption rate per astronaut was between 480 and 570 liters/day, which is equivalent to a caloric production of 2, 330 to 2, 760 kcal/day, or a mean caloric output of 2, 500 kcal/day. Thus, these Apollo astronauts apparently had a caloric deficit of the order of 800 kcal/day. If it is assumed that 80% of the deficit was made up from body fat stores, and 20% from the catabolism of body tissues, this would account for a body weight loss of 250 g/day, for an average total weight loss of 2. 2 kg during one of these Apollo missions. However, from Fig. 1 it may be seen that there appears to be little correlation between the duration of the flight and the degree of weight loss, and a careful study of pre- and post-flight in vivo body composition of astronauts remains to be done in order to ascertain the nature of the weight change.

A start in this direction has been made for the most recent Apollo flights, and the results of one such set of measurements as reported by Berry (2) are shown in Fig. 2 for the Apollo 14 mission. Unfortunately, in this particular mission, the flight Commander and Lunar Module Pilot uniquely showed a slight weight gain on return to Earth. It should also be borne in mind that they spent 1. 4 days of their 9-day mission on the Lunar surface at 1/6 g. However, looking at the data for the Command Module Pilot, who remained weightless during the entire mission, it may be seen that he displayed a very large decrease in total body water, which surprisingly was reflected as a decrease in plasma volume and intracellular water but no change in extracellular fluid volume.

There are several points to be made about these data. First, the loss of 18% of the total body water of an individual the size of an astronaut represents a loss of about 8 liters of water, or 8 kg of weight. Yet the total body weight loss in the Command Module Pilot was only 5. 5 kg. Thus, one would have to postulate a gain of 2. 5 kg in some other body compartment, such as depot fat, to account for the difference. However, in view of the fact that Apollo astronauts typically had a daily caloric deficit of 800 kcal, this last possibility seems unlikely.

Second, the loss of more than one fourth of the intracellular water implies either a remarkable increase in the osmolarity of the intracellular contents, which is highly unlikely, or a corresponding loss of one fourth of the osmotically active intracellular contents of the body. While some loss of intracellular contents probably does occur in weightlessness, as indicated from measurements of total body potassium, the estimate of 27% loss in this individual seems high and is possibly ascribable to the fact that intracellular water was estimated by difference between total body water and extracellular water, which leads to high variance in the estimate.

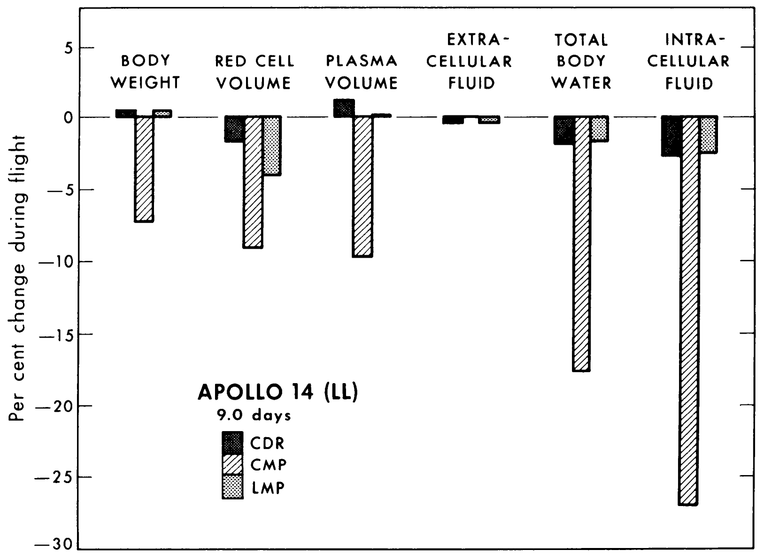


Fig.2. Body fluid compartment changes in the Apollo 14 astronauts.

Third, the decrease in plasma volume does not seem to be a constant consequence of weightlessness. Figure 3 summarizes the changes observed in plasma volume of the astronauts after the Gemini 4, 5 and 7 flights (12). Also included are the measurements from the Apollo 14 astronauts shown in Fig. 2. According to Berry (1), the plasma volume of the Apollo 7 through 11 astronauts did not change significantly. Thus, at present it must be concluded that there is no consistent change in plasma volume associated with exposure to weightlessness.

Only two serious USA attempts have been made to measure water and electrolyte balance during exposure to weightlessness; namely, in connection with the Biosatellite 3 monkey flight and with the Gemini 7 flight. The USSR has reported that balance studies were made in connection with the Cosmos 110 and Soyuz 9 flights, but no data have been published. The Biosatellite 3 metabolic balance experiment could not be completed because of the demise of the animal, so its value was limited (10). Thus, the results from the 14-day Gemini 7 mission represent the bulk of our information in this area at present, and even here some uncertainties exist because of difficulties with the quantitative collection of urine during the flight. Lutwak et al. (8) have reported the results in detail.

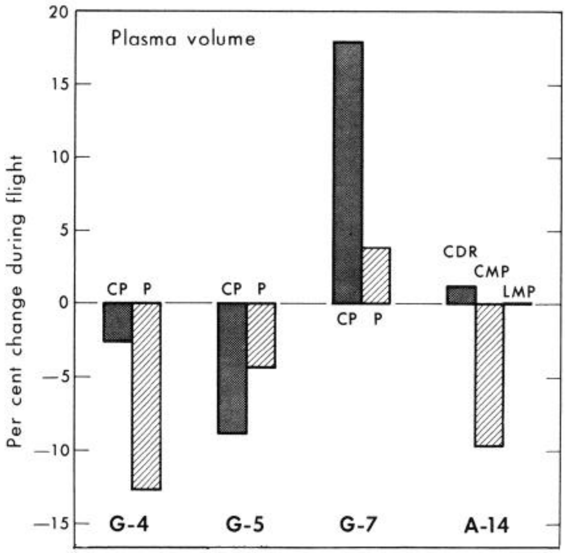


Fig.3. Plasma volume changes in the Gemini 4,5,7 and Apollo 14 astronauts.

There is little question that some urine spillage occurred during the Gemini 7 flight, apparently because of the cumbersome nature of the special urine collector developed by NASA for use in weightlessness. The urine from each of the two astronauts was collected in 2-day periods throughout the flight, and was returned to Earth with the excreted feces at the end of the flight. Analysis of the urine samples by Lutwak et al. revealed a substantial decrease in creatinine excretion rate during the flight, as seen in Fig. 4. Partly because it was known that some urine spilled in the spacecraft, and partly because urinary creatinine excretion rate did not change in a separate bed-rest study, Lutwak et al. concluded that it likewise did not change during the Gemini 7 flight. Accordingly, they corrected all other measured flight urine constituent excretion rates by the ratio of the pre-flight and post-flight creatinine values to the in-flight creatinine values.

Urine creatinine excretion rate was measured by our laboratory in collaboration with the Jet Propulsion Laboratory on the Biosatellite 3 monkey before and during flight (10), with the results seen in Fig. 5. It appears that in comparison with 4 ground-control animals the creatinine excretion rate was promptly and substantially reduced at the start of the flight, and remained low during the flight. In this experiment there was no question of urine leakage.

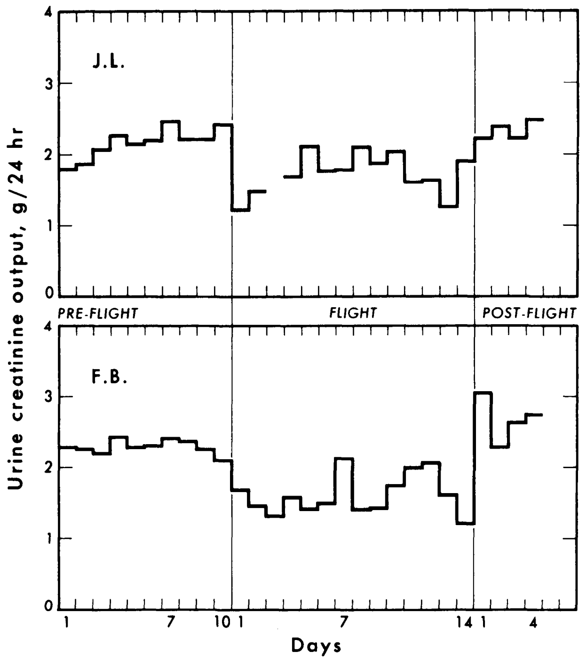


Fig.4. Urine creatinine excretion rates in the two Gemini 7 astronauts.

On this basis, I examined the assumption of Lutwak et al. more carefully. From their data in Fig. 4 it may be computed that the mean in-flight urine creatinine excretion rates were 68% and 78% of the pre- and post-flight values for Borman and Lovell, respectively. Even assuming a relatively low urine output of 1,000 to 1,200 ml daily, this means that each astronaut would have had to spill about 300 ml of urine daily throughout the flight to validate the assumption of no change in urine creatinine excretion rate. Such a high spillage rate seems most unlikely; therefore, it is possible that the Gemini 7 astronauts did exhibit a true reduction in creatinine excretion rate during their flight.

Accordingly, I have "decorrected" the in-flight urine data of Lutwak et al., and recomputed their metabolic balance data for comparison. Figure 6 shows the Albright-Reifenstein plot for calcium, phosphorus, nitrogen and sulfur balances for astronauts Borman and Lovell before, during and after the 14-day Gemini 7 flight as presented originally by Lutwak et al., and as "decorrected" for urine loss. In all probability the true state of affairs lies between these two sets of figures, and on this basis one can reach the following conclusions.

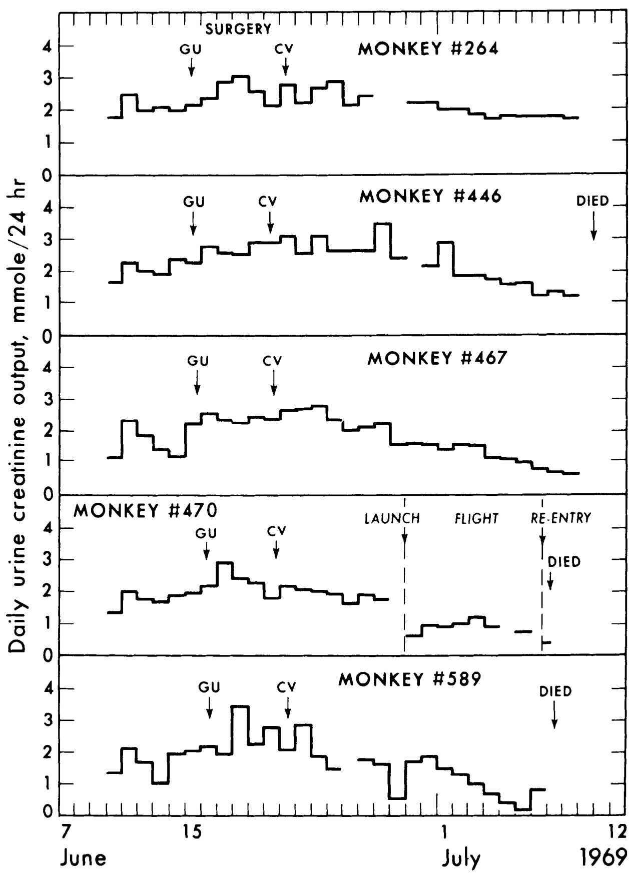


Fig.5. Urine creatinine excretion rates in the Biosatellite 3 flight monkey (#470), and 4 ground control monkeys.

Calcium balance appears to have been maintained in both astronauts despite earlier reports (9) of a decrease in X-ray density of the skeleton as a result of the flight. In this connection, it is of interest to note that Berry has recently stated (2) that examination of heel and arm bones of the Apollo 14 astronauts by a "monoenergetic photon absorption technique" before and after flight revealed no significant mineral losses during the 10-day mission. On the other hand, the Soviets have stated that X-ray density of the skeleton was significantly diminished in both the Cosmos 110 dogs and the Soyuz 9 cosmonauts (4). Thus, the entire question of whether or not bone demoneralization occurs during exposure to weightlessness is still open.

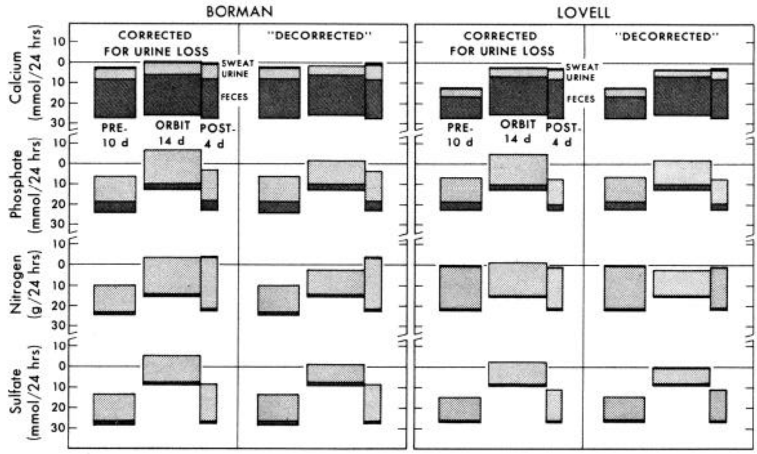


Fig.6. Albright-Reifenstein plots of calcium, phosphorus, nitrogen and sulfur metabolic balances before, during and after flight for the two Gemini 7 astronauts. Degree of negative balance is shown by the extent to which the bars are above the zero line.

In contrast to the situation with respect to calcium, the two Gemini 7 astronauts showed clear evidence of a negative phosphorus balance during flight. A possible explanation for this in the absence of clear evidence for skeletal demineralization might be that soft-tissue, such as muscle, loss may have occurred, and that there was a net loss of intracellular phosphorus.

Although the data in Fig. 6 are equivocal, it is probable that negative nitrogen balance occurred during flight. There are two reasons for this conclusion. One is the mounting evidence (5) that metabolically produced nitrogen gas, N_2, represents an additional and significant channel of nitrogen loss from the body, which is not accounted for in classical nitrogen balance measurements such as these. Second are the sulfur balance data shown at the bottom of Fig. 6. It seems fairly certain that both astronauts displayed a negative sulfur balance in flight. A likely source for the excess sulfur loss is the catabolism of tissue protein, and a negative sulfur balance would be expected to accompany a negative nitrogen balance under these circumstances.

Figure 7 shows similar plots for potassium, sodium and magnesium balances. There seems little question that the Gemini 7 astronauts experienced a large negative potassium balance as a result of the flight. It should be noted that the scale for potassium and sodium is 5 times that for the other graphs. Thus Borman had a negative potassium balance somewhere between 34 and 65 mmol/day, say 50 mmol/day, for 14 days, making a net loss of 700 mmols of body potassium during the entire flight. This represents almost 16% of his total body potassium, and is much more than could be accounted for by his loss of 5.2 kg of body weight, even if all his weight loss had been body tissue. Similarly, Lovell had a negative potassium balance between 12 and 23 mmol/day, say 17 mmol/day, for 14 days for a loss of 240 mmols of body potassium, or about 5% of his total body potassium. Again, this is a high figure judging from his body weight loss of 3.1 kg.

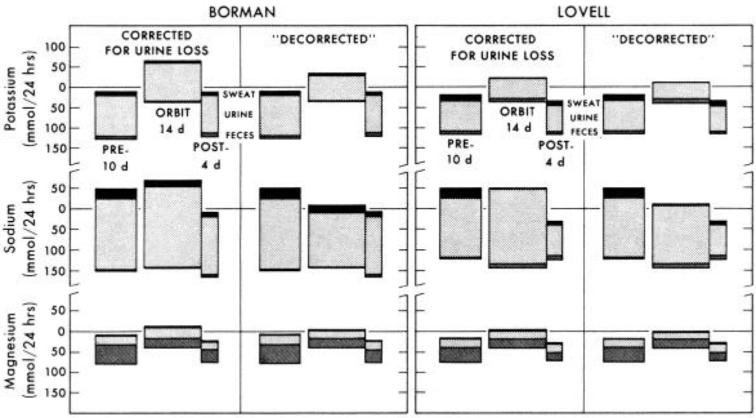


Fig.7. Albright-Reifenstein plots of potassium, sodium and magnesium metabolic balances before, during and after flight for the two Gemini 7 astronauts. Degree of negative balance is shown by the extent to which the bars are above the zero line.

Berry (2) states that total body potassium content was determined on the Apollo 13 and 14 astronauts by gamma spectrometry of ^{40}K, and on the Apollo 15 astronauts by the use of ^{42}K, before and after flight. According to him, a significant decrease in total body potassium was seen, but experimental details are not given. In a recent newspaper story (3), Berry is quoted as saying that the Apollo 15 astronauts showed a body potassium loss of up to 15%, and that two of them had abnormal heart beats during flight which may have been related to low potassium levels.

Both Gemini 7 astronauts also exhibited a negative sodium balance during the flight, and calculation shows that Borman lost 560 mmols, or 11%, of his total body sodium, while Lovell lost 420 mmols, or 8% of his total body sodium. The principal source for the sodium lost would have to be the extracellular fluid; yet, it may be recalled from Fig. 2. that the extracellular fluid volume in the Apollo 14 astronauts did not change. Thus, the nature of the large cation deficit apparently incurred by the Gemini 7 astronauts is a major question at present.

Finally, there is the suggestion that a small negative magnesium balance may have occurred during the flight. If this was indeed the case, it would seem likely that the source of the magnesium lost may have been the loss of muscle tissue rather than skeletal mineral.

Lutwak et al. (8) also reported measurements of urinary excretion rates of several hormones on the Gemini 7 astronauts during flight, and their results are summarized in Fig. 8. They corrected their measurements on the basis of urine creatinine for the ostensible urine losses during the flight, as before, and again I have included the "de-corrected" values. Little can be said concerning the significance of the urinary excretion rates of epinephrine and norepinephrine, other than that they were not dramatically different from the pre-flight values. However, it is apparent that striking changes did occur in the excretion rate of the adrenocortical hormones. It may be seen that aldosterone was elevated during the period of the flight, and that the 17-OHCS were substantially reduced in both astronauts, even on examination of the "de-corrected" data.

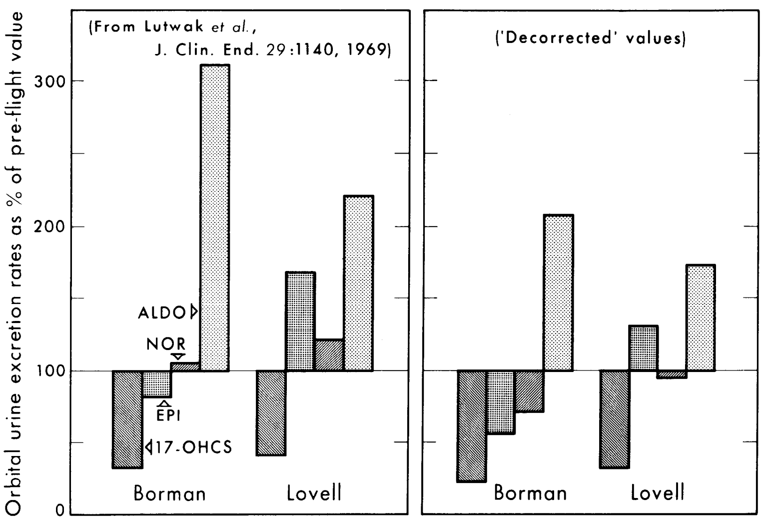


Fig.8. Mean change in urinary excretion rate of 17-hydroxycorticosteroids, epinephrine, norepinephrine and aldosterone for the two Gemini 7 astronauts during orbital flight.

Figure 9 shows the urinary excretion rate measurements for these hormones in more detail. Unfortunately, data for aldosterone excretion rates are lacking for the first 4 days of the flight, but it is clear that aldosterone was significantly increased over the pre-flight values during the last 10 days of the flight. Borman exhibited a return to pre-flight excretion levels on the third day after return to Earth, whereas Lovell showed elevated levels even on the fourth day following the flight.

The 17-OHCS, on the other hand, showed a prompt drop on entering orbit and remained depressed throughout the flight. On return to Earth there seemed to be an overshoot on the first day back, followed by a prompt return to the pre-flight excretion rate.

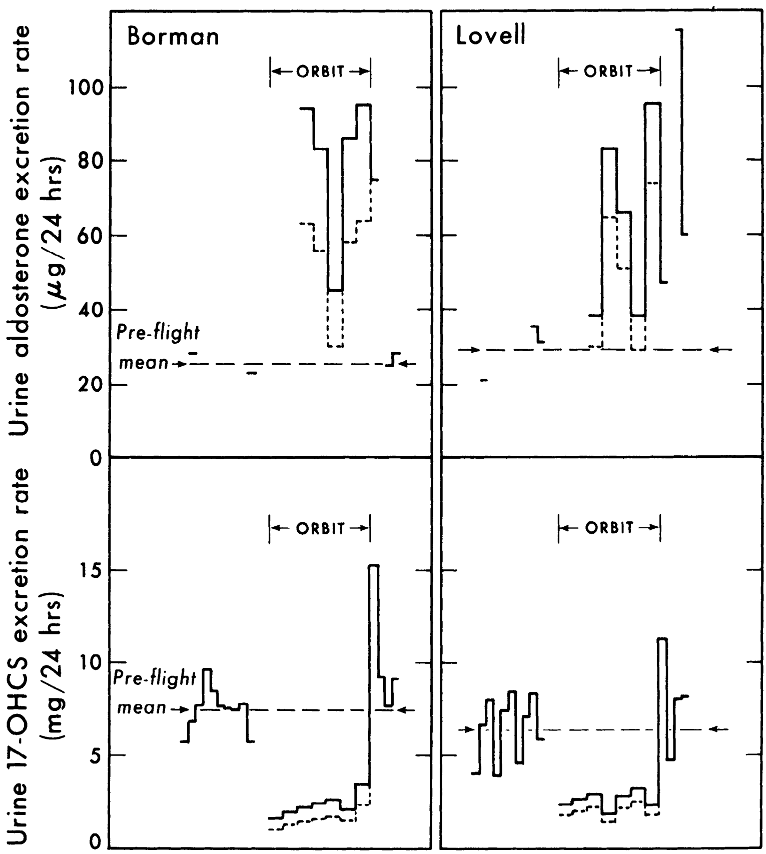


Fig.9. Urine 17-hydroxycorticosteroid and aldosterone excretion rates for the two Gemini 7 astronauts before, during and after orbital flight. Solid lines during orbital flight are the corrected values of Lutwak et al. (6). Dashed lines during orbital flight are the "decorrected" values.

There is no ready hypothesis to explain these substantial endocrine changes, although Leach et al. (7) have proposed an entirely theoretical sequence to account for some of the changes observed. Their scheme is presented by Berry (2). They postulate an initial triggering of the Henry-Gauer reflex as a result of redistribution of the blood volume to the chest on entering the weightless state, with a resultant decrease in antidiuretic hormone production and a simultaneous decrease in aldosterone production early in the weightless period, which supposedly leads to a diuresis and net water, sodium and potassium loss from the body. There is, however, no experimental evidence at present for these suggested endocrine changes.

They further postulate that at some unspecified later time during weightlessness aldosterone and antidiuretic hormone production tend to increase and as a result water loss ceases and a new electrolyte balance is reached. At the same time, they suggest that a "compensated intracellular acidosis" develops and other changes occur, including an increased lung ventilation and decrease in plasma carbon dioxide. Again, little experimental evidence exists to support the proposed scheme.

It may be added that Berry (2) states that analyses have been made on pre- and post-flight blood and urine samples from the Apollo astronauts which indicate post-flight elevations in antidiuretic hormone and aldosterone levels, and plasma angiotensin levels indicating increased renin activity. Actual experimental data have not yet been given, however.

It is of interest, and of possible relationship to the problem of weightlessness, that Knochel et al. (6) have recently described the occurrence of a large body-potassium deficit in subjects undergoing intensive physical conditioning in a hot climate, despite a normally adequate potassium and sodium intake, and which is accompanied by high excretion and secretion levels of aldosterone and high levels of plasma renin activity. Furthermore, in vivo body composition measurements on the subjects indicated that the potassium deficiency was not the result of catabolism. They propose that an overproduction of aldosterone under these circumstances facilitates continued excretion of potassium by the kidney despite serious depletion of the total body potassium. The parallelism of their findings with at least some of the major aspects of the weightlessness problem is deserving of further consideration.

In summary, I should like to say that the removal of man or other mammals from the influence of the normal gravitational acceleration field of the Earth during space flight clearly results in physiological changes. Prominent among these are substantial, and potentially critical, alterations in fluid and electrolyte balance and a variety of endocrine responses. At present, little is known of the detailed nature and time course of these changes during weightlessness, and whether they represent a new adaptive steady-state or whether they will progress further, perhaps to the point of physiological failure, with periods of exposure longer than the 3 weeks experienced up to now.

It is abundantly evident that careful study of the changes produced by weightlessness through well-designed animal experiments to complement the observations on man in space can contribute greatly, not only to an explanation of the effects of weightlessness, but even more importantly to our fundamental understanding of the role of gravity as a physiological shaping factor in our environment here on Earth. NASA is earnestly beseeched to make their unique spacecraft facilities available for the conduct of this much-needed basic biological research.

REFERENCES

1. Berry, C. A. Aerospace Med. 41: 500, 1970.
2. Berry, C. A. 4th Internat. Symp. Internat. Acad. Astronautics, Yerevan, Armenia, USSR, October 1971.

3. Berry, C. A. New York Times, p. 11, April 12, 1972.
4. Biryukov, Y. N., and I. G. Krasnykh. Space Biol. Med. 4(3): 58, 1970.
5. Cissik, J. H., R. E. Johnson, and D. K. Rokosch. J. Appl. Physiol. 32: 155, 1972.
6. Knochel, J. P., L. N. Dotin, and R. J. Hamburger. J. Clin. Invest. 51: 242, 1972.
7. Leach, C. S., W. C. Alexander, and C. L. Fischer. Physiologist 13: 246, 1970.
8. Lutwak, L., G. D. Whedon, P. A. LaChance, J. M. Reid, and H. S. Lipscomb. J. Clin. Endocrinol. 29: 1140, 1969.
9. Mack, P. B., P. A. LaChance, G. P. Vose, and F. B. Vogt. In: A Review of Medical Results of Gemini 7 and Related Flights. Management Center, Kennedy Space Center, Florida, August 1966, p. 83.
10. Pace, N., B. W. Grunbaum, D. W. Kiepert, D. F. Rahlmann, and G. D. Smith. NASA Contract NAS 2-4231 Report. University of California, Berkeley, December 1971.
11. Samonski, F. H., Jr., and E. M. Tucker. NASA Technical Note D-6718. Washington, D. C., March 1972.
12. Vogt, F. B. NASA Contract NSR 44-024-006 Report. Texas Medical Center, Houston, March 1967.

EFFECTS OF WEIGHTLESSNESS ON SIMPLE LIFE FORMS IN BIOSATELLITE II*

F. J. DE SERRES**
Biology Division
Oak Ridge National Laboratory, Oak Ridge, Tennessee

This symposium was preceded a few days ago by another milestone in the history of Biosatellite II, the publication of "The Experiments of Biosatellite II" with Joseph Saunders as editor. This publication, NASA-SP-204, is available from the United States Government Printing Office for $3.50. Those of you who want to read about the details of the Biosatellite II experiments will find them in this book; I do not intend to discuss the results except in a very general way during my presentation.

The title of my talk might be more aptly titled, "The Experiments of Biosatellite II: Reflections Five Years Later." I was not only an experimenter on this mission; I had the additional role of Experimenter's Representative. In my latter capacity it was critical to keep in mind the overall objectives of the mission rather than just those of my Neurospora experiment.

It is important to remember that the experiments on Biosatellite II were designed to determine the effects of weightlessness, both alone and in combination with known doses of radiation, on a variety of fundamental biological processes. Many different experimental organisms were used so that we could make a general survey and find out whether the same effects would be found in different organisms. It was intended as a broad-spectrum, exploratory experiment to determine whether there were any basic biological processes that would not function properly under weightlessness. If positive results were found it was planned to study them in greater detail in later flights.

The same general approach was used to study the combination of weightlessness and known doses of radiation as was used to study weightlessness alone. What we wanted to know from this set of experiments, basically, was whether the ground rules developed during 20 or more years of radiobiological experimentation on earth would be valid in the new space environment. Again, the basic philosophy was to use as many endpoints as possible to determine primarily whether any unexpected positive results would be found that should be studied more thoroughly on later flights.

---

* Research sponsored by the U.S. Atomic Energy Commission under contract with the Union Carbide Corporation.

** Present Address: Mutagenesis Branch, National Institute of Environmental Health Sciences, National Institutes of Health, Research Triangle Park, North Carolina 27709.

In the design of the Biosatellite II mission a 3-day flight was planned to investigate the effects of a total of 72 hours of weightlessness. It was hoped that any effects of weightlessness would be observable after this exposure period. For many endpoints, 72 hours was considered by the experimenters as an absolute minimum to make a meaningful evaluation of this new environment.

Obviously what we were actually interested in predicting was the effect of prolonged periods of weightlessness on man - and what we hoped to learn from our experiments with laboratory organisms was whether there were any effects of weightlessness on fundamental biological processes that could present a problem for men, either in laboratories in space or on flights of long duration.

The Biosatellite II mission carried several experiments with plant and animal systems that were designed to study the effects of weightlessness on growth, metabolism, cell division, and differentiation. These experiments will be discussed by Dr. Brown in the presentation to follow. The objective of the remainder of the experiments was to look for an effect of weightlessness alone on these same processes in other organisms, as well as to study the effects of radiation exposure under weightlessness. Since the levels of ambient radiation in space are low, the total exposure expected during a 72-hour flight would be too small to yield statistically reliable data, so gamma radiation from an onboard ^{85}Sr source was used to give high levels of exposure over a wide range.

Most experiments were designed so that dose-effect curves could be obtained for given endpoints both from the flight material and from simultaneously irradiated ground controls. The radiation experiments were performed in organisms that had been used to study the genetic effects of radiation, and the effects expected in ground-based radiation exposures were thoroughly studied prior to flight. These experimental organisms included the fruit fly Drosophila melanogaster, the parasitic wasp Habrobracon, the flour beetle Tribolium, the bread mold Neurospora, phage and lysogenic bacteria, and the blue wildflower, Tradescantia. Tradescantia, for example, has been used for many years by many well-known cytogeneticists to study radiation-induced chromosome aberrations, and more recently to study radiation-induced gene mutations. Both of these genetic effects were also studied in the Biosatellite II experiments with Drosophila and Habrobracon. In addition to many other endpoints, these test systems made it possible to study such fundamental processes as cell division in both somatic and germ cells.

We anticipated two types of results. We could either get no effect at all, or we could get an effect in either direction (antagonism or synergism). If we obtained no effect of weightlessness on all of these different endpoints, then it seemed that it would be possible to say with reasonable confidence that it was unlikely that weightlessness would have an effect on the same processes in man. If, on the other hand, an effect of weightlessness was found, this would provide justification for more detailed experimentation - first of all to rule out the possibility that the effect was associated with some other flight parameter such as vibration or acoustic noise that might be experienced during launch or reentry, and second to show that the effect was reproducible and to determine its magnitude in tests on a wider variety of organisms on later space-flight missions.

We did not get the 72 hours of weightlessness planned for Biosatellite II but only 45, because of an early calldown due to a tropical storm developing in the recovery area in the Pacific. Even with this shorter exposure, however, significant effects of weightlessness were observed in many of the experiments. Some of these effects have been summarized by Alan Brown in Table 1. In this table you can see the level of effect expected from radiation alone in ground-based experiments. If no effect of weightlessness had been found, the percentage in the final column would be 100. A lower percentage than 100 indicates an antagonistic effect of weightlessness, or a smaller effect than expected. A value higher than 100% indicates synergism, or a greater effect than expected. The main point to be derived from this table is that both antagonistic and synergistic effects were found. In some cases the effects were found to be the same in different organisms, in other cases they were not.

TABLE 1. Incidence of genetic defects related to the interaction of weightlessness and radiation[a]

Defect	Organism	Conditions[b]				ΔR	Δg		$\frac{0g + R^{d}}{\Delta R + \Delta g}$	Effect[e] of 0g
		1g	1g + R	0g	0g + R[c]	[(1g + R) - 1g]	(0g - 1g)	ΔR + Δg[c]	(%)	
Dominant lethality (female)	*Tribolium*	0	47.6	19.7	22.8	47.6	19.7	67.3	34	Antagonism
Blue to pink color	*Tradescantia*	0.2	7.3	0.3	4.4	7.1	0.1	7.2	60	Antagonism
Dominant lethality (male)	*Tribolium*	0	8.3	4.6	11.4	8.3	4.6	12.9	88	Antagonism
Chromosome translocation	*Drosophila*	0	0	0.56	0.80	0	0.56	0.56	143	Synergism
Altered nuclei	*Tradescantia*	0	0.06	0.25	0.55	0.06	0.25	0.31	177	Synergism
Deformed thorax	*Drosophila*	0	1.3	0	2.8	1.3	0	1.3	215	Synergism
Split wing	*Tribolium*	16.8	29.9	19.0	44.8	13.1	2.2	15.3	293	Synergism
Pollen abortion	*Tradescantia*	39.0	48.0	37.0	66.0	9.0	-2.0	7.0	944	Synergism
Stunted hairs	*Tradescantia*	10.5	12.9	10.1	26.6	2.4	-0.4	2.0	1330	Synergism

[a]Tabular entries taken directly or recalculated by Dr. A. H. Brown from published sources. Numerical values indicate percent incidence

[b]1g = normal gravity; 1g + R = normal gravity, radiation; 0g = weightlessness

[c]Prediction based on additive effects

[d]Observed incidence/predicted incidence

[e]Antagonism = desensitization to radiation-induced damage; synergism = enhancement of radiation-induced damage

Most disturbing in this bewildering array of effects is the evidence for a disturbance of fundamental life processes by weightlessness alone, as well as the synergism obtained in combination with radiation. We do not understand the basic mechanisms responsible for these effects in our experimental organisms, much less in man. It is important to note, however, that we have found significant effects of weightlessness on metabolism, cell division, and differentiation in both the plant and animal experiments. Many of the experimenters do not understand the effects that they have found in their experiments; and since they have not had an opportunity to follow up these observations with additional experimentation under weightlessness, they find themselves in the rather awkward position of having to extrapolate positive findings from exploratory studies with experimental organisms to man.

Extrapolation from test animals to man is a common problem in the area of toxicology, and in that field any positive effect obtained with a new chemical usually means that approval will not be granted for its use on man. The Biosatellite II experiments have clearly shown that there are effects of weightlessness on fundamental biological processes. There is no doubt that these are processes of importance for man.

In my judgment our original plan for evaluating the biological effects of the space environment was a sound one, and these preliminary results should be studied more thoroughly in experimental organisms. Many of the effects found do not make any sense, in that they differ greatly from the results of our ground-based experiments. It is significant that some of the effects have been duplicated on other space flights. In the *Tradescantia* experiment, for example, the effect on cell division was also found by the Russians. It is also important to note that many of the effects observed could not be duplicated in our postflight controls when the various parameters associated with space flight, such as vibration, were tested on the ground.

There has been an unfortunate tendency to minimize the significance of positive findings of the Biosatellite II mission because of the tremendous cost of space research. Our critics say that because the effects are not very large, and because we don't really understand them, that they are of no importance. But for the experimentalist the most vexing situation is to get an effect that he did not expect and does not understand. In his usual experiments in a ground-based laboratory, this is where the experimentation really begins, to try to get a better understanding of the new phenomenon he has discovered. We are in exactly this situation with much of the Biosatellite II data, but to repeat and extend the experimental observations is considerably more difficult.

As an experimenter on this mission and also on the Gemini XI mission, I hope to see more opportunities for this type of research made available in the near future. After considerable reflection, five years later I feel we have made a good start. But we are only in the exploratory phase of development. Our data tell us that there is something there to study, but it is important to remember that we have really only begun to explore the biological effects of this new frontier!

FUNDAMENTAL PROBLEMS IN THE GRAVITATIONAL PHYSIOLOGY OF PLANTS

ALLAN H. BROWN
University of Pennsylvania
Philadelphia, Pa.

Two broad experimental areas comprise the research potential referred to as the gravitational physiology of plants: geotropism (or gravitropism), the detection and response of plants to the direction of the g-vector, and gravimorphism, the influence of direction and magnitude of the g-force on plant development.

To investigate the gravitational physiology of plants an experimenter must alter the gravitational inputs to test organisms. He can increase the g-input by performing experiments on a centrifuge. He can decrease g only by sending his experiment aloft in a satellite. In space flight the limiting value, g = zero, may be closely approximated and this condition (weightlessness) may be the most interesting of all abnormal g situations for experimental studies on plants.

Most experimental manipulations of the plant's g-input have taken the form or reorientation of the test specimen - i.e., change in the direction of the plant's morphological axis with respect to the earth's gravitational vector. Of special interest to plant physiologists is the test situation in which a plant is held in a horizontal position and rotated slowly about its longitudinal axis with an apparatus termed a clinostat. The continuous reorientation achieved by a clinostat has the apparent effect of gravity compensation or "nullification" - a term which suggests that growth on a clinostat may simulate growth at zero-g.

Plant phenomena which need to be studied in terms of their g-functions include:

1. Behavior of statolith starch. We do not fully appreciate how statolith starch may function as a sensor in g-perception and there is not even general agreement that sedimentation of amyloplasts constitutes the physical basis of g-perception by the higher plant.

2. Plagiotropic angles of lateral organs. We cannot explain how plants determine the angle to be assumed by lateral roots, branches, or leaves even though such angles are precisely determined.

3. Interaction of the g-factor with other influences - e.g., the susceptibility to influence by ionizing radiation.

4. Pattern of development at the several levels of organization. We are largely ignorant of the diverse roles g-forces play in determining polarity and in other ways affecting development.

5. Circadian and other rhythms. Although we are ignorant of the fundamental mechanism of circadian timing in plants, several lines of evidence have implicated g-inputs in the phasing process.

6. Circumnutation. Whether nutational behavior is g-dependent still is moot point.

For each of the items listed a cogent argument exists which predicts that the results obtained could provide the answer to one or a series of specific, non-trivial, scientific questions.

Because of our scant understanding of the basic physiologic mechanisms which account for these plant phenomena, they are ripe for exploratory studies. If we experiment with well defined but poorly understood phenomena by entirely original methods, we may expect a better than average chance of making interesting scientific discoveries. Perhaps it is for this reason that the space laboratory has proved attractive to biologists in a variety of research specialties. It can provide an incontestably unique experimental environment.

Possibly the most promising area for experimentation on the gravitational physiology of plants is item 4, the effects of g-variation on morphogenesis. This area was accorded high priority in NASA's Bio-Satellite program for it seemed evident that to observe the development of a higher organism throughout its entire life cycle in an abnormal g situation should offer maximal opportunity for the biologist to discover hitherto unsuspected relations between the g-factor and the processes responsible for different stages of development. While this has been done in some cases for greater than normal g with plants growing on centrifuges, no higher organism - plant or animal - has been raised for a major fraction of its life cycle in an environment of less than the earth's one g.

Unfortunately weightlessness has been a very difficultly accessible test condition for plant physiological research. Of the six items on the above list of botanical research topics only the first three have been examined with plants placed in the extreme environment of weightlessness. Moreover, of those experiments which yielded substantive if scanty results, all were accomplished by a single space mission, the first successful flight of the Biosatellite Program.

Biosatellite II carried several small plant experiments to test the effects of weightlessness on: a) a variety of histological, cytological, and biochemical properties of very young wheat seedlings germinated under weightlessness, b) the kinetics of early development of the wheat seedlings, c) the plagiotropic angle of lateral wheat roots and of the leaves of Capsicum plants, d) the incidence of cytological abnormalities in root tips and floral buds of rooted Tradescantia cuttings, and e) interaction with effects of ionizing radiation delivered in the weightless condition.

Only some of the experimental results of plant space flight were anticipated (1). The distribution of so-called statolith starch was "randomized" more or less as expected. Microscopy and biochemical assays mostly showed no effects of weightlessness on the properties examined. However, some quite significant effects were revealed with respect to: nuclear volume and mitotic index (wheat); abnormalities of root tip nuclei and disturbance of mitotic spindle in mega- and microsporagenesis, flower production, and occurrence of micronuclei in pollen (Tradescantia); lateral root epinasty (Capsicum); and enhancement of ionizing-radiation damage causing pollen abortion, stamen hair stunting, increased pollen micronuclei, and disturbed mitotic spindles (all in Tradescantia).

Of special interest with botanical test subjects in satellite orbit is the degree to which the slowly rotating horizontal clinostat mimics the condition of weightlessness. Accordingly most of the relevant tests in Biosatellite were repeated on a clinostat. As some plant physiologists had predicted, some of the plant responses examined were significantly different on the clinostat and in space flight.

More surprising was the finding that in some cases space flight had highly significant effects on the sensitivity of plants to radiation. Although most of the radiation effects tested with plants were not influenced by weightlessness, some clearly were affected. It cannot be safely assumed that our extensive ground-based knowledge of biological effects of ionizing radiation can be freely extrapolated into the space environment.

REFERENCES

1. Saunders, J. F. (Editor) 1971. The Experiments of Biosatellite II. NASA Document SP-204.

SIGNIFICANCE OF BIOLOGICAL INVESTIGATIONS IN WEIGHTLESSNESS

ORR E. REYNOLDS
American Physiological Society
Bethesda, Md.

The significance of biological investigations in weightlessness, as in any other field of biological investigations is many-faceted. The significance, from the standpoint of purely scientific content, is one that I do not intend to spend much time on, because the members of the audience are in a position to assess this for themselves from the presentations of the preceding speakers.

However, I should say that since the birth of modern biology with the work of Charles Darwin until about one decade ago, gravity was the principle environmental condition of terrestrial life remaining unexplored. (Darwin himself commented on the impossibility of removing gravitational attraction, as one would modify light intensity or other environmental influences, and therefore the inaccessibility of geotropism to study). The number of surprises that may await us in the study, under null gravity, of the operation of previously studied functional processes is therefore high. We have already heard some examples of such surprises.

Another way of assessing significance is in terms of contributions to the scientific literature. As of July, 1971 we know of 2739 papers in scientific journals arising from the NASA Biological Science Program over the preceding 10 year period. A large proportion of these papers deal with gravitational studies either in weightlessness, or in ground control studies for weightless experiments. The Biosatellite Program itself produced between 250 and 300 papers, in over 50 scientific journals, monographs, reports and contributions to books.

A third area of significance of these biological investigations is the production of new technology strengthening the interface between biology and engineering, with spin-off to future flight experiment programs, the medical management of manned space flight, and advances in medicine, agriculture and environmental quality control.

Perhaps the most significant product of this program, however, has been the new experience, for biologists, of working in a highly organized engineering development system. Although this is a trying and difficult experience, it is the only way some problems can be successfully attacked. Therefore, the Biosatellite Program* may well serve as a model for future large operations, such as the development of health care delivery systems and environmental quality control systems.

This was a most demanding program in terms of management, learning new skills and languages, and maintaining a common responsibility

* A Motion Picture film "Biosatellite Primate Mission - Progress Report, 1968" was shown.

among a large number of people. (Approximately 5000 people worked on the Biosatellite Program, and at peak periods, as many as 2500 were working at the same time). The next opportunities for scientists to experiment in the area of the physiology of weightlessness will be in the Skylab Program, the Space Shuttle and eventually a Manned Space Station. I believe it is almost certain that the complexity of mounting biological experiments in these systems will be no less complex than was the case for Biosatellite. However, I think it is most important that this effort be made for the following reason.

One of the principal advantages of animal research is gained by discovery of a biological system that is more sensitive to the experimental variable than is man. Although the results from one animal's responses do not allow great confidence in the conclusion, it appears that the monkey may be more sensitive than man to the circulatory-fluid balance disturbance.

Thus it may well be possible, using monkeys as experimental animals, to discover whether complete adaptation to the weightless environment can be attained by appropriate remedial measures, such as adjustment of fluid and electrolyte balance, in flights of much shorter duration than would be required for man. Furthermore, the experiments on animals can be controlled to a much greater degree than is ever possible with human subjects.

Thus experiments with sub-human primates seems a very prudent measure to answer the question of long term adaptation to weightlessness, a question which the available data on man does not provide an answer.

NEWS FROM SENIOR PHYSIOLOGISTS

Dr. D. B. Dill reported the death of Charles D. Snyder, oldest member of the Society and submitted the following obituary:

Dr. Charles D. Snyder died March 21, 1973 at Los Altos, California. He would have been 102 years old on April 30, 1973.

Dr. Snyder was the oldest living graduate of Stanford University where he had been a roommate of President Hoover. He had been on the medical school faculty from 1908 until his retirement in 1941.

Born in Circleville, Ohio, he moved to the state of Washington with his family when he was 12. After graduating from Stanford, he obtained his doctorate from the University of California at Berkeley in 1905 and then obtained a fellowship for study at the Marine Biological Laboratory in Naples. Following that, he studied at the University of Berlin, where he met Jacobus van't Hoff, a Dutch chemist and winner of the first Nobel Prize. Dr. Snyder married the chemist's daughter Aleida, who died in 1971. The couple came back to the United States when he took up his post at Johns Hopkins University. He was professor of experimental physiology until his retirement.

Two studies done by Dr. Snyder received wide attention: The first, published in his doctoral dissertation, showed that temperature had similar effects on muscle and nerve responses as it does on chemical reactions. The second, done in the 1930's, rated cultural achievement of countries according to their performance in the Olympics, their number of Nobel Prize winners and the appearance of their natives in "International Who's Who." He concluded that small countries did better, but racial conclusions drawn from the study led to controversy.

Dr. Snyder is survived by his son, Dr. Thomas Snyder and two daughters, Mrs. Francina Jacobs, of Pittsburgh, and Mrs. Annaleida van't Hoff, of Andover, New Hampshire.

The following letters and notes were received by members of the APS Senior Physiologists Committee in response to their inquiry of 1972.

Milton Lee to Bruce Dill:

I keep busy, as much as health allows, at a number of interesting projects. Up to the time I moved from Miami, I was working with the Organization for Tropical Studies, and as nutrition consultant for a hospital in Miami. Since living here (Sarasota) I have delayed taking on some work with the Mot Marine Laboratory, but plan to begin there soon. Wish I had time to do some fishing!

Max Kleiber replied to Bruce Dill in his accustomed stimulating style:

Would for retirement a commiseration be more realistic than a congratulation? I feel not. Despite, at times frightening, observations of symptoms of senility during the decade since my own retirement I am still enjoying life and thus it is honest when I welcome a new member to the group of retirees. I cherish mutual love with the members of my family, and with my friends especially my former students who achieved recognition for me, even a "Kleiber Hall" on this campus. Recognition by peers is helpful for maintaining a cheerful mood at the age of decreasing physical and mental power. But some of my former students, and their students, (scientific grandsons) and other friends are contributing an even more important cause for my continued joy of life. They are keeping their old professor busy with lectures at various academic institutes and scientific meetings in this country and abroad. This stimulates my brain to a level of activity which together with some physical exercise - increases the oxygen supply and slows down the process of deterioration.

Such lectures numbered 15 in 1962, 26 in 1971, total 238. I and my associates continue writing papers: 2 in 1962, 4 in 1971, total, 34. This level of activity is enjoyable; when I tried to work faster I suffered under frustration and the feeling of failure. That reduced the efficiency of my work. I want to recognize clearly the decrease of my capacity for mental work, I want to remain alert with self critique. I want to take my time. I don't mind to show my age in fewer publications per year but would hate to exhibit it in the quality of the product.

My major handicap is the decrease of the power of my memory. If a retired professor could afford to pay a good assistant or a competent personal secretary to operate a good filing system and keep order in his office, and even critically check his writing, then his work might well go on without showing the effect of old age. But a personal secretary is, as a rule, beyond the financial means of a retired professor or of the institution in which he works. I wonder if it would be possible to counteract the entropic increase of chaos in my brain by a corresponding increase of order in my environment, especially in my office. Recently Dr. von Bekésy in the School of Medicine of the University of Hawaii described to me his system of cubby holes for notes and reprints and books, which helps him in the publication of the results of his research. I like to try such a system to support and partly replace my deficient memory as a lame man gets along with crutches. Possibly some psychologists have already worked out such memory crutches and in this case the institute of gerontology might organize a short course in the use of such means of improving the efficiency of mental work in old age. I would like to apply for admission as a student in such a course in the hope it would help me to work more effectively on a few problems, especially semantics, in the physiological sciences and possibly also in a wider field of human endeavor before I accept - hopefully in a cheerful spirit - the final call to rest.

He added a question I pass on to members of the Society: Do you know if such educational opportunities for example are organized by the Society of Gerontology? I might apply as a student, possibly more fittingly from active membership in the American Physiological Society to Gerontology.

Aurin Chase to Hy Mayerson:

I have an office and a small lab and whatever apparatus, etc. I need. I never have to be involved in an exam or send in a grade anymore so things are about ideal. However, the departmental chairman invites me and my retired colleague to staff meetings so I can keep up with things if I want to. I have been playing around with some time-lapse cinematography and things of that sort that I enjoy but was not able to take much time for before I retired. Away from the lab there is of course music, work around the house and yard, canoeing, swimming, mild hiking and some occasional modest traveling; in all of which things my wife takes part, and sometimes also our daughter and her husband. (He is a college teacher himself). I still go to scientific meetings if they're not too far away. This I do think a retired person should continue to do if he can. One about always picks up something interesting and it's nice to see far-flung acquaintances.

Maurice Friedman to Hy Mayerson:

It was wonderful to get your note. I had gotten fed up with life in the United States, especially Washington, and decided that the last years of life should be spent in a more serene, secure, and happy environment. We sold our home in Washington, and moved in the Autumn of 1969. We have made friends quickly, so that we have an active and interesting social life, and the Swiss environment has proven to be even better than we had hoped. Among our friends here is one Stella Deignan, formerly Stella Loesch, whom you knew at Tulane. I am truly retired, insofar as I do nothing in the way of scientific research. I have however, been doing some reading and digging into the question of the relation of diet, cholesterol, and other factors relating to coronary disease. For a while I was tempted to write a paper blasting all of this nonsense about cholesterol, but it seemed that gradually, at least some of the people in the United States were beginning to realize what hokum it is. Now, I see that the U.S. is embarking on a grand project to "study" this question anew, with much larding of federal funds. Most of all I have taken this leisurely time of my life to read the many things I had not time for during my active career. I do things at my own pace, and had hoped to travel around Europe a bit more - which is something we have not yet found time to do. We still own a summer house in the Pennsylvania mountains, so that up until this summer, we spent about three months there, and then four to five weeks with the children around Washington at Christmas time. I think the time is soon coming when we shall sell the summer house, and not feel obliged to spend so much time there. We shall then be able to travel more here. Please write again, and remember that we are here in this lovely land if you happen to come to Europe.

Ernst Huf to Hy Mayerson:

It is nice to know that one is not forgotten. This is one of the essential ingredients which makes life worthwhile, especially if one approaches retirement age. I am 66 years old now, true, and I probably will retire next July. I plan to do this not because I have a health problem, or feel worn out, at least I don't think so. Because I feel fine, I would like to spend a few more years in active research, (probably abroad) undisturbed by routine duties, committee work, and in the hope that I can keep myself far out of reach of administrators!

Lawrence Bennett to Hy Mayerson:

Shortly I shall be foot-loose and fancy free after 40 years of teaching. I am really looking forward to some fun and freedom to do many things I have not found time for up to now. Helen and I are ready to hook up the Airstream and really get the feel of several areas in this country of which we have had only tantalizing tastes or no experience at all. In the meantime we retain headquarters here in an Omaha apartment and a University office. As of July 1st the Regents have appointed me Professor Emeritus in this department. My laboratory equipment, essentially intact, will be used by Dr. C. Michael Moriarty and his graduate students in further transmembrane potential studies, with the assurance to me that I can horn in whenever my wanderlust fades. Having recognized a very minimal coronary occlusion about a year ago as a friendly warning, I have worked up to 15 pts. on my Aerobics and intend to abstain from sitting at a desk anymore. Aside from the very deep satisfaction I have had when medical students and colleagues have commended me for good teaching and when I see some of my graduate students far outstrip me as scientists, I suppose the biggest kick I've had out of physiology has been in improvising, designing and often fabricating the tools for research. I guess I am a gadgeteer at heart. If, after some months of travel, I should become restless for a place to work, I would be happy to be useful again at a laboratory work bench - no more administrative paper work, curriculum shuffling or heavy teaching schedules. I could see myself having fun, as I have this past year, teaching a small group of highly motivated college or professional students such as the sixteen physical therapy students I now know on a first name basis.

He added this note: That is as far as I got with my letter to you when the second coronary occlusion put me in the hospital again just three days before that magic retirement day. I am fortunate in that it appears to be small twigs that plug, and again I seem to recover quickly. I hope that the travel plans can proceed soon. Any future work schedule appears a bit more uncertain. I went back to the office for the first time today to pick up mail. My advice to those approaching retirement is "Do it and enjoy it before it is too late."

Jessamine Hilliard to Hy Mayerson:

I am indeed continuing my scientific activities and hope to have space available to me here at the VA for at least another year and a half. My words of advice for persons approaching retirement are "not to retire" as long as health permits some degree of contributory activity. Your current position at a 560 bed teaching hospital with "never a dull moment" sounds most enviable. Nice to hear from you.

Bob Cleghorn to Hy Mayerson:

I was pleased to hear that you had found new activity and pleasure in your second career. I am continuing scientific activities in the form of attending occasional meetings of a physiological or psychiatric orientation, and try to keep up with the relevant literature and consult with, if not advise, my active young colleagues. I am busy enough running a ward and doing a little practice and teaching at the Allan Memorial Institute. Advice for those who are approaching retirement: Retain a youthful outlook and continue to follow with indulgence the progress of the scientific activities which they no longer greatly influence.

Joe Peters to Hy Mayerson:

I am continuing my scientific activities with both teaching and some research. An article is due to be published in a forthcoming edition of Developmental Psychobiology. Since I am occupied and busy at this time in both teaching and research here at Xavier University, I have no interest in another position. Advice for others: As long as a person's health allows it, continue to provide from your own acquired skills some needed service to the people about you, young or old. Before the age of retirement acquire a "hobby" in which you can engage when diminished health slows one down, e.g., good reading habits, enduring music (with only a small amount of time for mere sports or just TV).

Carl Schmidt's friends staged an 80th birthday celebration for him more than three months in advance. It was held on April 15, 1973 at the University Museum in Philadelphia. In August 1972 he replied to Hy Mayerson's inquiry:

I find that time passes very pleasantly under a program of maintenance of a bay-front house complete with tropical planting, a swimming pool that provides constant challenge and considerable exercise for four grandchildren who live five miles away and who have become almost amphibians. Participation (on a small scale) in the teaching program in the department of pharmacology of the new medical school in the University of South Florida located about 30 miles away in Tampa. Trips to Philadelphia twice a year (early blossom and autumn foliage seasons) where we have a small apartment and can come and go as we wish. When we moved here three years ago I was full of enthusiasm for joining the Drug Abuse Program. The enthusiasm didn't last long, for several reasons. First, the people in charge were not looking for the sort of help I could give them and I was unfitted by disposition and experience to embark on a one-man crusade against the prevailing system. Second, it soon became evident that a new Florida law calling for instruction on drug abuse in all the public schools was not going to be enforced because it had been passed under a Republican state administration that had just been supplanted by a Democratic. Third, local experience indicated that the drug abuse problem is not amenable to the scientific (i.e. impersonal) approach. Rather it will have to be solved by personal contact and experience supplemented by highly emotional interventions and strong legal compulsions. A friend that my twelve year old grandson knew, knew about as much about drug actions as I did, which further discouraged me.

Last month my wife and I went to San Francisco to attend the Fifth International Pharmacology Congress. It was a heart-warming experience because I helped organize and was the first president of the Section on Pharmacology of the International Union of Physiological Sciences from which the International Union of Pharmacology separated in 1968. Physiologists (at least senior ones) will see here another child of Mother Physiology coming of age and following Big Sister Bio (Physiological) chemistry out of the old homestead to set up an independent existence. This younger child has grown prodigiously. At San Francisco more than 5000 registered in attendance and all the main events were overcrowded. I already have a title in the new medical school in Tampa and am not interested in an administrative position, having had enough experience in such matters to convince me that I am no good at them. I would be reluctant to move to another area. Life here is comparatively simple. There are no problems with snow and ice, and between our grandchildren and the students at the University of South Florida we have ample reasons to keep abreast with the course of events in the younger world. We visit our old friends in Pennsylvanis often enough to renew old memories and associations and to strengthen our contentment with life in Florida. I guess this sounds pretty stodgy. Perhaps I should add something else to the activities. Well, there is always gardening (I'm getting pretty good at it); fishing (haven't done any for more than two months); photography (my wife says my pictures aren't as good as they used to be but isn't that true of everything one does as one approaches his 80th birthday?).

Advice for those who approach retirement now looks to me like advice to youngsters about drug abuse. I don't know how to generalize about something the advisee knows a lot better than the adviser. In my own case I had the advantage of two unusual circumstances: Newton Richard's advice and example entitled: Keep out of the way of your successor; and a Civil Service job after retirement from the University that enabled me to defer payment on my annuity while it accumulated to an extent that has greatly simplified our financial problems. I simply quote the one and state the other. Now that Florida streets are free of demonstrators bound to and from the presidential conventions, senior physiologists can begin to plan pilgrimages to such shrines as Disney World, Busch Gardens Aquatarium and Sunken Gardens. Maybe you will be tempted: if you succumb drop in and see us. Thanks for the letter and best wishes to you and all Senior Physiologists.

Melvin Knisely sent Hy Mayerson a reprint and added:

We have done simulations on the limitation of the rates of oxygen supply to nerve cells, glucose supply to nerve cells, and I am hoping, also, to get at the limitation of the rates of supply of thiamine and niacin to nerve cells. Experimental work so far does not contradict the concepts predicted in the enclosed reprint and experimental work is continuing. I deeply appreciate your concern for helping the senior scientists to continue their work. This civilization should not cheat itself out of the continuing product of experienced scientists. It certainly is good to know that you are on the team steering the teaching hospital. From what I have seen, I believe that the steering of such an institution would pretty well be kept in the hands of men old enough to have made their unnecessary mistakes already.

The following notes and letters were received by the Committee in response to birthday greetings sent to Society members on their 80th and subsequent birthdays.

C. A. Mills to Bruce Dill:

It was indeed pleasant to receive the 80th birthday card from you. As I move along now in my ninth decade, life seems to hold an abundance of zest and intellectual sparkle, even though physical energies sag somewhat. I find the quiet and even tenor of retirement very much to my liking and very conducive to freedom of contemplative thought. I do miss very much the physical facilities of the University which could do much to ease the technical burdens associated with my studies. Lacking contact with laboratory facilities, I must rely only on my own unaided efforts and these efforts become very tiresome in statistical studies such as I am doing. However, I have made real progress in relating the gravitational pull of the moon to the batting performance of baseball players and am now relating this same pull to the timing of earthquakes over the earth. I am also well along in a study of the biology of American scientists, in what climates and in which seasons their birth rate is highest, where they are educated and where they do their major work, whether the National Academy of Sciences as the self-proclaimed representative and voice of Science in general is reasonably representative of the country's scientists, and some thoughts about the future of Science in its relation to society. At heart, I still find myself basically a physiologist.

Henry Laurens to Bruce Dill:

Thank you very much for your letter of congratulations on my 87th. It was very much appreciated. One thing I would like to mention is the death of my wife on the 7th of February, 1972. I still miss her.

Alan Boyden to Bruce Dill:

I am still in good health and hard at work on an exciting enterprise - the development of the lung in the Macaque, from early embryonic stages through to the young adult - in cooperation with our pediatricians who are focusing their experimental work on the respiratory distress syndrome, involving fetal and infantile stages of the same species. I assume from your letter that you are happily at work in your own field.

Alexis L. Romanoff to Hi Essex:

Thank you for your communication on behalf of the membership of the Society. For your information, I was born on May 17, 1892, officially retired at full age in July 1960, and still continue the preparation of monographic reference volumes in the field of avian embryology. The latest volume, which is in press, is entitled Pathogenesis of the Avian Embryo: An Analysis of Causes of Malformations and Prenatal Death, and will be published about the middle of September 1972. Author of a book of 80 poems, Alexis included in his letter this tribute to his life-long environment:

Between Hills and Lake

In earnest youth, some years ago,
I came to Ithaca - small town.
It was my fate; I did not know
That I for long would settle down.

At once, I saw enchanting hills,
Not far, deep blue Cayuga Lake,
Each bush, each tree man's hope fulfills
By keeping Nature green, awake.

There is tranquility and peace
Along the stretch of shady streets,
A scent of culture - ancient Greece-
From college heights, where youth competes.

The whole community has aims
To make the town a living place:
With study clubs, artistic claims ...
All human values to embrace.

Its most inspiring atmosphere
No thoughtful visitor forgets.
Here I reside, and hold it dear ...
My life is full, without regrets.

Dennis Jackson to Bruce Dill:

Thanks so much for the birthday greetings which you so thoughtfully sent me. They remind me of the stability and faithfulness of the society of which I became a member, I believe in 1910. It has been my special privilege to know the great men in the society at that time and for many years later. I recall the founding of the Federation about 1912. You mention my painting. I have had a few pictures on exhibition, but I have been so busy on research which I am very anxious to finish that I have let the painting wait. I have been working in strange and rather new territory where mistakes are the rule and not the exception. I am hoping to break the rule.

Yas Kuno sent Bruce a bronze plate with this message:

This bronze plate has been made by my friends and former pupils in celebration of my 90th birthday to be delivered to those who have been companions in my studies. The Japanese phrase on the plate has been taken from my own calligraphy. It means, "Boundless sympathy for the weak -- this we call The Way of the Doctor." It is really my great pleasure to be able to deliver to you my gratitude with this plate. Several of Professor Kuno's admirers joined in honoring his 88th birthday by contributing chapters to a book, "Advances in Climatic Physiology" published by Ikagu Shoin, Tokyo. Chapters authored by members of the Society were: Chapter 1. Peripheral Input to the Central Regulator for Body Temperature .. J. D. Hardy. Chapter 2. Spinal Cord and Temperature Regulation .. R. Thauer and E. Simon. Chapter 9. Desert Sweat Rates .. D. B. Dill. Chapter 10. The Effect in Man of Acclimatization to Heat on Water Intake, Sweat Rate and Water Balance .. O. G. Edholm. Chapter 11. Physiological Adaptation in Infant Mammals .. E. F. Adolph. Chapter 12. Man and Cold Stress ..S. M. Horvath. Chapter 18. Chronobiology of the Life Sequence.. M. Smolensky, F. Halberg, and F. Sargent II.

Esther Greisheimer to Maurice Visscher:

Thank you for your communication on my 81st birthday. I deeply appreciated it. I have watched your meteoric career with great interest since we met in September 1922. The ninth edition of Physiology and Anatomy appeared on the market in January 1972. I have retired after 51 years of teaching, and am giving much time to volunteer work in the First Presbyterian Church of Germantown. It is nice to be needed somewhere. May 1973 be a splendid year for you in every way.

McKeen Cattell to Maurice Visscher:

It gave me great pleasure to receive your greetings on the occasion of my 81st birthday, a reminder of our trip to Austria and that long ride on the "Opel Blitz" from Gratz via Salzberg to Innsbrück. It is nice to be able to report that, apart from an operation for cataract, to which I am now adjusting with a contact lens, I have kept well and continue to work full time, mainly as editor of The Journal of Clinical Pharmacology and service on various committees. You need not be concerned about any shift in my interests from physiology to pharmacology, since I have always maintained and emphasized that drugs act by modifying physiological functions. Nor have I forgotten that your contributions have included the use of cardiac glycosides in studies utilizing the heart-lung preparation. I cannot close without expressing my pleasure and appreciation for your continuing activity in promoting the interests of scientific medicine.

Percival Bailey to Hal Davis:

Many thanks for remembering my birthday. I am sorry that I have no interesting news for you. I am well except for those minor ailments that plague elderly people. I keep myself busy reading and occasionally writing essays, usually for the Chicago Literary Club. I have, of course, completely withdrawn from the practice of surgery. Really the only thing that has thrilled me recently is the translation into French of my book on Sigmund Freud.

John Ferguson to Bruce Dill:

Thank you for your card and good wishes on the occasion of my 80th birthday. Permit me to congratulate you on having reached that golden milestone and on your continued activity. You have had a very busy life and I hope that you continue your activity for many more birthdays.

Professor Genichi Kato to Maurice Visscher:

With great pleasure and many thanks, I have read the letter you have written and sent me on behalf of the Society on the occasion of my 83rd birthday. On that day, over a hundred of my old pupils, who had studied in my laboratory, met together, and we had a very happy and enjoyable evening. Your letter reminds me of the traveling lecture tour made by yourself as chairman and also by Prof. v. Euler and Prof. Fessard in 1960 which was very productive and enjoyed by all Japanese physiologists. The Tokyo Congress (1965) is an unforgettable event for me, because it was my long cherished desire to have it in Japan. Incidentally, I regret very much that many eminent physiologists who played a great part in the International Union of Physiological Sciences have died during the past few years: Profs. Heyman (Belgium), Houssay (Argentina), Stevenson (Canada), Brown (England), Duyff (Holland), and Fenn (USA), most of whom were younger than I am, except Houssay. I miss them very much. Thank you again for your kind letter and I wish you and my American colleagues good luck and a prosperous future.

Jesse McClendon on his 92nd birthday summarized in rhyme for Maurice Visscher and fellow physiologists his observations on the axolotl. He recommends that his creation be read to the cadence of the feet of soldiers on the march. That cadence he learned in World War I; it is real life and not childish fancy.

The Axolotl is a Cretin

The Axolotl - so dumb was he, he could not learn geometry
But in his native Mexican lakes, a crystal of iodine is all
it takes
To change him to Ambistoma* - Ambistoma Mexicana.
When you go to Mexico, visit Xochimilco - Dr. Stacpoole
ought to know.
It is he with his machine - injects salt with iodine
Joins Kimball, Marine and Boussingault, in the use of
iodized salt.

*Spelling is that of Prof. Hobart M. Smith, Univ. of Colorado, Boulder.

Jesse also expressed his ideas on the threat of acupuncture. He noted that Mao Tse Tung took over the Peking Union Medical College and ordered physicians to show Chinese medicine superior. He found spinal anesthesia needles and renamed them acupuncture needles, thus acupuncture was reborn. Jesse was sent to Japan in 1932 by the Rockefeller Foundation, but made a couple of trips to China on his own. He studied acupuncture there and in France in 1935. At that time he went to France to study chronaxie which happened to be studied in the same wards as acupuncture, which had been under investigation there since the 1920's. He states that, "I cannot get anyone to take me seriously, but if they do not, it will cost the USA a fabulous sum."

Gus Eckstein to Hy Mayerson:

I like to be forewarned that it's right the next stop -- My God, 82! If it gives you the least amusement - you've beaten everybody in, limbered me for the month to come. Of course, I have known you only a little, but it has the feeling of quite much. As for the years of meetings of the Society, I was always glad there was the back row of anonymity. I sat at what I wanted to hear. I did not sleep. I usually had no inclination to. I have through the years taught and written, and am doing that right today, am far into my book on Pavlov. So remarkable a man. You possibly knew him as much or more than I, but what I can say is that I know him better every day. Wait till you are an old man - you will be surprised. I am. I wouldn't have guessed at, say 65, or 70, or even 75, how nothing central is clearer, but the blur has more curiosity in it. I promise to write you a birthday letter at your 82nd, or send you a message from wherever.

Grayson McCouch to Hy Mayerson:

Many thanks for your cheering handwritten birthday greeting from the Committee on Senior Citizens. Permit me, however belatedly, to reciprocate with cordial greetings for your September 10th. I still putter around the lab. I am fortunate in enjoying the kindness of better men than I, men who do the work while I do the heavy looking on. At 84 what more could one ask? With deep appreciation of your kind greeting.

Ernst Gellhorn celebrated his 80th birthday on January 7, 1973; he lives with his son Professor of Law at the University of Virginia. He had written to Bruce Dill about a book he was writing, The Time Concertina - Meditations of a Humanist. This was published recently by Ernst and can be purchased from him for $3.00. His address is 15 Wendover Road, Charlottesville, Va. 22901. Bruce has purchased the book and found it reflects the wisdom and philosophy of the author. He closes with this comment on world affairs. "Destructive forces today endanger human life on earth. Yet, the answer to this problem is obvious. It lies in man's application of his superior brain power in an atmosphere of good will and his ability to overcome seemingly insuperable resistances through his infinite capacity to learn through experience. Thus, a second level of harmony can be established on a world wide scale through control of social action and natural forces."

Bruce Dill wrote to Hal Davis:

I was honored during the 1972 graduation exercises of the University of Nevada, Las Vegas by the award of an honorary LL.D. Another honor that has given me great pleasure is the recent publication by Prentice Hall of a book "The Harvard Fatigue Laboratory: Its History and Contributions." I am proud to add that the authors are my son-in law, S. M. Horvath and his wife, my daughter, Betty. Their accomplishment is magnificent as several letters they have received attest.

Jerzy Kaulbersz wrote from Cracow to Bruce Dill about his active year.

Extremely grateful for your birthday greetings. On July 3rd I went to the International Congress of Gastroenterology in Paris, where I presented a paper on the role of cholinergic innervation in pancreas secretion due to the action of endogenous and exogenous cholecystokinase pancreozymin. After the Congress I visited the Mont Blanc region, particularly the summits Brevent and Aignille du Midi above Chamonis. In the first half of August I enjoyed bathing in the Baltic Sea, in the second half I attended the Preolympic Scientific Congress in Munich, that included also sport medicine. There I gave a paper on exercise at high altitude in advanced age talking about the results observed one year ago during a sojourn on Jungfraujoch after the XXIV International Congress of Physiological Sciences in Munich. Then I attended the opening of the Olympiad on August 26th and Athletic Games on August 31st in the Olympic Stadium. September 10-18 it was my duty to participate in the meeting of the Polish Physiological Society, as it is arranged only once in three years, this time in Olsztyn in the region of the Masuric Lakes. There I presented for my pupil and successor in Cracow - Dr. Konturek a paper on digestable hormones. He is visiting and working now in Galveston and also in Los Angeles with Dr. Grossman. There was also a modest jubilee celebration of my 60 years' scientific activity - first papers in 1912 related to the biology of some Isopodes like Asellus aquation, their photo-and chemoreception particularly. The celebration also recognized 50 years' scientific activity of two other Polish physiologists, Dalaoski and Szabuniowicz. Now on the 100th anniversary Session of the establishment of the Academy of Sciences in Cracow - December 14 - I am charged with preparation of a report of the relations between this Academy and physiology in Poland. I am still connected with the College of Physical Education here.

Sydney Britton to Bruce Dill:

Most of my days seem to be spent outside on this mountain "retreat" on which my wife and I stay for about ten months of the year; a heavy snowbank is now nestling the ancient log cabin we inhabit. I take this opportunity to answer your kind greeting; it's a very happy institution, keeping in touch with the "old fellows," as the Society does. Our cabin has been modernized we must admit, but the three open fireplaces, plus huge chestnut beams in the main structure give evidence of the sturdy workmanship of yesteryear - actually, almost 200 years ago! The modern generation including our four children and a dozen grandchildren we house during visits in two nearby buildings which we put up over the years. Besides the fruit and vegetable garden (about one acre) which we maintain in season we squeeze in time for boat trips to see relatives in Europe and elsewhere. A cardiac pacemaker installed some months ago restricts me somewhat, however the British poets (Tennyson and Shakespeare especially), along with occasional science features, get more attention, but politics and world affairs get little of my time. Seventh heaven is said to be just above our 1200 ft. level!

A note from H. L. White to Dr. Hy Mayerson was published on page 375 of the November 1972 Physiologist. Dr. White wishes to have the following errors corrected: His name was listed as H. C. White instead of H. L. White. Dr. White wrote Dr. Mayerson that for the sake of his "amour-propre" he would also wish to call attention to errors in the French phrase with which he ended his note.

The phrase should read:

"On retourne toujours à son premier amour."

****

2nd WORKSHOP ON CONTRACTILE BEHAVIOUR OF THE HEART

The 2nd Workshop on Contractile Behaviour of the Heart will be held on September 6 and 7, 1973 in Utrecht, The Netherlands. The program will be presented as follows:

Sept. 6 - Morning Session: "Contractility" and Excitation-Contraction Coupling. Chairman: Dr. Dennis Noble, Laboratory of Physiology, Oxford University, Oxford, England.

Sept. 6 - Afternoon Session: "Contractility" and Heart Muscle Contraction. Chairman: Dr. Edmund H. Sonnenblick, Harvard Medical School, Boston, Massachusetts.

Sept. 7 - Morning Session: "Contractility" and the assessment of left ventricular function. Chairman: Dr. Paul G. Hugenholtz, Thorax Centre Medical Faculty, Rotterdam, The Netherlands.

Sept. 7 - Afternoon Session: "Contractility" and Heart Failure. Chairman: Dr. Eugene Braunwald, Harvard Medical School, Boston, Massachusetts.

A maximum of 200 registrants can be accommodated and requests will be met in the order received. All papers will be published in a supplement of the European Journal of Cardiology.

For further information please write: Dr. Frits L. Meijler,
Dept. of Cardiology, University Hospital Utrecht,
101 Catharijnesingel, Utrecht, The Netherlands

MABEL PUREFOY FITZGERALD - OUR SECOND CENTENARIAN

Born August 3, 1872, North Hall Preston Candover, Micheldever (later Basingstoke) Hants.

Mabel FitzGerald joins Charles Snyder in a rare role - a centenarian of the American Physiological Society. Her niece and next of kin, Mrs. Brian Purefoy wrote me on August 16, 1972 as follows:

"The famous birthday on August 3rd was a great success and she told one of her guests that she had enjoyed every minute of it which shows that she is in good health for one of her age. We had a family luncheon party in her own home - which included four generations. People and flowers poured in and out of the house all day.

"She had a visit from B. B. C. the result of which was several broadcasts in which her memories of the Pike's Peak Expedition were recorded. A few weeks ago representatives of the Canadian B. C.' visited her in connection with the work she did with Sir William Osler.

"We contacted her friend, Dr. Cunningham, who called on her birthday accompanied by Professor D. Whitting. Sir Richard Doll, Regius Professor of Medicine in Oxford University, also called. She received over 100 telegrams and cards from all parts of the world, including, of course, that from Her Majesty The Queen."

A great honor came to her on December 14, 1972; the award of an Honorary Degree of Master of Arts by Oxford University. I am indebted to her neighbor and friend, Mr. William G. Cannon for an account of the ceremony and events of the day.

"She was asked whether or not she would like a small ceremony at her home or go to a full ceremony at the Sheldonian Theatre in Oxford. Her prompt answer was, I prefer to go to a full ceremony. We were able to arrange this and a special ceremony was arranged for Miss FitzGerald, alone, in the Convocation House adjoining the Sheldonian Theatre. This was very pleasing to her as she was able to invite her own relatives and personal friends. She at once began preparing her list of persons to be invited and her niece and I sent out 180 invitations to persons she knew from all walks of life including Professors, Doctors, Lord Mayor, Chief of Police, etc. It was a really delightful ceremony and approximately 200 were present. On entering the Hall, dressed in her Cap and Gown, she waved to all her visitors on both sides of the Hall and was in very good form. She had many telegrams and letters of congratulations (approximately 200). To my surprise she asked me to arrange for her to be driven round the city on the journey back to her home as she wished to see any alterations that had been made.

"Miss FitzGerald is really a remarkable person. She reads her daily papers every day and takes a great interest in all world affairs. She also still has an exceptional memory. She still goes up and down stairs herself each day. She is slightly deaf but we have managed to get her an up-to-date hearing aid during the last month and she now hears quite well and is able to carry on a conversation. She is inclined to mislay some of the many letters she receives and is apt to forget to answer them, much to her own disgust when she realizes it.

"She was very interested in the "Moon Landing" and was keen to see it on television. I did manage to loan a television from a friend and she watched the "Take Off," "Moon Landing" and "Walk" on the moon and the "Splash Down." She was very observant and took it all in in every detail. She was also keen to see the Funeral of the Duke of Windsor and this I was able to arrange for her. Apparently her brother, Admiral Purefoy FitzGerald knew him quite well."

Hermann Rahn wrote me about the honorary degree and added this note:

"The publication I have admired for many years, and it is virtually unknown among most high altitude physiologists, is her paper which appeared in 1913 in the Philosophical Transactions, Series B, Vol. 203, p. 351-371, entitled 'Changes in breathing and blood at various high altitudes.' As you recall, she was not allowed to join the boys at the Pike's Peak rendezvous and thus saddled her mule, with her Haldane apparatus strapped on the side, and rode all by herself into the mining camps of Colorado, extracted from the miners their blood for hemoglobin concentrations, and an alveolar gas sample. This publication I believe is the first systematic description of the changes in alveolar PCO_2 and hemoglobin at different altitudes."

D. B. Dill, Chairman, Comm. Senior Physiologists