CONTENTS

NOTE: Council agreed to have the enclosed Resolution inserted in this issue of The Physiologist. Anyone who wishes may sign and return the affirmation statement as noted on the form.

APS MEMBERSHIP STATUS

September 1976

Regular Members	3,978
Retired Members	347
Honorary Members	13
Associate Members	559
Retired Associates	2
	4,899

DEATHS SINCE SPRING MEETING 1976

Edwin B. Astwood - 2/ /76 - Retired Member
Albert J. Bocage - 1/12/76 - Dept. Physiol., Louisiana State Univ. Medical Center, New Orleans
W. Ray Bryan - / / / - Retired Member
George S. Eadie - 4/15/76 - Retired - Duke Univ. Sch. Med., Durham
Norman M. Keith - 2/5/76 - Retired Member
Rolland J. Main - 4/16/76 - Retired Member
Nathan Millman - 5/17/75 - Ortho Pharmaceutical Corp., Raritan, NJ
Quillian R. Murphy - 2/8/76 - Dept. Physiol., Univ. of Wisconsin
James W. Pearce - 7/10/75 - Dept. Physiol., Univ. of Toronto
Wilder G. Penfield - 4/5/76 - Retired Member
Marion A. Reid - / / /
Peter Rieser - / / / - Dept. Biol., Boston College, Chestnut Hill, MA

The following members were granted retired status at the 1976 Fall Meeting:

L. J. Berry
H. B. Burchell
Hugo Chiodi
Leon Churney
J. W. Everett
John Field
V. M. Fiske
J. B. Hamilton
F. X. Hausberger
Hudson Hoagland
E. C. Hoff
C. D. Howell - Associate
Geoffrey Keighley
Victor Lorber
J. J. Martorano
A. T. Miller
J. D. Nyboer
E. A. Ohler
R. F. Pitts
W. E. Stone
L. A. Toth
K. N. Von Kaulla

NEWLY ELECTED MEMBERS

The following, nominated by Council, were elected to membership in the American Physiological Society at the Fall Meeting, 1976.

FULL MEMBERS

ALLISON, Trenton B.: VA Hospital, Newington, CT
ANDREW, George McC.: Sch. Phys. & Health Edu., Queen's Univ., Kingston, Ont., Canada
ARNAUD, Claude D.: Dept. Endocrine Res., Mayo Clinic, Rochester

BARCLAY, Jack K.: Dept. Biomed. Sci., Univ. of Guelph, Guelph, Ont., Canada
BARNHART, James L.: Dept. Int. Med., Univ. of Texas Hlth. Sci. Ctr., SW Med. Sch., Dallas
BEN-JONATHAN, Nira: Dept. Physiol., Indiana Univ. Med. Sch., Indianapolis
BORENSZTAJN, Jayme: Dept. of Pathol., Univ. of Chicago, Chicago
BOSE, Deepak: Dept. of Pharmacol. & Therap., Univ. of Manitoba, Winnipeg, Manitoba, Canada
CARLSON, Richard W.: Univ. of Southern Calif. Sch. Med., Los Angeles
CARTER, Norman W.: Dept. Int. Med., Univ. of Texas Hlth. Sci. Ctr., SW Med. Sch., Dallas
CONSTANTINOU, Christos E.: Div. of Urology, Stanford Univ. Med. Ctr., Stanford, CA
COULTER, Joe D.: Marine Biomed. Inst., Univ. of Texas Br., Galveston
DEMENT, William C.: Sleep Disorders Clinic & Lab., Palo Alto, CA
DOW, Bruce Mac. G.: Dept. of Neurophysiol., NIH, Bethesda, MD
EGAN, Edmund A. II: Dept. Pediat., Univ. of Florida, Gainesville
EVANICH, Myron J.: Dept. of Med., Univ. of Illinois Hosp., Chicago
FEIST, Dale D.: Inst. of Arctic Biol., Univ. of Alaska, Fairbanks
GARDNER, Daniel: Dept. of Physiol., Cornell Univ. Med. Coll., NY
GENNARO, Joseph F., Jr.: Lab. of Cellular Biol., New York Univ.
HALES, Charles A.: Mass. Gen. Hosp., Pulmonary Unit, Boston
HANSEN, Robert J.: Dept. Physiol. Sci., Univ. California, Davis
HERLIHY, Jeremiah T.: Dept. of Physiol., Univ. of Texas Hlth. Sci. Ctr., San Antonio, Texas
JANICKI, Joseph S.: University of Pennsylvania, Philadelphia
JOHNSON, Elsie E.: Dept. Anesthesia, Harvard Med. Sch., Boston
KAMPINE, John P.: Res. Service, VA Ctr., Wood, Wis.
KEIL, Lanny C.: NASA-Ames Res. Ctr., Moffett Field, CA
KOBRINE, Arthur I.: Dept. Neurosurg., George Washington Univ., Washington, DC
LALL, Amrit: Dept. of Pharmacol., Abbott Labs., North Chicago, IL
LEAK, Lee V.: Dept. of Anat., Howard Univ. Coll. Med., Washington, DC
LEFFLER, Charles W.: Dept. Physiol. & Biophys., Univ. of Louisville
LEMEN, Richard J.: Dept. of Physiol., Tulane Med. Ctr., New Orleans
LIEBMAN, Paul A.: Dept. of Anat., Univ. of Pennsylvania, Philadelphia
LIOY, Franco: Dept. of Physiol., Univ. of British Columbia, Vancouver, B. C., Canada
LIU, Maw-Shung: Dept. of Physiol., LSU Med. Ctr., New Orleans, La.
LOEGERING, Daniel J.: Dept. of Physiol., Albany Med. Coll.
MC HALE, Philip A.: Res. Physiologist, VA Hosp., Durham, NC
MCMAHON, Thomas A.: Dept. Appl. Mechanics, Harvard Univ., Cambridge
MADDOX, David A.: Div. of Nephrology, Univ. California, S. F.
MANGUM, Charlotte P.: Dept. Biol., College of William & Mary, Williamsburg, VA
MARTIN, Gregory E.: Walter Reed Army Med. Ctr., Dept. Neurophysiol., Washington, DC
MASLAND, Richard H.: Res. Labs., Mass. Gen. Hosp., Boston
MERCER, Paul F.: Dept. Physiol., Univ. of Western Ontario, London, Ont., Canada

MICHAEL, Ulrich F.: Nephrology Sect., VA Hosp., Tucson, AZ
MICHAELSON, Edward D.: Div. Pulmonary Dis., Mt. Sinai Med. Ctr., Miami Beach, FL
MICHAL, Edwin K.: Dept. of Physiol., Ohio State Univ., Columbus
MILLER, Arthur J.: Sch. Dent., Univ. of California, S. F.
MINH, Vu-Dinh: Pulmonary Div., Univ. Hosp. of San Diego
MOOLENAAR, Gwen-Marie: Dept. Physiol. & Biophys., Howard Univ., Washington, DC
MOORE EDE, Martin C.: Dept. of Physiol., Harvard Med. Sch., Boston
NEREM, Robert M.: Graduate School., Ohio State Univ., Columbus
NUNNELEY, Sarah A.: Sch. of Aerospace Med., San Antonio, Texas
PACE, Caroline S.: Dept. Pharmacol., Washington Univ., St. Louis
PARKER, James C.: Dept. Physiol. & Biophys., University Med. Ctr., Jackson, MS
PETTIT, George W.: USAMRIID-AA, Ft. Detrick, MD
PORTE, Daniel: VA Hosp., Seattle, WA
RAMP, Warren K.: Dental Res. Ctr., Univ. of North Carolina, Chapel Hill
RAWLINGS, Clarence A.: Coll. of Vet. Med., Univ. of Georgia, Athens
RECKNAGEL, Richard O.: Dept. of Physiol., Case Western Reserve Univ., Cleveland
ROBERTS, John L.: Dept. of Zool., Univ. of Massachusetts, Amherst
ROBERTS, Michael F.: John B. Pierce Fndn.Lab., New Haven, CT
ROBERTSON, R. Paul: Clin. Invest., VA Hosp., Seattle, WA
SCHOENER, Eugene P.: Dept. Pharmacol., Wayne State Univ., Detroit
SHANK, Richard P.: Dept. Physiol., Temple Univ. Sch. Med., Philadelphia
SHAPIRO, Bernard H.: Children's Hosp., of Philadelphia, Exptl. Pathol.
SHENG, Hwai-Ping: Dept. Physiol., Baylor Coll. Med., Houston, TX
SILVA, Patricio: Dept. of Med., Beth Israel Hosp., Boston, MA
SMILES, Kenneth A.: Carter Products Res., Cranbury, NJ
SNYDER, Gregory K.: Dept. Biol., Univ. of Colorado, Boulder
SODE, Jonas: National Naval Med. Ctr., Bethesda, MD
STAUBER, William T.: Dept. Physiol. & Biophys., Univ. of Iowa, Iowa City
STEER, Michael L.: Dept. of Surg., Beth Israel Hosp., Boston, MA
STINEBAUGH, Bobby J.: Dept. of Med., Baylor Coll. Med., Houston
TISI, Gennaro M.: VA Hospital, San Diego, CA
TROUTH, C. Ovid: Dept. Physiol. & Biophys., Howard Univ. Coll. Med., Washington, DC
TUCKER, Alan: Dept. of Physiol., Wright State Univ., Dayton, OH
UNGER, Roger H.: VA Hosp., Dallas, TX
WAHRENBROCK, Eric A.: Anesthesia Res. Lab., Univ. of Calif., S.D.
WANNER, Adam: Div. Pulmonary Dis., Mt. Sinai Med. Ctr., Miami Beach, FL
WEBER, Karl T.: Cardiovascular-Pulmonary Div., Hosp. of Univ. of Pennsylvania, Philadelphia
WEINMAN, Edward J.: Renal Metabolic Res. Lab., VA Hosp., Houston
WELCH, Hugh G.: Univ. of Tennessee, Knoxville
WENGER, Christian B.: John B. Pierce Fndn. Lab., New Haven, CT
WILLIAMS, Gordon H.: Peter Bent Brigham Hosp., Boston
WOLFE, Robert R.: Dept. Surg., Mass. Gen. Hosp., Boston, MA
YASUMURA, Seiichi: Dept. Physiol., Downstate Med. Ctr., Brooklyn

YAU, William M-W: Dept. of Med., Southern Illinois Univ., Carbondale
YELLIN, Herbert: Lab. of Neurochem., NINCDS, NIH, Bethesda, MD
YOUNES, Magdy K.: Respiratory Div., Montreal Gen. Hosp., Montreal, P.Q., Canada
ZAMEL, Noe: Mount Sinai Hosp., Toronto, Ont., Canada
ZEMAN, Frances J.: Dept. Nutrition, Univ. of California, Davis
ZINNER, Michael J.: Div. of Surg., Walter Reed Army Inst. Res., Washington, DC

ASSOCIATE MEMBERS

ASTERITA, Mary F.: Indiana Univ. Sch. Med., Gary, Indiana
BELLINGER, Larry L.: Dept. of Surg., SUNY, Buffalo, NY
CARUOLO, Edward V.: North Carolina State Univ., Raleigh, NC
CORNISH, Kurtis G.: Bowman Gray Sch. Med., Dept. Physiol., Winston-Salem, NC
DENTON, Joan E.: Inst. Environ. Stress, Univ. of California, Santa Barbara
EVANS, John N.: Dept. Physiol. & Biophys., Univ. of Vermont, Burlington, VT
GOSSELIN, Arthur J.: Miami Heart Inst., Miami Beach, FL
HARDIE, Edith L.: Dept. Physiol., Loyola Univ., Stritch Sch. Med., Maywood, IL
HARTENBOWER, David L.: VA Admin, Wadsworth Hosp. Ctr., Los Angeles, CA
HERBISON, Gerald J.: Dept. Rehabil. Med., Thomas Jefferson Univ., Philadelphia, PA
IMBRUCE, Richard P.: Norwalk Hosp., Sect. Chest Dis., Norwalk, CT
KOYAL, Sankar N.: Exercise Physiologist, Harbor Gen. Hosp., Torrance
LACY, Eric R.: Res. Asst., Mt. Desert Island Biol. Lab., Salsbury Cove, Maine
LAI, Yih-Loong: Mayo Clinic, Rochester, MN
LA MANNA, Joseph C.: Dept. of Physiol. & Pharmacol., Duke Univ. Med. Ctr., Durham, NC
LARSEN, Parry B.: Cardiovascular Surg., Miami Heart Inst., Miami
LEVINE, Sanford: Cardiovascular-Pulmonary Div., Hosp. of the Univ. of Pennsylvania, Philadelphia
MILLER, Samuel T.: Res. Assoc., Cornell Univ. Med. Coll., New York
MITNICK, Michael H.: Dept. of Physiol., Univ. of Pennsylvania Sch. Med., Philadelphia
NAGLE, Barbara T.: Phila. Coll. Osteopathic Med., Norwood, PA
O'KEEFE, Dennis D.: Surg. Cardiovascular Unit, Mass. Gen. Hosp., Boston, MA
O'LEARY, Dennis P.: Dept. Otolaryngol., Univ. of Pittsburgh Sch. Med.
PFEFFER, Janice M.: Health Sciences Ctr., Univ. of Oklahoma
PIETRAS, Richard J.: Dept. of Biol., Univ. of California, Los Angeles
PORCELLI, Robert J.: State Univ. of New York, Stony Brook
RILEY, Arthur L.: Renal Section, VA Ctr., Wood, Wis.
SCHAEFFER, Richard C., Jr.: USC Shock Res. Unit, Los Angeles
STRAUSS, Richard H.: Dept. of Physiol., Univ. of Hawaii Sch. Med. Honolulu
TANG, Lily C.: Res. Asst., Cornell Univ. Med. Coll., New York, NY
TAVEIRA DA SILVA, Angelo M.: Dept. of Physiol. & Biophys., Georgetown Univ. Sch. Med., Washington, DC

TEICHHOLZ, Louis E.: Dept. of Med., Mt. Sinai Sch. Med., New York
TUMA, Ronald F.: Dept. of Physiol., Temple Univ. Sch. Med., Philadelphia
TYLER, Thom L.: Dept. of Physiol., Univ. of Florida Sch. Med., Gainesville
YOUNG, Stephen L.: Dept. of Med., UCLA Ctr. for Hlth. Sci., Los Angeles, CA
WOODS, Walter T.: Univ. of Alabama Sch. Med., Birmingham
ZAMBRASKI, Edward J.: Res. Asst., VA Hosp., Iowa City, IA

CORRESPONDING MEMBERS

KOVACH, Arisztid G. B.: Exp. Res. Dept., Semmelweis Med. Univ., Budapest, Hungary
PIIPER, Johannes: Abteilung Physiologie, Max-Planck Inst. f. exptl. Medizin, Gottingen, W. Germany
SCHEID, Peter: Abteilung Physiologie, Max-Planck Inst. f. exptl. Medizin, Gottingen, W. Germany

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CURRENT SCHEDULE OF FUTURE MEETINGS

1977 - International Physiological Congress - Paris, France -July 18-23
1977 Spring - Chicago, Illinois - April 1-6; FASEB, 3-8
1977 Fall - Hollywood Beach, Florida - October 9-14

1978 Spring - Atlantic City, New Jersey - April 9-14
1978 Fall - St. Louis, Missouri - October 22-27
1978 Fall - Campus Specialty Meeting - Michigan State - Categorical Subject and Date to be announced

1979 Spring - Dallas, Texas - April 8-13
1979 Fall - New Orleans, Louisiana - October 14-19

1980 Spring - Anaheim, California - April 13-18
1980 Fall - Miami Beach, Florida - October 12-17

1981 Spring - Atlanta, Georgia - April 12-17
1981 Fall - Boston, Massachusetts - October 4-9

1982 Spring - New Orleans, Louisiana - April 18-23
1982 Fall - San Diego, California - October (dates to be announced)

THE PHYSIOLOGIST - NEW FORMAT

This is the last issue of The Physiologist to be printed in this format. The response to the proposal outlined in the February 1976 issue has resulted in the decision to alter the size and frequency of publication for future issues.

Beginning with the first issue in 1977, The Physiologist will increase in size to 8-1/2 x 11 inches and will be published bimonthly instead of quarterly.

All recipients of The Physiologist will also receive The Physiology Teacher which will be inserted in all but the August issue. The Physiology Teacher is a newsletter published five times a year. It contains descriptions of physiological experiments useful to teachers of undergraduate biology and physiology. The publication also includes material of general interest to these teachers. APS will continue to make this newsletter available separately to subscribers.

The first issue of The Physiologist for 1977 will be published in February. Succeeding issues will be published in April, June, August (Fall Meeting Abstracts only), October and December. The closing date for the receipt of items for publication is 45 days prior to the first day of the month of that issue. Therefore, items for the February 1977 issue must be received by December 15, 1976.

Annual subscriptions to The Physiologist, with The Physiology Teacher insert, are available to non-members at $12.00 in the U.S.; $12.50 in Canada and $13.00 for subscribers in other countries.

Annual subscriptions to The Physiology Teacher are $5.00 in the U.S.; $5.50 in Canada and $6.00 in other countries.

THE AMERICAN PHYSIOLOGICAL SOCIETY

Founded December 30, 1887; Incorporated June 2, 1923

OFFICERS 1976-77

President - E. E. Selkurt, Indiana University Medical Center, Indianapolis, Indiana

President-Elect - W. F. Ganong, University of California, San Francisco

Past-President - B. M. Schmidt-Nielsen, Mt. Desert Island Biological Laboratory, Salsbury Cove, Maine

Council - E. E. Selkurt (1978), W. F. Ganong (1979), B. M. Schmidt-Nielsen (1977), J. O. Davis (1978), F. J. Haddy (1979), Jere Mead (1977), W. C. Randall (1980)

Executive Secretary-Treasurer - O. E. Reynolds, 9650 Rockville Pike, Bethesda, Maryland 20014

STANDING COMMITTEES

Publications - A. P. Fishman (1978), Chairman; R. M. Berne (1979), R. W. Berliner (1979). Ex officio - E. E. Selkurt, President; O. E. Reynolds, Executive Secretary-Treasurer; S. R. Geiger, Publications Manager.

Finance - E. B. Brown (1977), Chairman; D. C. Tosteson (1978), A. C. Guyton (1979). Ex officio - W. F. Ganong, President-Elect; O. E. Reynolds, Executive Secretary-Treasurer; W. A. Sonnenberg, Business Manager; A. P. Fishman, Chairman of Publications Committee.

Education - L. S. Jefferson (1978) Chairman; E. M. Renkin (1979), F. N. White (1979), P. N. Farnsworth (1978), R. H. Kellogg (1978), B. M. Twarog (1978), F. N. Briggs (1977), R. B. Gunn (1977). Ex officio - O. E. Reynolds, Education Officer.

Membership Advisory - B. P. Bishop (1978) Chairman; G. A. Castro (1979), E. O. Feigl (1978), E. W. Stephenson (1978), Sidney Cassin (1977).

Program Advisory - H. M. Goodman (1978) Chairman; S. D. Gray (1978), A. P. Somlyo (1978), L. R. Johnson (1977).

Public Affairs & Public Information - B. A. Curtis (1978) Chairman; B. A. Horwitz (1979), J. A. Holloway (1977), M. S. Kafka (1977), Ping Lee (1977).

Senior Physiologists - D. B. Dill (1977) Chairman; E. F. Adolph (1979), Philip Bard (1979), Hallowell Davis (1978), M. B. Visscher (1978), H. S. Mayerson (1977).

Perkins Memorial Fund - J. R. Pappenheimer (1980) Chairman; W. C. Randall (1979), D. F. Bohr (1977), Hermann Rahn (1977). Ex officio - Mrs. J. F. Perkins, Jr., O. E. Reynolds.

Porter Physiology Development Program - A. C. Barger (1977) and E. W. Hawthorne (1977) Co-Chairmen; J. L. Kostyo (1979), E. P. Radford (1979), Clem Russ (1978), H. V. Sparks, Jr. (1978), Melvyn Lieberman (1977).

Animal Care and Experimentation - W. J. Tietz, Jr. (1977) Chairman; M. H. Hast (1979), K. A. Gaar (1978), G. H. Stabenfeldt (1977).

Committee on Committees - F. J. Haddy (1977) Chairman; E. H. Wood (1979), Sid Robinson (1978), Eugene Jacobson (1978), A. B. Otis (1977), Jean Marshall (1977).
Daggs Award - J. M. Brookhart (1977) Chairman; Ernst Knobil (1979), R. E. Forster (1978).
Legal Council - W. H. Pattison, Jr.

REPRESENTATIVES TO OTHER ORGANIZATIONS

Federation Board - W. F. Ganong (1979), E. E. Selkurt (1978), B. M. Schmidt-Nielsen (1977).
Federation Executive Committee - W. F. Ganong (1979).
Federation Life Sciences Advisory Committee - F. P. Ferguson (1979).
Federation Publications Committee - C. S. Tidball (1979).
Federation Meetings Committee - F. E. Yates (1977).
Federation Program Committee - O. E. Reynolds
Federation Public Affairs Committee - B. A. Curtis (1979).
Federation Public Information Committee - M. S. Kafka (1979).
Executive Officers Advisory Committee of the Federation - O. E. Reynolds
U. S. National Committee for International Union of Physiological Sciences - F. J. Haddy (1979), D. C. Tosteson (1978), W. F. Ganong (1978), J. R. Brobeck (1977).
Assembly of Life Sciences - O. E. Reynolds
American Association for the Advancement of Science - D. S. Gann (Dec. 1976), L. S. Lilienfield (Dec. 1976), O. E. Reynolds (Dec. 1976).
National Society for Medical Research - W. J. Tietz, Jr. (1977).
American Society for Information Science - S. R. Geiger (1977).
Council of Academic Societies of the Association of American Medical Colleges - W. G. Van der Kloot (1978), R. M. Berne (1978).

PUBLICATIONS

Publications Committee - A. P. Fishman (1978) Chairman; R. M. Berne (1979), R. W. Berliner (1979).
Publications Manager and Executive Editor - Stephen R. Geiger
American Journal of Physiology: Heart and Circulatory Physiology - M. N. Levy, Editor; Associate Editors: P. C. Johnson, Paul Martin, W. W. Parmley, Kiichi Sagawa, Mario Vassalle. Renal, Fluid and Electrolyte Physiology - T. E. Andreoli, Editor; Associate Editors: J. J. Grantham, F. S. Wright. Endocrinology, Metabolism and Gastrointestinal Physiology - Rachmiel Levine, Editor; Associate Editors: R. N. Bergman, L. R. Johnson, Daniel Porte, Jr., David Rodbard, George Sachs. Cell Physiology - Paul Horowicz, Editor; Associate Editors: P. J. DeWeer, H. A. Fozzard, F. J. Julian, C. F. Stevens, J. S. Willis, Saul Winegrad. Regulatory, Integrative and Comparative Physiology - F. E. Yates, Editor; Associate Editors: F. P. Conte, D. S. Gann, B. M. Schmidt-Nielsen.
Journal of Applied Physiology - L. E. Farhi, Editor; Associate Editors: A. P. Gagge, E. R. Buskirk, Claude Lenfant, Joseph Milic-Emili, S. M. Tenney.
Journal of Neurophysiology - E. V. Evarts, Chief Editor
Physiological Reviews - H. E. Morgan, Editor; R. C. Rose, Associate Editor; D. S. Parsons, Chairman, European Committee.

Handbooks of Physiology - J. R. Pappenheimer, Chairman Editorial Committee; S. R. Geiger, Executive Editor.
The Physiologist - O. E. Reynolds, Editor
The Physiology Teacher - O. E. Reynolds, Editor; Mary Dittbrenner, Executive Editor
Physiology in Medicine - A. P. Fishman, Editor; S. R. Geiger, Executive Editor (Monthly in New Engl. J. Med.)

PAST OFFICERS

Presidents - 1888 H. P. Bowditch. 1889-1890 S. W. Mitchell. 1891-1895 H. P. Bowditch. 1896-1904 R. H. Chittenden. 1905-1910 W. H. Howell. 1911-1913 S. J. Meltzer. 1914-1916 W. B. Cannon. 1917-1918 F. S. Lee. 1919-1920 W. P. Lombard. 1921-1922 J. J. R. MacLeod. 1923-1925 A. J. Carlson. 1926-1929 Joseph Erlanger. 1930-1932 W. J. Meek. 1933-1934 A. B. Luckhardt. 1935 C. W. Greene. 1936-1937 F. C. Mann. 1938-1939 W. E. Garrey. 1938 W. T. Porter, Honorary President. 1940-1941 A. C. Ivy. 1942-1945 P. Bard. 1946-1947 W. O. Fenn. 1948 M. B. Visscher. 1949 C. J. Wiggers. 1950 H. C. Bazett (April to July); D. B. Dill. 1951 R. W. Gerard. 1952 E. M. Landis. 1953 E. F. Adolph. 1954 H. E. Essex. 1955 W. F. Hamilton. 1956 A. C. Burton. 1957 L. N. Katz. 1958 H. Davis. 1959 R. F. Pitts. 1960 J. H. Comroe, Jr. 1961 H. W. Davenport. 1962 H. S. Mayerson. 1963 H. Rahn. 1964 J. R. Pappenheimer. 1965 J. M. Brookhart. 1966 R. E. Forster. 1967 R. W. Berliner. 1968 L. D. Carlson. 1969 C. L. Prosser. 1970 A. C. Barger. 1971 J. R. Brobeck. 1972 R. M. Berne. 1973 D. C. Tosteson. 1974 A. C. Guyton. 1975 B. M. Schmidt-Nielsen.

Secretaries - 1888-1892 H. N. Martin. 1893-1894 W. P. Lombard. 1895-1903 F. S. Lee. 1904 W. T. Porter. 1905-1907 L. B. Mendel. 1908-1909 Reid Hunt. 1910-1914 A. J. Carlson. 1915-1923 C. W. Greene. 1924-1929 W. J. Meek. 1930 A. C. Redfield. 1931-1932 A. B. Luckhardt. 1933-1935 F. C. Mann. 1936-1939 A. C. Ivy. 1940-1941 Philip Bard. 1942 C. J. Wiggers. 1943-1946 W. O. Fenn. 1947 M. B. Visscher.

Treasurers - 1888-1892 H. N. Martin. 1893-1894 W. P. Lombard. 1895-1903 F. S. Lee. 1904 W. T. Porter. 1905-1912 W. B. Cannon. 1913-1923 Joseph Erlanger. 1924-1926 C. K. Drinker. 1927-1936 Alexander Forbes. 1937-1940 W. O. Fenn. 1941 C. J. Wiggers. 1942-1946 Hallowell Davis. 1947 D. B. Dill.

Executive Secretary-Treasurer - 1948-1956 M. O. Lee. 1956-1972 R. G. Daggs. 1973 - O. E. Reynolds.

CONSTITUTION AND BYLAWS
(Adopted April 1953, as amended April 1976)

CONSTITUTION

ARTICLE I. Name

The name of this organization is THE AMERICAN PHYSIOLOGICAL SOCIETY.

ARTICLE II. Purpose

The purpose of the Society is to promote the increase of physiological knowledge and its utilization.

BYLAWS

ARTICLE I. Principal Office

SECTION 1. The Society shall have its principal place of business at 9650 Rockville Pike, Bethesda, Maryland 20014. The Central Office shall house all activities delegated to the employees of the Society.

ARTICLE II. Corporate Seal

SECTION 1. The corporate seal of the Society shall be a circle surrounded by the words, THE AMERICAN PHYSIOLOGICAL SOCIETY. The seal shall also show the founding date and the date and place of incorporation.

SECTION 2. The Executive Secretary-Treasurer shall have custody of the seal. It shall be used on all official documents requiring it, and shall be placed on the documents by the Executive Secretary-Treasurer upon approval by Council.

ARTICLE III. Membership

SECTION 1. The Society shall consist of regular members, corresponding members, honorary members, associate members, retired members and sustaining associates.

SECTION 2. Regular Members. Any person who has conducted and published meritorious original research in physiology, who is presently engaged in physiological work, and who is a resident of North America shall be eligible for proposal for regular membership in the Society.

SECTION 3. Corresponding Members. Any person who has conducted and published meritorious research in physiology, who is presently engaged in physiological work and who resides outside of North America shall be eligible for proposal for corresponding membership in the Society.

SECTION 4. Honorary Members. Distinguished scientists of any country who have contributed to the advance of physiology shall be eligible for proposal as honorary members of the Society.

SECTION 5. Associate Members. Advanced graduate students in physiology at a predoctoral level, teachers of physiology, and investigators who have not yet had the opportunity or time to satisfy the requirements for regular membership shall be eligible for proposal for associate membership in the Society provided they are residents of North America. Associate members may later be proposed for regular membership.

SECTION 6. Retired Members. A regular or associate member who has reached the age of 65 years and/or is retired from regular employment may, upon application to Council be granted retired member status.

SECTION 7. Sustaining Associates. Individuals and organizations who have an interest in the advancement of biological investigation may be invited by the President, with approval of Council, to become sustaining associates.

SECTION 8. Nominations for Membership. Two regular members of the Society must join in proposing a person for regular membership, honorary membership or associate membership, in writing and on forms provided by the Executive Secretary-Treasurer. The Membership Committee shall investigate their qualifications and recommend nominations to Council. Council shall nominate members for election at the Spring and Fall meetings of the Society. A list of nominees shall be posted for consideration by the members attending the meeting two days prior to the Business Meeting at which the election occurs.

SECTION 9. Election of Members. Election of regular members, corresponding members, honorary members and associate members shall be by secret ballot at Spring and Fall business meetings of the Society. A two-thirds majority vote of the members present and voting shall be necessary for election.

SECTION 10. Voting. Only regular members shall be voting members. Corresponding, honorary, retired and associate members shall have the privilege of attending business meetings of the Society but shall have no vote.

ARTICLE IV. Officers

SECTION 1. Council. The management of the Society shall be vested in a Council consisting of the President, the President-Elect, the immediate Past-President, and four other regular members. The terms of the President and of President-Elect shall be one year. The terms of the four additional Councilors shall be four years each and they shall not be eligible for immediate reelection except those who have served for two years or less in filling interim vacancies.

A quorum for conducting official business of the Society shall be five of the seven elected members of Council.

The Chairman of the Publications Committee; the Chairman of the Finance Committee; and the Executive Secretary-Treasurer are ex-officio members of the Council without vote. The Council may fill any interim vacancies in its membership. Council shall appoint members to all committees.

SECTION 2. President. A person shall serve only one term as President, except that if the President-Elect becomes President after September 30 he shall continue as President for the year beginning the next July 1. The President shall chair all sessions of the Council and business meetings of the Society and shall be an ex officio member of all committees without vote.

SECTION 3. President-Elect. The President-Elect shall serve as Vice-President of the Society and as official secretary of the Council. Should he have to function as President prematurely, the Council shall select from among its own members an official secretary.

SECTION 4. Election of Officers. Nominations for President-Elect and for members of Council will be made by mail ballot before February 1 of each year. Each member may nominate no more than one candidate for each office. If a member wishes to nominate a certain person for President-Elect and for Council he must nominate that individual for each position. The ten candidates that receive the highest number of nominating votes will appear on the appropriate ballot for President-Elect or for Council.

Election of the President-Elect and members of Council will be made by mail ballot prior to April 1 of each year. Each voting member must indicate on the ballot his rank preference for all of the candidates on each ballot. The ballots will be counted according to the Election Plan. Two ballots, one for President-Elect and one for Council will be mailed together. The results of the elections will be announced at the Spring Meeting of the Society and the newly elected officers will take office on July 1 following their election.

SECTION 5. Executive Secretary-Treasurer. The Council shall be empowered to appoint and compensate an Executive Secretary-Treasurer who shall assist it in carrying on the functions of the Society including the receipt and disbursement of funds under the direction of the Council. He shall be responsible for management of the Central Office of the Society under general supervision of the Council.

ARTICLE V. Standing Committees

SECTION 1. Publications Committee. A Publications Committee composed of three regular members of the Society appointed by Council shall be responsible for the management of all of the publications of the Society. The term of each member of the Publications Committee shall be three years; a member may not serve more than two consecutive terms. The Council shall designate the Chairman of the Committee who shall be an ex officio member of the Council, without vote. Council is empowered to appoint and compensate a Publications Manager who shall assist in carrying out the functions of the Publications Committee under the supervision of the Executive Secretary-Treasurer. The President, Executive Secretary-Treasurer and the Publications Manager shall be ex officio members of the Publications Committee without vote. The Committee shall have the power to appoint editorial boards for the Society's publications. The Committee shall present an annual report on publications and policies to the Council for approval and present an annual budget coordinated through the Executive Secretary-Treasurer, to the Finance Committee for its approval and recommendation to Council.

SECTION 2. Finance Committee. A Finance Committee, composed of three regular members of the Society appointed by Council, shall receive the total coordinated budget proposals annually from the Executive Secretary-Treasurer and shall determine the annual budgets, reserve funds and investments of the Society, subject to approval by the Council. The term of each member of the Finance Committee shall be three years, a member may not serve more than two consecutive terms. The Council shall designate the Chairman of the Committee who shall be an ex officio member of the Council, without vote. Council is empowered to appoint and compensate a Business Manager who shall assist in carrying out the functions of the Finance Committee under the supervision of the Executive Secretary-Treasurer. The President-Elect, Executive Secretary-Treasurer and the Business Manager shall be ex officio members of the Finance Committee, without vote.

SECTION 3. Membership Committee. A Membership Committee, composed of six or more regular members of the Society appointed by the Council, shall receive and review processed applications for membership and make recommendations for nomination to the Council. The term of each member of the Membership Committee shall be three years; a member shall not be eligible for immediate reappointment. The Chairman of the Committee shall be designated by the Council.

SECTION 4. Education Committee. An Education Committee, composed of five or more regular members of the Society and representatives of such other societies as may be designated by the Council appointed by the Council, shall conduct such educational, teaching and recruitment programs as may be required or deemed advisable. The term of each member of the Education Committee shall be three years. The Chairman of the Committee shall be designated by the Council. The Executive Secretary-Treasurer may act as Executive Director of the educational programs with approval of the Council. The Committee shall present an annual report to the Council and an annual budget through the Executive Secretary-Treasurer to the Finance Committee for its approval.

SECTION 5. The Council may appoint such special and other standing committees as it deems necessary or that are voted by the Society. The Council may name regular members of the Society as representatives to other organizations whenever it deems such action desirable.

ARTICLE VI. Dues

SECTION 1. Annual Dues. The annual dues for regular members, corresponding members and associate members shall be determined by the Council and shall be paid in advance of July 1. Honorary members and retired members shall pay no membership dues.

SECTION 2. Non-payment of dues. A regular or associate member whose dues are two years in arrears shall cease to be a member of the Society,unless after payment of his dues in arrears and application to the Council, he shall be reinstated at the next meeting by vote of the Council. It shall be the duty of the President-Elect to notify the delinquent of his right to request reinstatement.

SECTION 3. Retirement. A regular or associate member who has been granted retired membership status is relieved from the payment of dues but retains the other privileges of his former membership status, except voting privileges.

ARTICLE VII. Financial

SECTION 1. Society Operating Fund. The Society Operating Fund shall consist of all funds, other than Publication Operating Funds and Publication Contingency and Reserve Funds, restricted or unrestricted, uninvested or invested, short or long term. The Executive Secretary-Treasurer shall be the responsible agent to the Council with signatory powers. Signatory powers may be delegated to the Business Manager by the Executive Secretary-Treasurer.

SECTION 2. Publications Operating Fund. The Publications Operating Fund shall consist of all funds that involve receipts, expenses, short-term investments relating to the annual receipts, disbursements and continuing operation of the Society's publications. The Executive Secretary-Treasurer shall be the responsible agent to the Council with signatory powers. Signatory powers may be delegated to the Publications Manager and/or the Business Manager by the Executive Secretary-Treasurer.

SECTION 3. Publications Contingency and Reserve Fund. The Publications Contingency and Reserve Fund shall consist of the long-term capital investments of publication earnings. The Executive Secretary-Treasurer, with advice from the Finance Committee, shall have discretionary and signatory powers, except for withdrawals. Authority for any withdrawal from this fund, shall require the following five signatures: 1) The Chairman of the Publications Committee (Alternate, the senior member of the Committee);2)The President of the Society(alternate, the President-Elect); 3) the Executive Secretary-Treasurer (alternate, the Publications Manager); 4) and 5) any two members of Council. The Finance Committee shall not recommend to Council the expenditure of any of this capital fund for non-publication purposes without the consent of the Publications Committee. The Finance Committee shall be responsible for the separate investment of the reserve fund for publications; any capital gains from such investment shall accrue to the fund (capital losses will, however, reduce its value). Any dividends, interest or income, other than capital gains, from this invested fund may be used for emergency support of any of the activities of the Society, including publications, as determined annually by the Council but the primary goal shall be to increase the investment capital.

SECTION 4. Fiscal Year. The official fiscal year shall be from January 1 through December 31.

SECTION 5. Audit. All statements of net assets and related statements of income, expenditures and fund capital shall be audited annually by an independent auditing firm.

SECTION 6. Bonding. All persons having signatory powers for the funds of the Society shall be bonded.

ARTICLE VIII. Publications

SECTION 1. The official organs of the Society shall be the American Journal of Physiology, the Journal of Applied Physiology, Physiological Reviews, the Journal of Neurophysiology, The Physiologist, and such other publications as the Society may own. All publications shall be under the jurisdiction and management of the Publications Committee unless otherwise designated by the Council. The names of the journals

and publications may be changed by the Council on recommendation from the Publications Committee and any publication may be dropped by Council on recommendation from the Publications Committee.

ARTICLE IX. Meetings

SECTION 1. Spring Meeting. A meeting of the Society for transacting business, electing officers and members, presenting communications, and related activities, shall ordinarily be held in the Spring of each year.

SECTION 2. Fall Meeting. A Fall meeting of the Society shall be held at a time and place determined by the Council for presenting communications, electing members, and for transacting business except for the election of officers and adoption of amendments to the Bylaws. Under exceptional circumstances Council may cancel such a meeting.

SECTION 3. Special Meetings. Special meetings of the Society or of the Council may be held at such times and places as the Council may determine.

SECTION 4. Quorum. At all business meetings of the Society fifty regular members shall constitute a quorum.

SECTION 5. Parliamentary Authority. The rules contained in Roberts Rules of Order, Revised, shall govern the conduct of the business meetings of the Society in all cases to which they are applicable and in which they are not inconsistent with the Bylaws or special rules of order of the Society.

ARTICLE X. Society Affiliations

SECTION 1. The Society shall maintain membership in such organizations as determined by Council.

ARTICLE XI. Regulations

SECTION 1. General Prohibitions. Notwithstanding any provision of the Constitution or Bylaws which might be susceptible to contrary interpretation:

a. The Society is organized and operated exclusively for scientific and educational purposes.
b. No part of the net earnings of the Society shall or may under any circumstances inure to the benefit of any member or individuals.
c. No substantial part of the activities of the Society shall consist of carrying on propaganda, or otherwise attempt to influence local, state or national legislation. (All activities of the Society shall be determined by Council). The Society shall not participate in, or intervene in (including the publishing or distributing of statements) any campaign on behalf of any candidate for public office.
d. The Society shall not be organized or operated for profit.

SECTION 2. Distribution on Dissolution. Upon lawful dissolution of the Society and after payment of all just debts and obligations of the Society, Council shall distribute all remaining assets of the Society to one or more organizations selected by Council which have been approved by the United States Internal Revenue Service as organizations formed and dedicated to exempt purposes.

ARTICLE XII. General

SECTION 1. Records. All official records, archives and historical material shall be held in the Central Office in the custody of the Executive Secretary-Treasurer.

SECTION 2. Procedures and Customs. The Society shall maintain a current Operational Guide detailing the procedures and current customs of the Society operations as well as the duties and responsibilities of officers, committees, and major employees. The Operational Guide shall be maintained current by the Executive Secretary-Treasurer as determined by the Council.

ARTICLE XIII. Amendments

SECTION 1. Presentation. Amendments to these Bylaws may be proposed in writing, by any regular member, to Council at any time up to three months in advance of the Spring meeting, or at a business meeting of the Society. Such proposed amendments must be presented in writing at the following Spring business meeting for action by the Society.

SECTION 2. Adoption. These Bylaws may be amended at any Spring business meeting of the Society by a two-thirds majority vote of the regular members present and voting.

WHAT'S NEW IN APS PUBLICATIONS

By now, members of the APS cannot help but realize that the reorganization of the Society's journals goes into effect this coming January. But, anticipation of the accomplishment should not obscure dramatic progress on other publication fronts.

A monumental achievement of another kind will be the publication, by the end of the year, of cumulative indexes of the AJP and the JAP. For the AJP, the period covered will be 1952-1975; for the JAP, 1948-1975. Provision is being made for these long lapses between cumulative indexes not to recur. The APS is indebted to Mr. Geiger, Mrs. Rauner and the publications staff for making this heroic effort to catch up. These extremely useful volumes will be distributed without charge to subscribers to the AJP and JAP as a supplement to the November issues of the journals. Non-subscribers will be able to purchase them separately.

Nineteen hundred and seventy-seven should also see the appearance in print of the symposium "Disturbances in Body Fluid Osmolality" edited by T. E. Andreoli, J. J. Grantham, and F. C. Rector. The proceedings were part of the 1976 meeting of the APS. The contributions have been extensively revised and should make an important contribution to the literature on the subject. In addition, the success of the book will serve as a trial balloon with respect to future publications of symposia.

Also moving along is the Handbook series. Early in 1977 the Handbook on "Reactions to Environmental Agents," edited by D. H. K. Lee, H. L. Falk, and S. D. Murphy, will appear. The first volume of the revised Handbooks on Neurophysiology, "Cellular Biology of Neurons," edited by E. R. Kandel, is expected in time for the Spring FASEB meeting. Two new volumes are underway for the Handbooks on the circulation. One, devoted to "heart" is being edited by R. M. Berne; the other, devoted to "vascular smooth muscle" by D. F. Bohr. Plans have been drawn for new topics in the Handbook series.

Plans for a new monograph series are underway. The intention is to publish leisurely a series of monographs in the classical style of Krogh, Sherrington, and Haldane. These are intended to be overviews of some aspect of physiology by a distinguished physiologist who has developed an original perspective in physiology as a result of a lifetime of scholarship and research. The Publications Committee recognizes that there will not be many of these. However, it looks forward to cultivating each one as the opportunity presents.

Meanwhile, the Journal of Neurophysiology and Physiological Reviews are prospering. Both have long records of excellence. But, the Editorial Boards of both Journals are not resting on their laurels; instead, they are now exploring the adequacy of the scientific coverage that they provide as well as the possibility of fresh initiatives and new directions in keeping with the changing scene in physiological research.

Clearly, 1977 will be a busy year in publications for the APS. To cope with this increase in activity, the Publications Committee has the advantage of fresh blood: Drs. Robert M. Berne and Robert W. Berliner. The Publications Committee looks forward to the prospect of heightened activity and would welcome comments and advice from the members of the Society.

Alfred P. Fishman
Chairman
Publications Committee

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1977 HARWOOD S. BELDING AWARD IN ENVIRONMENTAL PHYSIOLOGY

The Temperature Regulation Section of the American Physiological Society will present the Annual Award to a graduate student at the Temperature Regulation Dinner during the Federation Meetings, April 3-8, 1977. The Award includes a prize of $150.

Requirements:

1) The graduate student applicant must plan to give the paper at the Federation Meetings. He or she must be first author on the abstract which is published in the Federation Proceedings.

2) A requirement for receiving the Award is the attendance of the student at the Temperature Regulation Banquet. In case of illness he or she could still receive the Award by a vote of the Award Committee.

3) The typewritten copy of the presentation with illustrations should be submitted. Alternatively, a manuscript which is ready for publication may be submitted. Manuscripts must be received by the chairman of the Temperature Regulation Group by March 1.

Manuscripts for the Belding Award should be mailed to:

Dr. Ethan R. Nadel
John B. Pierce Foundation Lab.
290 Congress Avenue
New Haven, CT 06519

JOURNALS - 1977

Dear Member:

By now, I'm sure you are aware that, starting in January, you will have the opportunity of receiving any of the Society's five new journals. Once again, though, we urge you to enter your subscription to the journal or journals of your choice. I hope that you will take a moment either to complete one of the order forms already mailed to you, or to drop us a line entering your subscription, so that we can process your order in time for the first issue.

We are optimistic that the dramatic changes in the Society's journal publishing program will be warmly received by the membership. Because of the changes that have occurred in the discipline of physiology, the new program will provide you with appropriate vehicles both for publishing your own original research, and for reading current research in your area of specialization.

As you will recall, the editorial scope of the Journal of Applied Physiology has been limited to papers in respiratory, environmental and exercise physiology ($42.50). The following new journals will be published:

American Journal of Physiology: Cell Physiology ($15.00)
American Journal of Physiology: Endocrinology, Metabolism and Gastrointestinal Physiology ($22.50)
American Journal of Physiology: Heart and Circulatory Physiology ($27.50)
American Journal of Physiology: Regulatory, Integrative and Comparative Physiology ($15.00)
American Journal of Physiology: Renal, Fluid and Electrolyte Physiology ($20.00)

The articles contained in these five new journals will be published simultaneously in one consolidated American Journal of Physiology ($62.50). The Journal of Neurophysiology ($25.00) will remain an important vehicle for the publication of original contributions on the function of the nervous system. The prices listed above are annual subscription rates for 1977 for APS members. They are one-half the nonmember rates.

We thank you for your help in making this new and important venture a success, and look forward to receiving your subscription order.

Yours sincerely,

Stephen R. Geiger
Publications Manager
and Executive Editor

FUTURE MEETINGS - SPECIAL FLIGHTS

XXVII INTERNATIONAL PHYSIOLOGICAL CONGRESS
PARIS, FRANCE, JULY 1977

Based on responses to the questionnaire you received from Chevy Chase Travel, Inc., travel plans have now been finalized and we have arranged for three charter flights to Paris and London.

The brochure detailing the departures will be mailed to you by separate cover, with the call for abstracts and program announcement.

We want to stress that the deadline dates for deposits and final payments are in accordance with CAB regulations and are real and must be adhered to. The various dates are noted under each flight. You will be billed well in advance for your payments but if you do not send in payment to be received by the date shown - you will automatically lose your seat.

All the rules stipulated in the brochure are TGC regulations. No doubt you have read about the new ABC Charter concept, which have less stringent regulations. If this type of flight proves to be advantageous for our travel, we will revert to this type of charter and you will be advised accordingly. Please be aware, however, that this does not mean the fares will be any lower - but it could mean that the booking and cancellation rules will be easier.

1977 APS FALL MEETING
HOLLYWOOD BEACH, FLORIDA, OCTOBER 9-14

Group travel is being arranged from a number of major U.S. cities to Miami, Florida. Connecting buses will be provided to Hollywood Beach.

Schedules and Reservation forms will be mailed to you in April.

APS/ASZ TASK FORCE ON COMPARATIVE PHYSIOLOGY

Since the previous report on the formation of a joint task force on Comparative Physiology (The Physiologist, Vol. 19, Number 1, 1976) in February of this year, significant progress has been made toward the development of an intersociety organization that would integrate the efforts of American comparative physiologists in both societies. A steering committee has been appointed by the presidents of both societies and a survey on the current status of comparative physiology in the U.S. and Canada has been conducted.

The steering committee is composed of the following individuals with nearly equal representation among the two societies:

Howard A. Bern	John R. Brobeck
Michael J. Greenberg (Co-chairman)	Ronald H. Alvarado
John L. Roberts	Ann E. Kammer
Frank P. Conte (Chairman)	James N. Cameron

Knut Schmidt-Nielsen (Interunion Commission on Comparative Physiology)

The first meeting of the steering committee took place on August 18 during the joint APS/ASZ Fall meeting in Philadelphia and had as one of its first actions the unanimous approval for a resolution requesting the APS Council sanction the committee to organize a new section of Comparative Physiology in APS which could provide the integrative mechanism between ASZ(DCPB) and APS members. Based upon the data derived from the recent ASZ/APS survey on Comparative Physiology, over one hundred respondents indicated that at the present time they were members of both societies. In addition, 283 ASZ(DCPB) respondents indicated a desire to become affiliated in some type of membership with APS. Letters of invitation to join APS along with application forms are being distributed to these individuals by the Chairman of the task force. If any present member of APS wishes to affiliate with the new section, they should contact Dr. Orr Reynolds, Executive Secretary of APS for information. In addition, discussion on several potential problem areas (research resources and undergraduate teaching) were made with some possible solutions being offered; however, two areas had immediate and definable needs and the steering committee appointed sub-committees to handle these matters. Charlotte P. Mangum, Chairman-Elect of the ASZ(DCPB) and Ronald H. Alvarado agreed to co-chair a publications media sub-committee while Ann Kammer and Michael Greenberg agreed to co-chair a sub-committee on Long Range APS/ASZ Programs.

Following a brief discussion with F. Eugene Yates, Editor; F. P. Conte and Bodil Schmidt-Nielsen, Associate Editors of AJP:Regulatory, Integrative and Comparative Physiology (RICP), the publications media sub-committee was charged with the task of defining a mechanism whereby the integration of the present policies of the DCPB editorial board of the Journal of Experimental Zoology with those general editorial policies presently being formulated for the new AJP (RICP) could be achieved. Integrated policies to be considered are those concerning the contextual scope for comparative physiology aspects of the AJP journal; identification

of areas in comparative physiology which are new frontiers that could be encouraged to publish manuscripts in the new journal especially those areas which interface with other traditional disciplines (i.e. biochemistry, ecology, etc.) rather than the sub-disciplines within physiology; coordinate with the associate editors the search for nominees to serve as members for the editorial board of the new AJP journal to handle the substantive matters of acceptance or rejection of manuscripts and lastly, to stimulate the membership of the newly formed APS Comparative Physiology section to endorse these actions by submitting manuscripts to AJP: Regulatory, Integrative and Comparative Physiology journal which begins publication in January 1977.

The Program Planning Sub-committee was charged with the task of proposing and developing scientific topics for future meetings and coordinating and integrating the future scientific meetings, workshops and symposia of the newly organized APS section with the program officer of ASZ/DCPB (Jack Hudson) with the expressed purpose of improving communications and exchange of scientific information among comparative physiologists attending joint APS/ASZ meetings. In addition, the Sub-committee will coordinate its activities with the representative of the Interunion Commission on Comparative Physiology sponsored by UUPS, IUBS and IUPAB (Knut Schmidt-Nielsen) thereby linking the activities of the American comparative physiologists to their counterparts in other countries of the world. In this way, any suggestion coming from an American comparative physiologist that relates to planning of international congresses, symposia, and other meetings, will be promptly considered by the commission and submitted with appropriate support.

Lastly, many respondents to the Survey of Comparative Physiology requested that information collected be reported back to the joint membership. The following serves as an abbreviated report: The Comparative Physiology Survey consisted of two separate questionnaires which were mailed respectively to ASZ(DCPB) members or selected APS members in late June 1976. The ASZ mailing was to 1,932 members of DCPB with 402 (21%) of the membership responding while the APS mailing was limited to 238 members who had registered a special interest in either "Cells," "Tissues and Organs" or "Comparative Physiology" but did not indicate that they were at the present time members in ASZ. The number of APS members responding were 73 (31%). Some of the selected data derived from the survey are expressed as percentage based upon the number who replied to the specific question. Those who answered NA were not included in these values.

1. Does your institution have a graduate program?
   APS: Yes (94%) No (6%) ASZ: Yes (82%) No (18%)

2. At the present time do you have a research grant that is supported by the federal government?
   APS: Yes (76%) No (24%) ASZ: Yes (49%) No 51%)

3. Should the societies actively engage in identifying the need for federal support of comparative physiological research?
   APS: Yes (89%) No(11%) ASZ: Yes (87%) No(13%)

4. Would you be a member of ASZ if a joint membership could be achieved?
   APS: Yes (56%) No (44%)

5. Would you be a member of APS if a joint membership could be achieved?
   ASZ: Yes (87%) No (13%)

6. Do you think there is a need for a new journal (other than JEZ, AJP, PZ) for comparative physiology?
   APS: Yes (30%) No (70%) ASZ: Yes (20%) No (80%)

7. Has it been difficult to find either an acceptable or appropriate journal to which to send your manuscripts?
   APS: Yes (13%) No (87%) ASZ: Yes (10%) No (90%)

8. Does your library have the AJP?
   APS: Yes (99%) No (1%) ASZ: Yes (90%) No (10%)

9. If a new AJP section had pages devoted to the publication of ASZ-DCPB symposia as an adjunct to the American Zoologist would you subscribe to AJP?
   APS: Yes (33%) No (67%) ASZ: Yes (58%) No (42%)

10. If a new AJP section were devoted to manuscripts emphasizing laboratory experiments useful in the teaching of comparative physiology and biochemistry, would you recommend library acquisition?
    APS: Yes (90%) No 10%) ASZ: Yes (90%) No (10%)

11. Would you subscribe to AJP if the scope of a section were restricted to comparative physiology (and biochemistry)?
    APS: Yes (23%) No (77%) ASZ: Yes (54%, No (46%)

12. Which, if any, of the following areas of comparative physiology do you find poorly served by existing journals.
    APS/ASZ Physiological ecology - 37%
    Physiological chemistry - 15%
    Comp. structure and Function of Macromolecules - 17%
    Other - (≤5%)

13. Have you used The Physiology Teacher in any instructional activities?
    APS: Yes (46%) No (54%) ASZ: Yes (46%) No (54%)

14. Have you served as a reviewer of manuscripts for a scientific journal?
    APS: Yes (82%) No (18%) ASZ: Yes (60%) No (40%)

15. Have you served on an editorial board?
    APS: Yes (34%) No (66%) ASZ: Yes (15%) No (85%)

16. Would you like to serve as a referee, editor, or reviewer for a scientific journal?
    APS: Yes (78%) No (22%) ASZ: Yes (81%) No (19%)

17. Are you in favor of continuing the APS/ASZ(DCPB) joint meetings?
    APS: Yes (93%) No (7%) ASZ: Yes (92%) No (8%)

18. Do you find the joint meetings of ASZ(DCPB) and APS more or less attractive with other divisions of ASZ?
    ASZ: More (72%) Less (28%)

19. Do you find the joint meetings of ASZ(DCPB) and APS more or less attractive with other FASEB societies?
    APS: More (60%) Less (40%)

20. How many national meetings of APS or ASZ have you attended in the last three years.
    APS: 0 18% 1 24% 2 25% 3 25% 4 7% 5 1%
    ASZ: 0 26% 1 28% 2 25% 3 15% 4 3% 5 3%

Details on other questions are being collated by task force personnel and will be presented as an addendum in future newsletters. A great deal of thanks is given to the entire APS/ASZ membership for their time and effort given to this matter.

VISITING PROFESSOR EMERITUS PROGRAM

The Visiting Professor Emeritus Program, started by the Association of American Medical Colleges, was established at AAMC on July 1. This program provides a mechanism through which we can assist medical schools with temporary faculty needs by supplying the names of recently retired or semi-retired faculty interested in continuing to work in their field. A preliminary survey showed a high interest in this project. The success of the program will depend upon the responces of the schools in expressing their needs and nominating suitable faculty. Copies of a descriptive brochure are being sent to the Deans of the medical schools.

More specific information can be obtained from the Department of Institutional Development, Visiting Professor Emeritus Program, AAMC, One Dupont Circle, NW, Washington, DC 20036, (202) 466-5108.

ANNOUNCEMENT BY THE SECTION OF NEUROPHYSIOLOGY

Several symposia on neurophysiology are planned for the Spring Meeting of the American Physiological Society, to be held with FASEB, in April of 1977 in Chicago. Instead of the traditional format of three or four hour-long lectures held in a ballroom, these sessions will consist of a larger number of shorter invited communications, and will be scheduled in auditoriums of reasonable size, facilitating the participation of the audience in the discussions. The Federation Meetings provide a natural setting for the exchange of information between neurophysiologists and investigators in other disciplines, and many of the symposia will deal with subject matter of overlapping interest. We hope that our colleagues whose work relates to other organ systems will attend these symposia, and we will ask the speakers to keep their remarks concise and conceptual instead of exhaustive and factual. The tentative dates are from Sunday, April 3 at noon until Wednesday April 6, mid-day.

The following are the topics of the Neurophysiology symposia:

Synaptogenesis

Organizer: Phillip Nelson, NIH

Investigations in vitro and in vivo of the formation of junctions between neurons. This symposium will naturally complement the Federation Workshop on Methods of Tissue Culture.

Auditory Communication between Animals

Organizer: Robert Capranica, Cornell University
Co-chairman: Ronald Hoy, Cornell University

Behavioral and neurophysiological aspects of sound emission and sound reception.

A related evening discussion is also scheduled on the topic: "Do pure tone stimuli lead to artefactual interpretation of auditory function?" Both sides of this question will be articulated. There will be invited discussants, but no timetable, and no prepared speeches. There will also be opportunity for the audience to take part in the discussion.

Cellular Pacemakers

Organizer: David Carpenter, National Naval Medical Center

From heart and guts to brain, from invertebrates to mammals, the questions of "spontaneously" recurrent excitation in healthy tissue as well as in paroxysmal discharges, clonus and tremor, will be considered.

The Integration of Information at the Level of Single Neurons

In the chair: Barbara Gordon-Lickey, University of Oregon

Program: George Somjen, Duke University

Convergence of different sensory modalities on single neurons, and the role of neurons in ordering sensory information, in the exploration and organization of space; in the detection of movement; in the detection of noxious stimuli; and related topics will be considered.

Neuronal Mechanisms in Temperature Regulation

Organizer: Dennis Poulos, Albany Medical College

Hypothalamic, brain stem, and spinal mechanisms regulating heat production and heat dissipation will be discussed.

The Neural Control of Renal Function

Organizer: Gerald DiBona, University of Iowa

This sometimes neglected but very important topic will get an airing.

If possible, the volunteer paper and poster sessions will also be concentrated on the same days, but avoiding direct conflict of overlapping subject material. The Neurophysiology Cash Bar will take place on one of the three evenings, probably on Monday, April 4th.

The Steering Committee of the Neurophysiology Section now has the following members:

David Carpenter, M.D., Neurobiol. Dept., Armed Forces Radiobiol. Inst., Bethesda, Md 20014
Morton Cohen, Ph.D., Dept. Physiol., Albert Einstein Coll. Med., Bronx, NY 10461
Donald Humphrey, Ph.D., Dept. Physiol., Emory Univ., Atlanta, Ga 30322
Kiyomi Koizumi, M.D., Dept. Physiol., Downstate Med. Ctr., Brooklyn, NY 11203
John Manning, M.D., Dept. Physiol., Emory Univ., Atlanta, Ga. 30322
Phillip Nelson, Ph.D., Behavioral Biol. Br., Natl. Inst. Child Health, Bethesda, Md. 20014
Lloyd Partridge, Ph.D., Dept. Physiol. Biophys., Univ. of Tennessee, Memphis, Tn. 38103
Dennis Poulos, Ph.D., Dept. Physiol. Neurosurg., Albany Med. Coll., Albany, NY 12208
Henry Ralston, Ph.D., Dept. Physiol., Sch. Dentistry, Univ. Pacific, San Francisco, CA 94115
George Somjen, M.D., Dept. Physiol. Pharmacol., Duke Univ. Med. Ctr., Durham, NC 27710, Chairman of the Committee

This Committee welcomes your suggestions.

AUDIOVISUAL REVIEW

The following presentation was reviewed and rated highly during the test establishment of audiovisual review centers in 1974. In the November 1975 Audiovisual Aids Supplement to The Physiologist, this review was inadvertently omitted. The review is presented here with our apology for the earlier omission.

Illustrated Lectures in Respiratory Physiology. John B. West, M.D., Ph.D.

This course is designed to help medical and dental students with their course in respiratory physiology. It is also suitable for chest physicians who want to up-date their knowledge of respiratory function. The tapes have also been used extensively by respiratory therapists and other paramedical personnel.

Content: 9 (excellent); Production quality: 9 (excellent)
Useful as: Primary Educational Instrument and Enrichment Material
Available from: AV/MD
Division of Steven K. Herlitz, Inc.
850 Third Avenue
New York, NY 10022

Recommended: Basic Science: Medical, dental, graduate, graduate nursing, and allied health
Continuing Education: Medical, allied health

201 Structure and Function of the Lung. 2 Cassettes. 25 Min. 36 Slides
A discussion of the relationships between pulmonary structure and function, including the blood-gas barrier, airways, blood vessels. There is also a short section of the physical gas laws.

202 Ventilation. 2 Cassettes. 45 Min. 28 Slides
Includes a discussion of lung volumes, total and alveolar ventilation, anatomical deadspace, physiological deadspace, and regional differences in ventilation.

203 Diffusion. 2 Cassettes. 40 Min. 22 Slides
Includes a discussion of diffusion and perfusion limitations of gas transfer, oxygen uptake along the pulmonary capillary, measurement of diffusing capacity, reaction rates with hemoglobin, and CO_2 transfer across the blood-gas barrier.

204 Blood Flow. 2 Cassettes. 45 Min. 50 Slides
Discussion of the pressures within and without the pulmonary blood vessels, pulmonary vascular resistance, measurement of pulmonary blood flow, distribution of blood flow, hypoxic vasoconstriction, water balance in the lung, and the metabolic functions of the lung.

205 Ventilation-Perfusion Relationship. 2 Cassettes. 45 Min. 25 Slides
Includes a discussion of oxygen transport from air to tissues, hypoventilation, shunt, ventilation-perfusion inequality including regional differences in the normal lung and effects of uneven ventilation and blood flow on overall gas exchange.

206 Gas Transport to the Periphery. 2 Cassettes. 45 Min. 29 Slides
A discussion of hemoglobin, the oxygen dissociation curve and the factors which shift it, carbon dioxide dissociation curve, acid-base status of the blood, and blood tissue gas exchange.

207 Mechanics of Breathing. 2 Cassettes. 58 Min. 35 Slides
Includes muscles of respiration, elastic properties of the lung, compliance, surface tension, regional differences in ventilation, airway closure, airway resistance, dynamic compression of the airways, work of breathing.

208 Control of Ventilation. 2 Cassettes. 46 Min. 20 Slides
A discussion of the factors determining the rhythmicity of breathing, respiratory centers, ventilatory response to carbon dioxide, oxygen and pH, reflexes from the lung and chest wall, control of ventilation during exercise, and abnormal patterns of breathing.

AMERICAN SOCIETY OF BIOMECHANICS

To stimulate research and encourage communications and cooperation in the field of biomechanics, the formation of the American Society of Biomechanics is proposed. Regular meetings will be structured to allow an exchange of information and discussion among those engaged in applying the principles of mechanics to biological problems. A working committee consisting of Richard A. Brand (Medicine); Don B. Chaffin (Ergonomics); F. Gaynor Evans (Biology); James G. Hay (Physical Education); and Albert B. Schultz (Engineering) is investigating the details of forming the Society. Persons actively engaged in biomechanics research and publication are asked to indicate their interest by contacting Gary L. Soderberg, Physical Therapy, The University of Iowa, Iowa City, Iowa 52242.

HONORS AND AWARDS

NATIONAL MEDAL OF SCIENCE

On June 4, President Ford announced the winners of the National Medal of Science for 1975. The medal, established in 1959, is presented to individuals who "are deserving of special recognition by reason of their outstanding contributions to knowledge in the physical, biological, mathematical, or engineering services."

APS member, Hallowell Davis, was one of the 15 recipients of the medal.

Dr. Davis, Central Institute for the Deaf, St. Louis, was cited for: "Fundamental research on nerve potentials, electroencephalography, and mechanisms of hearing that have formed the basis for advances in neurophysiology, neurology, otolaryngology, audiology, acoustics, occupational health and safety, and pediatrics."

KITTAY SCIENTIFIC FOUNDATION PRIZE

The largest award in the field of mental health, the $25,000 prize from the Kittay Scientific Foundation, was shared this year by two APS members. James Olds,* Bing Professor of Behavioral Biology at the California Institute of Technology, has concentrated on mapping the brain. He located the so-called pleasure centers of the brain and was currently studying the relationship of reward to learning. Half of the prize will go to Hans Selye, renowned for his studies of stress and its physiological and/or psychological effects. Dr. Selye is Director of the Institute of Experimental Medicine and Surgery at the University of Montreal.

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* Dr. Olds, age 54, died August 21, 1976.

NATIONAL ACADEMY OF SCIENCES

Two APS members were elected to the National Academy of Sciences during its 113th Anniversary celebration. Dr. Edward V. Evarts, Chief, Lab. of Neurophysiology, National Institute of Mental Health; and Harry Grundfest, Professor Emeritus of Neurology, Columbia University.

Award winners in biology-related disciplines included APS member, Julius H. Comroe, Jr., Director of the Cardiovascular Research Institute and Professor of Physiology, University of California Medical Ctr., San Francisco, who received the Jessie Stevenson Kovalenko Medal for work in understanding the human lung.

1976 PASSANO LAUREATES

Roger Guillemin, Professor, The Salk Institute, La Jolla, Calif., is cited for his pioneering research which provided decisive biological and chemical evidence that the hypothalamus secretes specific substances that control the release of pituitary hormones. In particular, Dr. Guillemin is honored for his research on the isolation, identification, and synthesis of the thyrotropin releasing factor of the hypothalamus; identification of the luteinizing hormone releasing factor and the synthesis of antagonists to this factor, potentially useful in population control; and the isolation as well as the synthesis of the somatotropin releasing-inhibiting factor of the hypothalamus.

INSTITUTE OF MEDICINE

Twenty-five new members were elected to five-year terms in the Institute of Medicine.

New members are elected from among candidates chosen for major contributions to health and medicine or to such related fields as the social and behavioral sciences, law, administration or engineering.

Four APS members were elected to the Institute:

Jack D. Myers, University of Pittsburgh School of Medicine
Jack Orloff, National Heart, Lung, and Blood Institute, Bethesda
Richard S. Ross, Dean of Medical Faculty, Johns Hopkins Univ.
Charles A. Sanders, Massachusetts General Hospital, Boston

For the first time in the Institute's five-year history, 70 of its original members were re-elected to a second term. APS members re-elected are:

Robert W. Berliner, Dean, Yale University School of Medicine
Vincent P. Dole, Rockefeller University Hospital
Donald S. Fredrickson, Director, NIH, Bethesda, Maryland
Donald Kennedy, Dept. of Biological Sciences, Stanford University
William B. Schwartz, Dept. of Medicine, Tufts University Sch. Med.
William A. Spencer, Baylor Coll. of Med., and Texas Institute for Rehabilitation and Research, Houston
James V. Warren, Dept. of Medicine, Ohio State University Hosps.

PAST-PRESIDENT'S ADDRESS

The Joys and Responsibilities of a Physiologist

BODIL SCHMIDT-NIELSEN

In this bicentennial year, we often marvel at the wisdom of our founding fathers in writing the Constitution of the United States of America. Similarly, I think that we as members of the American Physiological Society have a right to marvel at and to be proud of the Constitution and Bylaws of our Society. Having served on Council for the past five years, I have become increasingly impressed with how the affairs of our Society are handled due to the wisdom written into our Bylaws. Let me give you an example. When Council agrees to propose a change in Bylaws, it must be proposed in writing prior to the Spring meeting. The amendment can be adopted only by a 2/3 majority of the regular members present and voting. If the seven members of Council have overlooked some important aspect of a problem, we are sure to have it pointed out in the business meeting when the members of the Society discuss the Bylaw change. Disappointed, a little irritated, but mostly wiser, we go back to the drawing board, and when the irritation has subsided, we find that the objections raised were indeed valid and that we must come up with a better amendment.

The process is not unlike the process each or most of us must go through when we submit a paper to our beloved and highly respected American Journal of Physiology. We have labored over the paper and take great pride in it. Then back it comes from the reviewers with all kinds of critical remarks.

Now in thinking over the tradition of the Past-President's address, I have come to the conclusion that here again our founding fathers showed great wisdom. Let us say that instead of having the Past-President speak, they had decided that the incoming President should give an address; then when he stood up in front of his distinguished audience and presented his personal views, you might think to yourself: "It's too bad that we have to put up with this President for a whole year." However, when you listen to the Past-President, you can do so with the comfortable inner knowledge that it is all over; he or she is no longer in the driver's seat.

This arrangement works two ways. It also gives the Past-President some freedom and makes it possible for the Past-President to express his or her own views without too much restraint.

I have given this address the title "The Joys and Responsibilities of a Physiologist." While laboring over the address, I have often wondered why I chose this particularly difficult subject. Dr. Robert Berne said in his Past-President's Address that from the time he became President-Elect, he started worrying about his Past-President's Address. I don't think I started quite that early, but in June 1975, flying back to Maine from Washington, I picked up a Harper's magazine. In it I read a reporter's review of the Asilomar Conference (February

1975). At this international conference the moratorium on gene recombination research was lifted following intense and often heated discussion. The reporter's observations and comments were not very flattering to some of the scientists. Shortly after my return to Maine, I received from AAAS the booklet prepared by John T. Edsall on "Scientific Freedom and Responsibility" with the request from the executive officer of AAAS that I call it to the attention of my Society. Thus, being reminded of the issue of the social responsibility of the scientist which had long been in the back of my mind, I clearly felt that I had to deal more directly with the subject.

From as early as I can remember, I learned that the pursuit of knowledge is intrinsically good. New knowledge in the field of physiology as well as in other fields will invariably increase the health and well-being of mankind as well as deeply satisfy the investigator who pursues it. Up until the Second World War, I think there was little doubt in any scientists's mind that this was so. Furthermore, we felt that our social responsibilities were largely fulfilled by our efforts in increasing knowledge through research and teaching. This philosophy is reflected in the Constitution of the American Physiological Society which simply reads: "The purpose of the Society is to promote the increase of physiological knowledge and its utilization."

Following the dropping of the atom bomb, many eminent physicists who had participated in the theoretical work on the bomb asked themselves the question if they should not have foreseen or even prevented the destructive use to which the atom bomb was put. I remember well sitting in Phillip Handler's living room when Dr. Otto Frank in the early 1950's raised these questions. Such issues, however, were not to stir any serious questions in the minds of most biologists. Only during the past decade have the questions of where a scientists's responsibility begins and ends come so much to the foreground that even the most optimistic physiologist can no longer ignore them. I shall quote here from the Ciba Foundation Symposium on "Civilization and Science - In Conflict or Collaboration?" from 1972. In the introduction, Dr. Hubert Bloch states: "The question of the worthwhileness of scientific activities was almost taboo when it was first mentioned at the meeting in 1967 (Ciba Foundation Symposium on Decision-making in National Science Policy). But now powerful voices from scientific as well as non-scientific quarters are saying that the scientist should become more socially responsible, that science should be tolerated and supported only as long as its results are socially relevant and that science must be constitutionalized and controlled if it is not to destroy our civilization. It is said that the scientist's lack of values has left him helpless to prevent science from being used for exploitation and destruction. In the minds of many, science, all the way from nuclear physics and engineering to biology and medicine,has become a most dangerous evil." (p. 1).

He goes on to state the questions to which the discussants at the conference should address themselves. "What is the impact of science on the quality of life, on our work and leisure, on our environment, on human values - in short, on civilization? How does scientific progress influence civilization and how do the two interact to determine each

other's course? To what extent is science involved in, or even responsible for, present world crises? Where does the scientist's responsibility for the consequences of his efforts begin and end? To whom is he responsible? How free is he, or should he be, in choosing his subjects and carrying out his work? And who should tell him what he can and what he cannot do?" (p. 2).

Before I go into these ominous questions, let me quote from some well-known physiologists the love they felt for their subject. E. H. Starling called it "the best sport in the world" (Bard, p. 16). Robert F. Pitts said that it gives you "the most complete and lasting happiness and sense of fulfillment" (p. 1). Ragnar Granit, the Swedish neurophysiologist, wrote when he was a young man a book called "Ung Mans Väg till Minerva" ("Young Man's Way to Minerva," published in 1941). This book made a tremendous impression on us who were beginning our academic careers at that time. Ragnar Granit, now an older man, wrote in 1972 about the book: "I found it, indeed, a book by a younger man than my present self, written for young men fired by enthusiasm for a life devoted to science. The tutor, slightly older than his listeners, speaks to them about the courting of Minerva: he tells them of her apparent fickleness and real austerity, of her views on ambition and success, and of much else, not forgetting to mention the radiance of her smile on the rare occasions when she bestows it." (p. 1).

Other investigators often tend to compare their role and their feelings with that of the mountain climber. Walter B. Cannon in his delightful book, "The Way of an Investigator," wrote: "Long before experimental methods of advancing knowledge began to enthrall investigators in science, venturesome men found their satisfaction in geographical excursions. They crossed uncharted oceans; they wandered over unmapped territory. But such possibilities have largely disappeared. Untrodden places on the earth are now rare. In the United States, a progressive civilization has long since obliterated our rugged frontiers. In the world itself, both poles have been visited. Everest has been nearly conquered, and in almost all ranges the nooks and crannies of continents have been examined. The thrill of being first to find a spot which has not before been reached and to view it 'with a wild surmise' is quite exceptional. The happy fortune of enjoying such an event befell my wife and myself on our wedding journey. Since the adventure gives me an opportunity to compare the motives and experiences of explorers of the earth and investigators in laboratories of scientific research, the story is worth telling" (pp. 22-23).

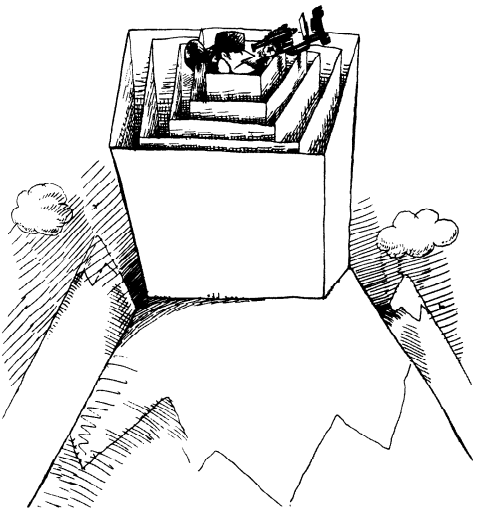
Cannon goes on to relate the story of how he and his wife were the first to climb a mountain then called "Goat Mountain" at the foot of Lake MacDonald in what is now known as Glacier National Park. The mountain was later named Mt. Cannon. In comparison, Cannon spoke of the search for knowledge as an adventure or a series of adventures which involves taking risks similar to those which he and his wife encountered during their mountain climbing. He says: "The boundary of knowledge . . . is pushed forward with painful slowness, and always, as an advance is achieved, further territory to be explored is revealed. We may feel grateful that the attractions, the excitements, and the satisfactions of pioneering are still provided in the realm of scientific investigation" (p. 28).

Granit as an older man no longer compared science to a beautiful woman. He leaned more towards the Swedish philosopher Hans Larsson who thought of discoveries as being towers. "The discoverer himself may not always climb to the top of his own towers. Others make haste to reach it, outpacing him. In the end, many people are there, most of them trying to do much the same thing. The discoverer himself should be excused if he is possessed by a desire to find a peaceful retreat where he can do something else and quietly erect another lookout" (p. 4).

I have borrowed the illustrations from Daniel S. Greenberg's article in the Smithsonian magazine, "Scientists Wanted - Pioneers Needn't Apply; Call AD 2000." (Figure 1). Greenberg does not worry so much that the pioneer may not be the first to climb his mountain, but what the maze of regulations on top of the mountain peak might do to the conquering spirit. (Figure 2). Greenberg visualizes what would happen when Walter Reed, an army surgeon, submitted his plan to test his hypothesis that yellow fever is transmitted by mosquitos by using human subjects. Reed would receive the following:

> "Memorandum from the Surgeon General, U.S. Army
> To: Dr. Walter Reed
> Subject: Human Experimentation, Regulations Concerning

Everest of research falls before our intrepid, if shortsighted, mountaineering scientist.



Will the maze of regulations on top of tomorrow's peak be as yielding to the conquering spirit?

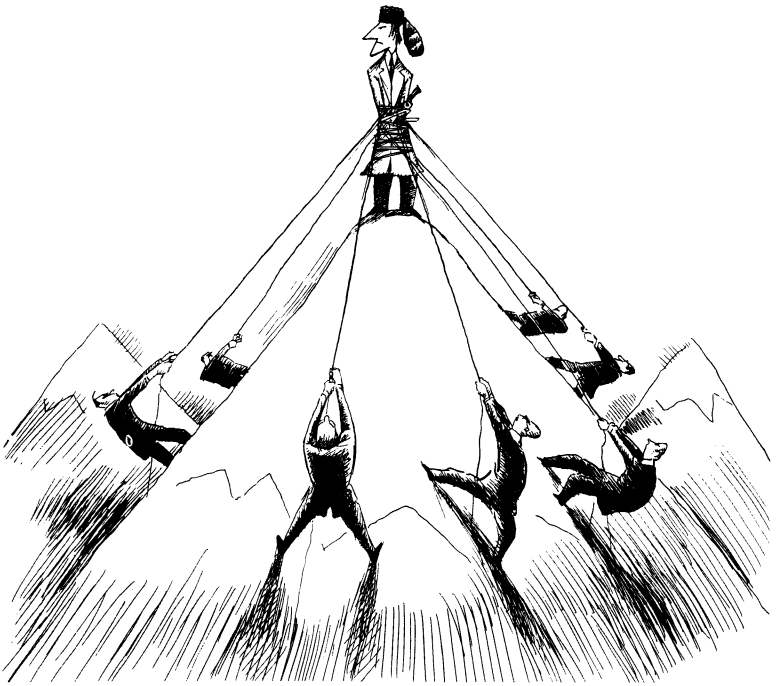
As we are sure you are aware, any experimentation involving human subjects must conform to the informed-consent regulations that the Department of the Army has adopted from the Department of Health, Education and Welfare in accordance with directives of the Federal Council for Science and Technology. As a preliminary step toward fulfilling the requirements for application for issuance of a human-experimentation permit, it will be necessary for you to submit a detailed protocol of animal studies. In conjunction with regulations concerning animal welfare, it will also be necessary for you to provide evidence that the preliminary studies cannot be accomplished without the use of animals.

Failure to comply with this memorandum will result in disciplinary action" (p. 60-61).

Another view of what may happen on the mountaintop is shown in Figure 3. It reads: "Beset on all sides by legislators, budget planners, lawyers, economists and anxious citizens who think they have him harnessed, the scientists's gaze remains fixed on the unregulated peaks beyond" (p. 63).

Now let us examine the reasons for the recent crisis of confidence in medical and other sciences. While the citizens welcome science because of the expectations of practical benefits to their lives, they have become disenchanted with many of the results of applied science and technology. In some ways, it is the total lack of coordination among

the various branches of applied science that has caused some of the major problems. A prime example is the spectacular benefits of medical research which have caused the death rate to be reduced to an all-time low. This in turn has contributed to the unprecedented population increase. As Bertrand Russell wrote already in 1950: ". . . European and American medical missions do much to diminish the infant death rate; the consequence is that more children die painfully of famine at the age of five or six. The benefit to mankind is very questionable" (p. 100).



Beset on all sides by legislators, budget planners, lawyers, economists and anxious citizens who think they have him harnessed, the scientist's gaze remains fixed on the unregulated peaks beyond.

When we think of the radiation hazards, the failure in control of food additives and drugs, the thalidomide tragedy and the many undesirable effects on our environment caused directly or indirectly by technological progress, we cannot wonder why the average citizen looks at scientific progress with mixed emotions.

In analyzing the crisis in science, Edward Shils came to the conclusion that it is a crisis in the external institutional relations of science. It is a crisis in the technological, economic and political relations of science, not in its external intellectual relations. The modern critics leave the intellectual side of science relatively untouched. The validity

of the findings of science is unquestioned; the reliability of the methods of science has been immune from doubt. It is not alleged that science has reached a dead end and that it is incapable of going on to make further important discoveries. In general, the purely intellectual reputation of science has never been better and the intellectual prospects seem to be regarded as no less favorable than they have ever been.

This view is comforting, but the scientists are still left with the problems, which I shall divide into two categories:

1) The conflict we ourselves feel because of the lack of definition of our responsibilities or, in other words, the lack of a code of ethics in science, and

2) the ambivalence of society's attitude towards science, which in turn results in the unpredictable funding for research and the maze of regulations.

As Greenberg put it, the scientist is being watched, but who watches the watchers? (Figure 4).

Who will watch the watchers themselves and under what microscope will it—can it—be done?

It has been mentioned repeatedly from many quarters (see Goodfield-Toulmin) that the scientists themselves do not have a proper ethical code, but how should we arrive at such a code? The questions are complex and ill-defined. Should scientists take over the politicians' job? Indeed, are they equipped to become politicians? Would science itself not suffer were scientists to devote their time to political activism rather than to fundamental research? Fifty years ago, when the problems facing the civilization and the scientist seemed less complex, political activism was mostly confined to fighting the antivivisectionist. Were a scientist today to devote the time necessary to be effective in political activism, he would soon find himself in deep trouble. Universities, already

reluctant in granting tenure to their professors, would become more so if tenured professors were to lose their NIH grants and neglect their teaching duties in order to be political watchdogs, watching over the use the government and industry make of scientific discoveries.

Now, if the scientist has neither the time, the training, nor the inclination for watching over the use that the society makes of his discoveries, and if he does not trust the political and industrial complex to do so, who should do it? The best answer to this question is in my mind the answer given by Dr. Masanoa Toda, a trained physicist who became a professor of psychology. Toda suggests that what we need is a science of civilization. He suggests that civilization is in danger and that the danger is derived from the acceleration of social processes. He compares these processes with the acceleration of a high speed sports car. Indefinite acceleration is obviously impossible. Now the sports car may be slowed down or arrested by depressing the brake pedal or by an accident. Toda says: "It is true that, at least in the so-called developed countries, we have so far enjoyed the acceleration of this sports car named civilization. However, some of the passengers, cowards like myself, have begun to feel a little uneasy about the speed it has acquired. The vision through the front window becomes blurred, and as a result, one observes another unprecedented event: that many serious adults are beginning to argue seriously about the future of mankind! This scene may look comical but it may foreshadow the panic of the majority. Sooner or later most passengers will begin to realize that no one knows the location of the brake pedal, or even that of the steering wheel, of this super-automated machine. Since they cannot jump off this accelerating vehicle, the first thing they will do in the ensuing panic, human nature being what it is, will be to attack directly the vital parts of the car, either the engine or the carburetor. And it requires little imagination to recognize that the engine of the present civilization is 'technology', and the carburetor feeding the engine is 'science.' Destruction of the engine or the carburetor of a sports car accelerating at high speed is fatal. The car is likely to blow up. And should there be any injured survivors left after the explosion, they could perhaps console themselves by observing the ruined car named civilization and acknowledging, 'Now at last we are free from acceleration and pollution. Let's walk slowly' "(p. 192).

A science of civilization based on the grand scale experiments which we call history, capable of making conditional predictions for the future, could indeed be the super-watchdog we are looking for. While groups of specialized scientists can call attention to the dangers posed directly by their own research efforts (an example of this is the famous moratorium on gene recombination research), only a science of civilization can look at the multiple factors involved and make predictions for their interactions. As Toda put it, these scientists must look through a macroscope rather than through a microscope, they must look at civilization from the outside, if possible, rather than from the inside. Such a science has also been suggested by J. W. Forrester, and attempts in this direction are underway, as any reader of Science magazine can attest to. More or less successful experiments in this macroscopic view of multidisciplinary studies are underway at many colleges and universities. If this science

can grow and mature, there is a hope that we can safely locate the brake pedal and steering wheel of our speeding sports car before it is too late.

In conclusion, I should like to bring this message back to the role of our scientific societies in general and the American Physiological Society in particular. Through specialization, the scientific frontiers can be pushed forward, but the view from the tallest mountain tops can only be gained when we combine the knowledge from several fields.

Physiology, itself a specialty field, combines many specialty groups. It is a primary role of the American Physiological Society to keep these specialty groups within our Society. This is why we in Council have been encouraging the formation of specialty groups within our Society while doing our best to keep these groups happy as part of the Society. It is also a primary role of our Society to interact with other biological societies in order to gain a more macroscopic view of biology in general. Examples of this are our membership in FASEB and our recent readherence to AIBS. Finally, all scientific societies must combine their efforts in order to make it possible for the infant science of civilization to grow.

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PRESIDENT'S MESSAGE

EWALD E. SELKURT

The August meeting of the Society in Philadelphia was a memorable one in several ways, but was also accompanied by nostalgia since it may be the last meeting of this type for some time to come. Starting next year we will switch to the so-called "city-resort area" meetings later in the fall, during October. However, it may be that after five or six years of trying the new format of the Fall meetings, we may wish to come back to the old type of meeting. The new meetings are planned for about six years ahead. On the other hand, Council also considered regional meetings for specialty groups, a type that we have had in the past during the late summer, perhaps in August. These meetings might continue to be held on college and medical school campuses. In other words, it would be a kind of carry-over of the original type of meeting but devoted to specialty groups rather than the whole society. Thus, we would like to preserve the flavor of the classical fall campus meetings through the specialty group meeting. In fact, some forward planning has already begun in this direction. These plans will be officially announced when final arrangements have been consummated. So perhaps eventually we will retain some of the flavor of the old-type meeting plus a new experiment in the fall meeting, the "big city or resort" type. There are advantages and disadvantages, of course, to both types of meetings. We feel that the Fall, big city-type meeting could encourage the return of exhibitors who would help us with our costs, perhaps leading to reduction in the membership fees.

Considerable activity of the Council at the Fall Meeting had to do with the amendments to the Bylaws, which were discussed and approved by Council. These will be published in detail in the next issue of The Physiologist, for your careful consideration, to be acted upon at the Spring Meeting in Chicago in 1977. Some of the changes involved new membership categories, under recommendations proposed by the Membership Committee, chaired by Dr. Beverly Bishop. The Bylaw amendment approved at the 1976 Spring Meeting added the Corresponding Membership category. The Bylaw amendment proposed for consideration at the 1977 Spring Meeting provided for a new Student Membership, literally an offshoot of the old Associate Member category and a new Associate Membership category which has been re-defined as: Persons who are engaged in research in physiology or related fields and/or teaching physiology shall be eligible for proposal for Associate Member in the Society provided they are residents of North America. Associate Members may later be proposed for regular membership. It is intended that this be a somewhat elevated category over the old Associate Membership and involve well established scientists from other disciplines who might be attracted to the Society and might enter by way of this category. The new category of Student Membership would encompass graduate students in physiology who have completed their preliminary examinations for their doctorate degree, provided they are residents of North America, but who could not remain in this category for more than five years. This lets in the graduate student at the level of having passed his or her preliminary examination. It is considered that he or

she will move into the Regular or Associate Membership category when ready.

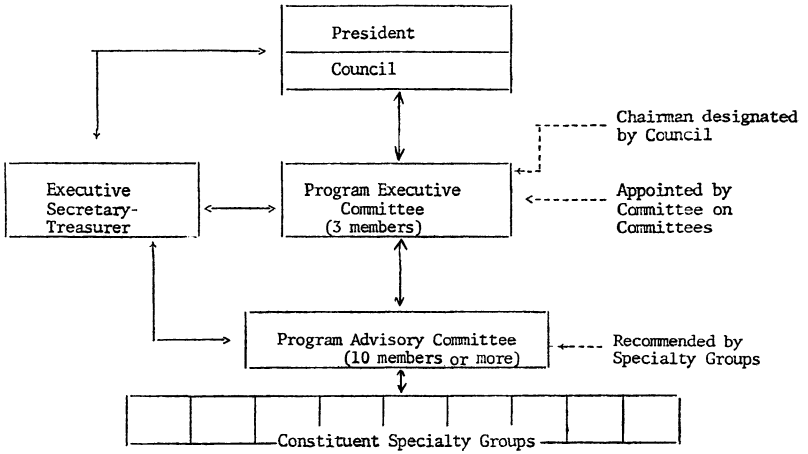
The Program Committee, under the chairmanship of Dr. H. Maurice Goodman, has been busily engaged in further development of an issue extensively reported in the May Physiologist (p. 94). One of the important responsibilities given to the Committee was to consider the reconstruction of the Program Committee, as was brought up for consideration at the Spring 1976 Meeting.

Let me review a paragraph from the article: "The Program Committee recognizes that greater sensitivity to the programming needs of specialty groups within the Society may combat the growing trend toward fragmentation within Physiology. We are seeking to open channels of communication with special interest groups within the Society and with related societies with regard to selection of session chairmen, symposia topics and so forth." To pursue this matter further, an ad hoc committee was appointed, composed of Dr. Alfred P. Fishman, Chairman, Dr. Goodman, Dr. Jere Mead, and Dr. George Somjen, and ex-officio, Dr. Orr Reynolds and Dr. Bodil Schmidt-Nielsen. This Committee has come back with a recommendation that is summarized in Figure 1, which does in effect, expand the original Program Committee, with a structure quite different from what it has been in the past. The plan proposes to establish a liaison with the many constituent specialty groups that exist in the Society; there may be as many as 20 or 30 of these groups. Rather than a rather haphazard communication back and forth between the Program Committee and these specialty groups, a channel will be set up whereby recognized groups communicate directly with a certain member(s) of the Program Advisory Committee. For example, we might say that one of the Advisory Committee members will represent the Heart and Circulatory Physiology. This member could speak for existing specialty groups in Cardiovascular, such as the Circulation Group of the APS, Cardiac Muscle, Microcirculation, etc. It is intended to establish a rather firm liaison here, and with it, better organization and better control of programs all the way up to the Council, the President of the Society, and the Executive Secretary-Treasurer of the Society. The core of the plan is to organize the Program Advisory Committee of approximately 10 members (or more) who will then communicate with the constituent specialty groups. This will be overseen by a Program Executive Committee of three members, which is currently being appointed by the Committee on Committees.

Suggested special interest groupings of the Program Advisory Committee appear in the lower part of Figure 1. These are tentative groupings, for purposes of illustration and discussion; we may want more than 10 in this Committee. In the event that publications arise out of this type of programming, an entré into our sectional journal structure is reflected here.

It is hoped that a unifying force would operate here, via the interrelationship of the constituent Specialty Groups through the Program Advisory Committee. Thus there will be a two-way street between these Sections and the Council, in a coherent form, which doesn't exist at the present time. The comments and opinions of the membership are welcomed.

General Features of Reorganization of Program Committee:



Suggested Members of Program Advisory Committee:

1. Neurophysiology
2. Heart and Circulatory Physiology
3. Renal, Fluid and Electrolyte Physiology
4. Endocrinology, Metabolism
5. Gastrointestinal and Hepatic Physiology
6. Cell Physiology
7. Regulatory, Integrative Physiology
8. Comparative Physiology
9. Respiratory Physiology
10. Environmental and Exercise Physiology

Figure 1

Brief comment on other activities of the Program Committee is appropriate at this time.

A new experiment in programming has been set up for the Spring 1977 meetings. This arises from the earlier convening of our Society (April 2), ahead of the remainder of the FASEB schedule. This opens a more extensive and flexible use of facilities, and accordingly, Dr. Goodman and his Committee have arranged an extensive series of symposia, probably the most extensive in the history of the society's Spring Meetings. As an example, the Neurophysiology Task Force has brought in an extensive series of sub-topics: synaptogenesis,

auditory communication, cellular pacemakers, integration of information at the singular neuron level, neuronal mechanisms in temperature regulation, and neural control of renal function. More details on the program will be published in the next issue of The Physiologist.

The Education Committee, headed by our new Chairman, Dr. Leonard Jefferson, has among other things, been very busy with further development and production of the Audio-visual aids. At the present time there are 14 packages available through the company, Herlitz, that markets them. The gross sales thus far have been about $100,000. Of this, we have captured 40% of the net profit, about $20,000 to date; our take is going to be increased in the near future to 25% of the gross sales, which will increase our income a little bit. We are also looking at the foreign market for these, and that is the next big push, to see if we can sell these out of the country. And with this we hope to obviously increase the overall sales. The new one on acid/base, which will be made up of five tapes, will be available in January. And in production are five more renal tapes and six cardiac tapes, which are more advanced than the ones that are out now, and are supposed to be integrated with and follow-up on the current tapes. This will give us a total of 13 renal tapes, and 12 cardiac tapes. It should be pointed out that the Society is concerned with the evaluation of the tapes, and a very important aspect of the continued use of the tapes is going to be in rigid evaluation. This job has been turned over to selected members of the Education Material Reviews Board, composed of about 105 members, and reports are that they are working hard on the important job of reviewing the tape quality.

Just a word about the activities of the Publications Committee, under Dr. Al Fishman. You may recall that he presented a very extensive report in the May Physiologist, giving the breakdown of the proposed section alignment of the journal. Dr. Fishman reported very encouraging trends in terms of manuscripts ready for the first issue in January 1977, and he was very confident that it would fly and fly well. He did, however, feel that there were not enough papers coming in for the one category, viz., Cell Physiology, since we are short of manuscripts to date (September). I want to encourage anyone who has a paper or knows of someone who would like to submit it to the Section on Cell Physiology to do so, and bring it to the attention of the Publications Committee.

We are pleased to be able to announce, as relayed from Dr. E. B. Brown, Chairman of the Finance Committee, that the finances of the Society are on an even keel; that means that we are within the limits prescribed by the Council for each sector of activity. I think it worth pointing out, however, that the Society has decided to embark on three activities that involve investment of ventured capital. The first is in additional handbook series; here advanced money is balanced, indeed more than balanced, by an inventory of bound volumes. The second is that we have an active Education Office, and particularly, we are involved in the production of new audio-visual tapes. Council agreed to put forward $50,000 for each of three years to get the tape operation into effect. Thirdly, we are going to new sectionalized journals; the budget projected for this item has been projected conservatively. We hope that the actual income from journals will be higher than we had projected, for safety's sake, in the coming year.

One additional activity that deserves comment, but which doesn't immediately bring monetary rewards, is the fact that the Council has decided to increase its activity, and change its pattern relative to programming. Furthermore, as part of this, it is planned to increase the investment of capital from our present level of a little over $8,000 to $12,000 in an upward direction to be used in expanded activities of the Program Committee. It is important to cover part of this cost of programming, so consequently the price of the Fall Meeting registration fee will be at a level which will provide not only for the cost of the meeting but a small amount of the actual programming cost.

Finally, we are all looking forward to the next International Congress of Physiological Sciences, scheduled for Paris, France, July 18-24, 1977. Dr. W. Francis Ganong, President-Elect of our Society, was elected Chairman of the USA National Committee for IUPS; an important job will be to coordinate the activities of APS, the General Physiologists, and the Comparative Physiologists in relation to the IUPS. Among the actions of this Committee are to elect and instruct delegates to the assembly meeting which occurs at the Congress, to consider a variety of matters in relation to the Congress. In this regard, we have taken a strong stand on the question of free access of scientists, and specifically came out with a stand in support of the IUPS view.

Dr. Ganong's Committee will also be working hard to establish funds for international travel to the Congress. A pilot poll of members present at the August Philadelphia meeting gave virtually unanimous support to the suggestion that membership contribute an annual $2.00 to the membership dues, to build up a fund for travel support to subsequent International Congresses. The Society will hear more about this plan in the near future.

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PORTER DEVELOPMENT FELLOWS

The following graduate students were Porter Development Fellows for the current year:

1. Pamela Gunter Broomfield at Emory University
2. Karen B. Green at Tulane University School of Medicine
3. Reclaire W. Whitfield at Tulane University School of Medicine
4. Jean Flagg at Harvard Medical School
5. Lorraine G. Miller at Stanford University School of Medicine

A. C. Barger
E. W. Hawthorne, Co-Chairmen
Porter Development Committee

FREE PUBLICATIONS AVAILABLE

The following publications may be obtained free of charge by writing to APS Headquarters.

September 1975 IUPS Newsletter. The Newsletter includes reports of the officers and affiliated societies as well as reports on the satellite symposia conducted in association with the 26th International Congress held in New Delhi in Cctober 1974.

Bibliography, Water Relations in Membrane Transport in Plants and Animals. A series of four separate special bibliographies covering the BIOSIS sponsored symposium conducted at the August APS Meeting in Philadelphia. These bibliographies were derived from the BIOSIS Data Base for each of the symposium topics and are made available to us by BIOSIS. The four separate volumes are titled: I. Water and Solute Transport in Plant Cells; II. Water and Solute Transport in Cells of Invertebrates; III. Epithelial Transport of Solutes and Water; and IV. Water Relations in Membrane Transport in Plants and Animals.

BIOELECTROCHEMISTRY AND BIORHEOLOGY - NEW DEVELOPMENTS IN PHYSIOLOGY

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Columbia University
College of Physicians and Surgeons

Introduction

While serving as Physiologist for the Office of Naval Research, London, during 1974-1975, I traveled extensively in Europe and wrote articles and reports on new developments. One of the reports dealt with Bioelectrochemistry and Biorheology as new developments in Physiology. The two areas are similar in that each represents the combination of Physiology with a physical science. For this reason, the report also discussed the growing importance of interdisciplinary research. Since ONRL reports generally have a limited circulation, I felt that it would be useful to write a summary of the contents for a wider audience of physiologists. An additional reason for considering the findings now comes from the recent report "Science Indicators 1974", issued early in 1976 by the National Science Board, which concluded that the U.S. lead over other nations in science and technology was eroding. It appears that the trends described as general in the national report, were noted earlier in the case of Physiology, with some analysis of the factors involved.

A View of Progress in Biology

In recent years, interdisciplinary research appears to have become an important (perhaps indispensable) factor in scientific progress. This is probably due to the fact that science has become more highly organized and automated (i.e., machine dominated), and that it appears to have changed its traditional patterns of development. The activities of scientists do not conform to the patterns that have been described by leading analysts of scientific development. The most frequently quoted opinions of K. R. Popper (1) and T. Kuhn (2) differ regarding the nature of scientific progress, but both agree that the old Baconian description of science as an inductive process (i.e., observation leading to hypothesis) is wrong. Yet, most of the scientific activity I saw is probably best described as Baconian.

Popper's ideas on scientific development are easiest to summarize in his own words "problems - theories - criticism" (3). "Science . . . begins with theories, prejudices, superstitions, myths; or rather, it begins when such a myth is challenged and breaks down." This breakdown (i.e., the problem) leads to a proposed explanation (i.e., the theory) which is then tested (i.e., the criticism) under conditions where one deliberately tries to falsify the hypothesis. The criticism leads to a rejection or reformulation of the hypothesis and a repeat of the process. "Thus . . . knowledge grows as we proceed from old problems to new problems by means of conjectures and refutations ... The method of science is, very simply, that it systematizes the prescientific method of learning from our mistakes."

Kuhn has focused on the revolutionary periods and the bold new steps in science (e.g., the overthrowing of the phlogiston theory in Chemistry, the Copernican revolution in Astronomy, the development of Quantum Mechanics in Physics), and views science as developing in major quantized steps. Between the revolutionary steps there are periods of "normal science" where scientists are busy doing research on the prevailing paradigms. (Paradigm is a term that is used interchangeably with theory or model.) Therefore, for most of their time, scientists are elaborating the consequences of a paradigm. Real scientific development occurs only when the contradictions that have arisen as a result of the normal science activity can no longer be tolerated and a new paradigm is presented to offer solutions for some of the outstanding contradictions.

(The two major points of view about scientific progress focus on different aspects and are really compatible, at least on a superficial level. Logically the structure of science has developed as Popper has indicated, and Kuhn agrees. On the other hand, Kuhn has shown that the rate of development is uneven.)

Bearing these ideas in mind, I tried to detect these processes at work, but most scientists I talked with described their activities only in terms of the technique they were using and the particular system they were applying it to. Very few mentioned the problem they were investigating. No one said anything about a theory he was testing, let alone one he was deliberately trying to falsify. The scientists were engaged in data gathering, but not for the purpose of testing, or elaborating a paradigm. Although their activity resembled what Kuhn has characterized as "normal science," it was deficient in the puzzle-solving aspect of that term. Hence, according to the Popper or Kuhn criteria there was very little, if any, science involved. The tentative conclusion I have come to is that, unlike the physical science of the past, recent developments in Biology, suggest that the Baconian process in a modified form can describe the activity and even some of the significant progress in the field, e.g., the determination of the double helix structure of DNA (4).

This process - the inductive method, where observations lead to hypotheses - used to be synonymous with scientific method, but it was discredited largely because one cannot merely observe; it is essential to make observations in terms of some expectations. However, one does not need a terribly sophisticated hypothesis to focus one's attention. For example, measurements can be made with a newly developed instrument to see if there are differences between the particular system under investigation and a previously measured system, or if there is a correlation between the new property and an older one. Indeed, it appears that this is often the "hypothesis" that is being "tested" by observation. And it is in this amended sense that the old Baconian description applies to much of the research that I came across during my year at ONRL. It is probably true for other fields of science as well.

Overcoming Constraints on Science

The recent changes in the pattern of development in science are probably the result of many factors, but I will mention only two. First, the vital role of external, and frequently mission oriented, funding in the development of any academic field today requires the scientist to spend a growing proportion of his time writing applications, reports, etc.; and since many evaluative procedures take scientific publications as evidence of productivity, the scientist is tempted to write papers and do experiments that will result in a quick publication, rather than pursue a scientific problem that may require a long term effort.

Secondly, just like his lay counterpart, the scientist has grown more and more dependent upon machines (i.e., scientific instruments) in his daily life. While these machines have greatly aided him in his work, they have also limited his maneuverability for the formulation and testing of new hypotheses. A scientist with a laboratory full of expensive instruments that are maintained by specialized technicians must think in terms of problems that will utilize the abilities of his equipment and staff. As one electron microscopist said to me, when referring to the huge amount of equipment in his laboratory, "I have a hungry lion to feed, and if I stop he'll eat me up."

Obviously, some scientists have found ways to overcome the effects of the new constraints on their activities. A frequently used method can be understood using terms introduced by A. Koestler (5), who suggested that the common element of creativity in humor, art and science is the solution of a problem (i.e., when progress in a "situation is blocked" using the standard approaches) that involves switching from one way of thinking ("matrix of thought") to another that is not normally included in that context. He believes that creativity is brought about by the "collision of matrices," i.e., when two different ways of thinking about a situation are deliberately focused on a problem, and the conditions are ripe for an interchange. These ideas are in line with those of Popper, who has indicated that problems are the beginning of the scientific process, as well as with those of Kuhn, who has noted the importance of problems in creating the conditions for the changing of paradigms. However, Koestler's description of creativity suggests that one can promote creative responses by arranging a "collision of matrices." This idea appears to have been utilized within the framework of normal science by the creation of new interdisciplinary areas of research, journals and scientific societies.

Organized interdisciplinary activity has been spurred on for a variety of reasons, some of which have little to do with science (e.g., political - a new society or journal generates new prestigious officers). But not all of these activities fulfill the criterion for creativity; most represent multidisciplinary approaches, such as the teaming up of scientists from two or more disciplines, generally to apply the techniques of a non-biological field to a biological system. In sharp contrast Bioelectrochemistry and Biorheology have the potential for demonstrating the creativity that is characteristic of ideal interdisciplinary research. The two branches of each hybrid discipline have a common origin and this may explain why there are many possibilities for "collision of matrices."

Bioelectrochemistry and Biorheology

Many textbooks on Physiology mention the famous controversy between two eighteenth century Italian scientists who tried to explain the contraction of the muscles in a frog's leg when the innervating nerve was touched by metals. Galvani claimed that "animal electricity" was the cause, while Volta claimed that the effect was due to the properties of the metals in contact with aqueous solutions. The experimental observations and the proposed explanations gave rise to two lines of investigation that we now call electrophysiology, where the emphasis is on the behavior of living cells, and electrochemistry, which is concerned with the properties of non-living systems. Although the two subjects are concerned with similar phenomena, there has been relatively little communication between scientists in the two areas.

A similar story can be told about the study of flow behavior in living and non-living systems. In the 1840's Poiseuille, a French biologist, studied flow in capillary tubes and determined the relation between the flow velocity and the geometry of the tube, in order to understand the factors that govern the flow of blood in the capillaries of the circulatory system. This work stimulated the development of both hydrodynamics and hemodynamics with little contact between the scientists in the two fields.

The differentiation and estrangement processes, common in living systems with the passage of time, are therefore expected in science and among scientists. However, the existence of a common origin raises certain possibilities for meaningful communication on a level over and above that due to bringing together scientists from unrelated fields to form a research team. The special advantage when one re-unites the elements of an old scientific tradition occurs in areas where they have developed unique views of the same phenomena as a result of separation over the years. This can be illustrated with the following example.

Let us consider the paradigms of the physiologist, electrochemist and rheologist as applied to the natural membrane (see Table 1). The physiologist considers the natural membrane from the point of view of its components in a particular arrangement, and has developed ion-carrier and pore models to explain transport phenomena as well as equivalent circuits for electrical events. The electrochemist has dealt with systems that require knowledge of ion activities and conductances, surface charges, electrochemical potential differences, etc., to describe electrical phenomena. When the electrochemist sees the physiological phenomena, he is bound to suggest interpretations that have not been part of electrophysiology. The electrochemist will look at the same phenomena with a background that will not allow him to accept the physiological constructs as explanations. This will be the "collision of matrices" or the problem that is apt to lead to new solutions.

(It is interesting to note that although the development of electrochemistry and electrophysiology have been along different lines, they have occasionally followed the same path with respect to the development of instrumentation. But even here they have not always talked the same

language. I was at a meeting of scientists from the two disciplines when many of those present were surprised to learn that the "voltage clamp" of electrophysiology was the "potentiostat" of the electrochemist. Apparently, they were doing the same kind of operations on experimental systems, but calling them by different names.)

Table 1. PARADIGMS OF THE NATURAL MEMBRANE

Discipline	Membrane Composition	Arrangement of Components	Function
Physiology	Polar lipids and Polymers including some specialized molecules (e.g. enzymes, carriers)	An ultra-thin chemically asymmetric bilayer, containing permselective structures (e.g., pore).	A physical boundary for separation and concentration of cell constituents that also serves as a matrix for enzymatic reactions and electrical phenomena.
Electrochemistry	Dielectric material, ions and dipoles	Phase boundaries, oriented dipoles and asymmetric charge distribution.	Charge transport and variations of membrane potential.
Rheology	Elastic, viscous and plastic (yield) elements.	Equivalent circuit of rheological elements.	Strain, yield and flow under mechanical stresses.

Returning to Table 1, we see that the rheologist looks at the natural membrane in terms of elastic, plastic and viscous elements and uses their related equations to explain the behavior that the physiologist knows must be due to the inter-molecular interactions within the membrane structure. The imposition of the rheologist's approach on the physiological model is bound to lead to hypotheses assigning particular behavior to specific membrane components or types of organization. By and large, the physiologist has ignored the rheology of the membrane until recently, and it is only the imposition of the rheologist's view that has led to an initial understanding of these membrane properties.

The emergence of Bioelectrochemistry as a distinct field is relatively recent. The first international meeting dedicated to this subject took place in 1971, in Rome, Italy, a historically appropriate site. The meeting was organized by Prof. G. Milazzo of the University of Rome, who is also the editor of a new journal, entitled "Bioelectrochemistry and Bioenergetics." The first volume of the new journal published all of the papers presented at the second international meeting on Bioelectrochemistry held in Pont a Mousson, France, in 1973, and organized by Prof. R. Buvet of the University of Paris. The third international meeting on this subject, held in 1975 in Juelich, West Germany, was organized by Prof. H. W. Nurnberg.

In sharp contrast to the level of activity in Europe, less has been going on in the U. S. There was an excellent workshop in Bioelectrochemistry held in Princeton in 1971, under the co-sponsorship of the NSF and the ESB Inc. Technology Center, but the proceedings were not part of the open literature. There have also been smaller symposia related to this subject in the Electrochemical Society and in the Division of Colloid and Surface Chemistry of the American Chemical Society. But the activity in the U. S. does not appear to have crystallized in quite the same way as in Europe.

During my year at ONRL, I attended two large symposia on Bioelectrochemistry and visited a number of laboratories engaged in research in this area. One symposium included papers on such subjects as membrane transport and composition, enzyme reactions (especially those associated with oxidative and photophosphorylation), the properties of biopolymers (e.g. nucleic acids, collagen and hemoglobin) and surface films. At the other symposium, there were quite different topics (e.g. electrical double layer theory, artificial bilayers, ion binding and adsorption at membrane surfaces). The list of subjects covered by the title Bioelectrochemistry can be extended still further, since many membrane processes (e.g., excitation, mechano-electrical transduction, active transport) involve the flow of ions under special conditions, and many enzyme systems involve ionic cofactors (e.g., the ATPases involved in the "pumping" of ions). Surely Bioelectrochemistry is not just a new boundary line that has been drawn to include many parts of Cell Physiology, and Biochemistry. It is a fresh look at problems bringing together two separate paradigms and catalyzing new insights.

Biorheology as a society had its formal beginning with the first International Congress in 1972 at Lyons, France, again a historically appropriate country. Prof. A. L. Copley of New York Medical College was the President of the first Congress. The Society actually was a direct outgrowth of the Hemorheology Society, founded in 1963 at the Fourth Congress of Rheology in Providence, R.I. Hemorheology is therefore an important part of the subject, and at the second International Congress, held in 1975 at the Weizmann Institute with Prof. A. Silberberg as President, there were many contributed papers on this subject. But Biorheology is much broader than the study of blood flow related processes, and the interests of many participants at that meeting reflected the new areas. The major new subjects discussed were symposia on "Glycoprotein and Proteoglycan Based Systems," "Cytoplasmic Streaming and Ameboid Movement," and papers in various parts of the program on natural membranes.

These new areas in Biorheology have catalyzed contact between scientists who are working on seemingly unrelated subjects (e.g., erythrocytes and tracheal mucus), but who may have similar problems to contend with regarding flow behavior. In addition, the introduction of the rheological approach may have even more important effects on the study of specific problems. For example, motility in biological systems can involve muscle movement, cytoplasmic streaming or flagellar movements, but these are seldom considered as closely related problems. At a meeting on muscular contraction in England, just before this Congress, there

was no mention of the other two types of movement. At the Biorheology Congress the problem of motility was considered as a general phenomenon. We were told that the muscle proteins, actin and myosin, are found in many non-muscle cells and that related substances are present in flagellar structures. One may therefore be able to learn about muscle contraction from such processes as the gel-sol transformation, Ca^{++} ion control and membrane events that occur during pseudopod formation in ameboid movement. Biorheology addresses the question of biological motility in its most general form.

Conclusion

Bioelectrochemistry and Biorheology, the two old-new interdisciplinary approaches in Physiology, are developing in many centers in western Europe. This activity was reported by the Office of Naval Research - London at various times during 1974-1975, and was summarized in a report (6) which recommended that we establish a strong research capability in these areas in the U. S. More importantly, if true interdisciplinary research represents the cutting edge of scientific progress today, we might be well advised to re-examine our research structure and our procedures for selecting research fields for emphasis.

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2. Kuhn, T. The Structure of Scientific Revolutions, University of Chicago, 1969.
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5. Koestler, A. The Act of Creation, Dell, 1967.
6. Blank, M. Report ONRL-12-75, entitled "Interdisciplinary Approaches in Science - Bioelectrochemistry and Biorheology as New Developments in Physiology", is available from ONRL, Box 39, FPO New York 09510.

NATIONAL SOCIETY OF CARDIOPULMONARY TECHNOLOGISTS

The National Society of Cardiopulmonary Technologists will hold its second annual fall seminar December 3, 1976 at the Del Webbs Hotel Sahara, Las Vegas, Nevada.

A highly concentrated educational program has been planned for the cardiopulmonary technologist who is interested in learning about new techniques and advancements in the field. The technologists who attend this seminar will find applications which can be put to daily use in the laboratory. Corporations will be exhibiting table top displays.

Program topics will include: Clinical Applications of Cardiac Pacing; Clinical Applications of Blood Gases; Laboratory Management Techniques; Registry Examination Workshop.

For further information contact: National Society Cardiopulmonary Technologists, Inc., #23, 3535 University Blvd. W., Kensington, MD 20795. (301) 933-5055.

The National Society of Cardiopulmonary Technologists' Committee for the 10th Anniversary Conference also invites the submission of abstracts for presentation at the Anniversary Conference in San Francisco, California, May 25, 26, 27, 1977.

The Committee invites abstracts by technologists on all scientific aspects of cardiopulmonary technology dealing with original investigation as well as observations and modifications of standard methods.

Only a limited number of papers can be presented at the annual meeting during the time allocated. Abstracts must be received by December 31, 1976.

Typing Specifications for Abstracts:

1. Limit abstracts to 250 words, including important data and conclusions. Type title on each page.
2. Five copies, typed and double spaced are required.
3. Type the names and any academic degrees as well as membership classification in the Society (if any) and complete address of author and co-authors on the first page. The name of the presenting author should be listed first.
4. Charts and tables should be attached to aid in the selection of papers.

Send abstracts to: Virginia Burleson, Chairperson, Conference Committee, NSCPT, #23, 3535 University Blvd., W., Kensington, Md. 20795.

COMPARATIVE MAMMALIAN RESPIRATORY MECHANICS*

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Harvard School of Public Health

Man's awareness of the differences among mammals is as old as the hills and as natural as breathing. His interest in their similarities is more recent. The study of some of these similarities and differences among animals is the province of comparative physiology. In 1971 the Physiology Training Committee of the NIGMS characterized Comparative Physiology as unique in using kind of animal as one experimental variable, an approach which affords biological generalizations not otherwise obtainable (10). The Committee went on to discuss five broad areas of application of comparative physiology to human welfare.

First, it puts human physiology into an evolutionary perspective which points toward insights into mechanisms. The evolution of the vertebrate kidney is an example of such studies. Second, the study of animals' adaptations to their environments gives understanding of the range of physiological solutions to problems resulting from environmental stresses. It assists man's exploitation of his own environment, as in heat, cold, and altitude, and also in such undertakings as selection and breeding of animals and management of pest species. Third, interpretation of physiological, pharmacological, and other experiments in animals and their application to man need to take account of relevant species differences. In addition, spontaneous or induced diseases and abnormalities provide useful models of human diseases. Fourth, species differences pose problems to veterinary patho-physiology and medicine which are not encountered in humans. Not only successful animal husbandry, but also agriculture and human medicine require knowledge of comparative physiology, including that of insects, parasites, and other pests. Fifth, the solution of critical problems in cellular physiology has sometimes depended upon specific physiological preparations. The giant axon of squid is only one such example. These five headings provide a basis upon which to judge the value and potential value of specific fields of comparative physiology including mammalian respiratory mechanics.

Let us turn, then, to a selective survey of some issues in the comparative physiology of mammalian respiratory mechanics. It is addressed to physiologists not specializing in respiratory mechanics, and touches upon background and well-known principles, definitions, and conventions, presents examples of current methods, problems, and findings, and suggests a few intriguing questions for the future, both specific and general.

Figure 1 is taken from one of Dr. Knut Schmidt-Nielsen's enchanting talks. Mammals vary in size from bats and shrews weighing less than

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*Tutorial Lecture presented at the American Physiological Society Fall Meeting, San Francisco, October 9, 1975. Supported by USPHS Grant HL-14580.

10 gm to whales weighing over 100 metric tons - about 7 orders of magnitude. Kleiber (8) and others have shown a general relationship between body weight and metabolic rate: a mammal's oxygen consumption varies roughly with the three-quarters power of body weight. That is to say, weight for weight, the shrew uses roughly 25-50 times more oxygen per unit time than does the whale; the laboratory mouse five times more than a man. Thus the lungs appear to be required to transfer relatively more O_2 and CO_2 in smaller animals, and so we might expect their lungs to be in some way bigger in relation to body weight. What measures of lung size are useful?

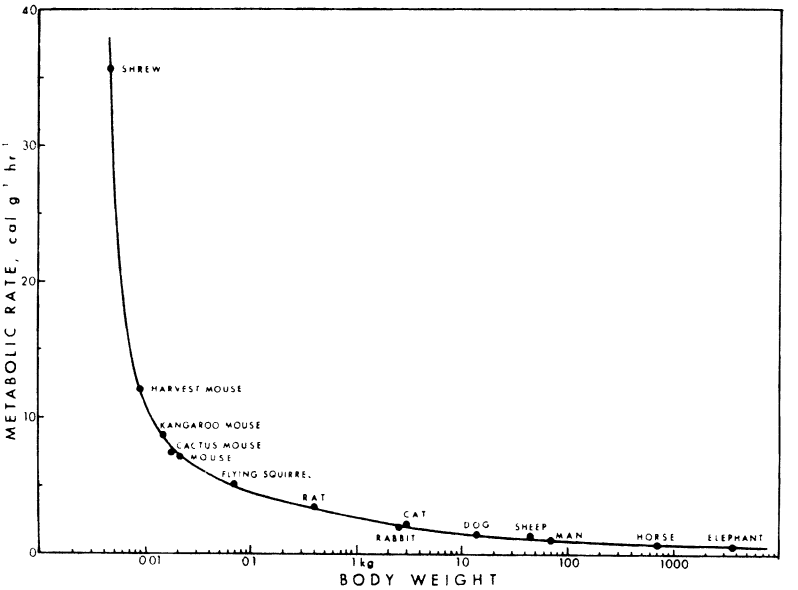

Fig.1. Variation of metabolic rate with body weight among mammals. From Schmidt-Nielsen (11).

Lung weight is one. But several authors have examined this and find that lung weight varies with the first power of body weight. That is to say, lung weight is about 1% of body weight in all mammals regardless of the animal's size.

Perhaps lung volume would be better? Here again, any of several definable lung volumes varies with the first power of body weight, as shown in Figure 2 from a paper by Tenney and Remmers (16). The log-log plot is a standard representation in the field; the slope of the regression line is the exponent expressing the variation of volume, in this case, with body weight. The slope here is 1.02; Stahl reported a slope of 1.06 for TLC and 1.03 for vital capacity, the latter having a value just under 60 ml. per kg body weight (14). Incidentally, Stahl's

methods predict a VC larger than the TLC in small animals, an indication of the limits of these data and regression analyses. But there are other measures of lung size more directly related to its function as an organ of gas exchange. Tenney and Remmers measured surface area in their excised lungs, (Figure 3) and demonstrated a relationship with resting oxygen consumption in ml/minute. The slope is 1.0. In other words, lung surface area appears to be tied to gas exchange requirements; that is, to the absolute value of the total oxygen flux, and not to body weight per se.

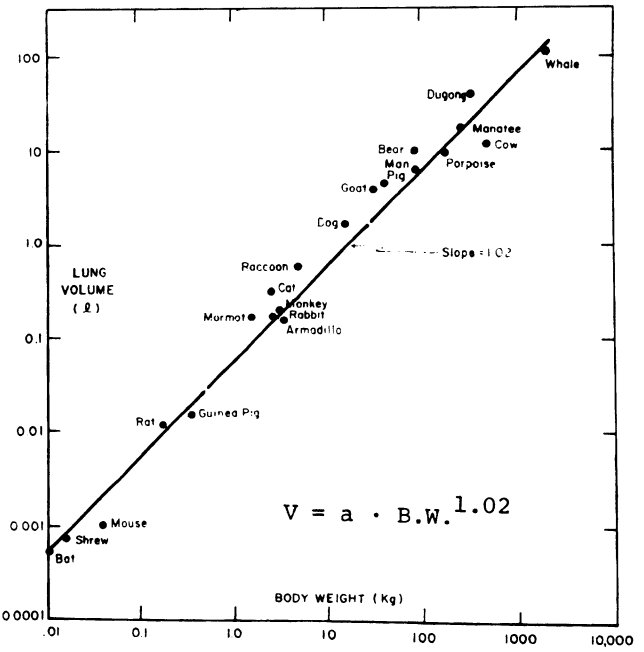

Fig.2. Variation of lung volume with body weight among mammals. From Tenney and Remmers (16).

These examples - that is, the dependence of lung weight and lung volume on body weight, on the one hand, and of alveolar surface area on the three-quarters power of body weight, on the other, exemplify a grand generalization: in the respiratory system (and in others) things having to do with size go as the first power of body weight, while things having to do with function (in this case gas exchange), go as the three-quarters power of the body weight, i.e., with metabolism. There are things which have to do with neither, as we shall see.

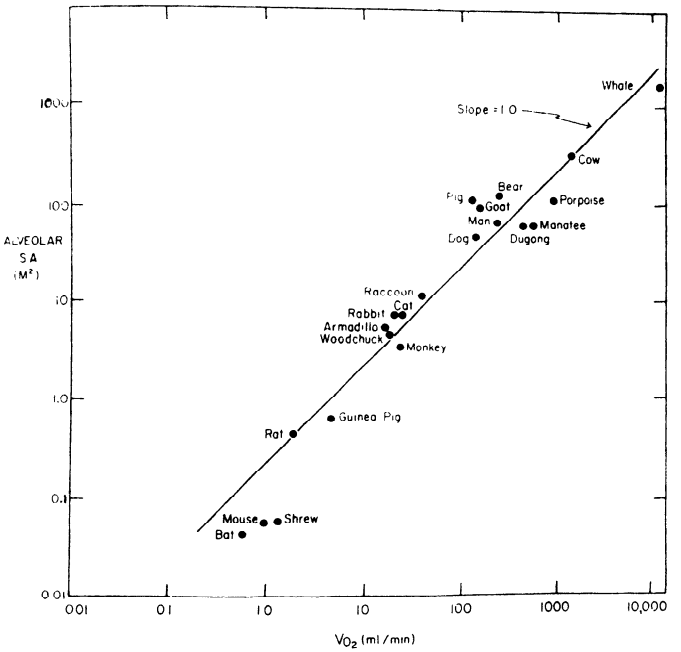

Fig.3. Variation of alveolar surface area with oxygen consumption among mammals. From Tenney and Remmers (16).

From the survey by W. R. Stahl, I have pulled additional examples of that generalization, separating them into size-related and function-related groups (Table 1). I have starred two of Stahl's items: the FRC of big animals may be bigger than that of small animals, proportionately; and the chest wall may be less compliant, i.e. stiffer, in larger animals. I'll return to both points later.

TABLE 1

Variable = a . Body Weight^b

Variable	b
Total lung weight	0.99
Total lung capacity	1.06
Vital capacity	1.03
Functional residual capacity	1.13*
Tidal volume	1.04
Deadspace	0.96
Lung compliance	1.08
Chest wall compliance	0.86*
Work per breath	1.08
Minute volume	0.80
Oxygen uptake	0.76
Total airway resistance	-0.70
Power of breathing	0.78

Stahl, J. Appl. Physiol., 1967

Stahl is explicit about the variability of the values he was able to pull from the literature. But variations of ± 50% and even more were not a big issue, considering the big ranges of body weight he covered. Such departures from normal mammalian design specifications can be of two kinds: the first I'll call noise - due to variations in method or materials, either in the animal of interest or in those used to establish the normal; and the second, signal - due to real differences among species, attributable to adaptation or specialization. Departures from mean values, by their nature, tend to be anecdotal in the sense that they apply to single studies or single species. In many cases it is difficult or impossible to tell whether departures of ± 50% are signal or noise. But because I find them interesting and fruitful topics, I will devote part of this discussion to such departures, with examples representing both signals and noise.

First, however, let's return for a moment to Tenney and Remmers' paper in 1963. They suggested that a relative increase in surface area, without a corresponding change in lung volume, ought to be associated with a more highly compartmented lung. That is to say, animals with high oxygen consumptions in relation to their body weight should have alveoli with small diameters. Such a tendency is confirmed in Figure 4, taken from that paper. Alveolar diameters range from over a millimeter, in the dugong and manatee, down to 30 or 40 microns in bats and shrews. Their whale's alveoli were only 150-200 microns, about the same as a man, and $\dot{V}o_2$/kg the same; but this was a very small whale, for the lung volume is given as only 100 liters. Other authors report values up to 1 millimeter, for alveolar diameter in the great whales.

The surface tension at the gas-liquid interface in the lung accounts for a significant part of the lung's tendency to collapse; that is its recoil forces, usually expressed in terms of the pressure difference across the lung under static conditions. Since the pressure difference across a curved surface in tension varies inversely with the radius of curvature, one might expect that surface forces would tend to cause airspaces to pop shut at some critical diameter as the lung was allowed to decrease in volume. Indeed this appears to happen; and the closure and reopening, or recruitment, of lung units at low lung volumes is an important though not well-understood part of lung behavior.

But the tendency for closure is minimized by the remarkable behavior of the surface-active material which appears to cover the gas-liquid interface. The surface tension of this lipid-rich surfactant, measured on a surface balance, increases to about 40 or 50 dynes per cm as the surface it covers is being stretched, and it decreases to nearly zero while the surface is being compressed. For comparison, the surface tension of water is about 72 dynes/cm and that of wetting agents like detergents and ethanol is about 20-30 dynes/cm. Measurement of surface tension values in the lung is not secure, because of uncertainty about alveolar shape and size changes during lung volume change.

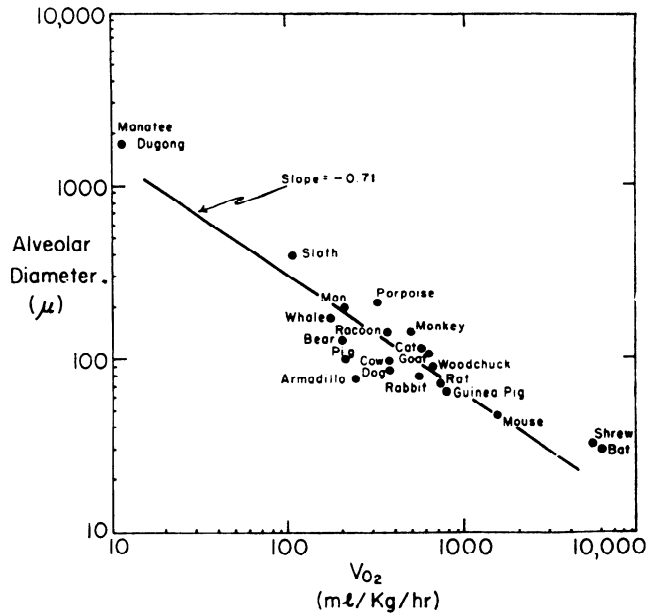

Fig.4. Variation of alveolar diameter with metabolic rate among mammals. From Tenney and Remmers (16).

Clements and his colleagues (5) have shown that the quantities of most of the lipid fractions extracted from lungs vary with lung weight and therefore probably serve functions in the cells; but the quantity of one, dipalmitoyl phosphatidycholine, varies with lung surface area and is more than sufficient for a monomolecular layer to cover that area (Figure 5). So it looks as if this is the surfactant, that it is present even in amphibia, and that it is present in similar quantities relative to lung surface area, in animals over a wide range of size.

Up to this point we have reviewed issues which are properly considered gross and microscopic anatomy and biochemistry. Now we are ready to ask some questions about static and dynamic behavior of the mammalian respiratory system. These properties come under the heading of respiratory mechanics, that narrow branch of respiratory physiology which deals with shapes, displacements, and forces in breathing, that is, the elastic, flow-resistive, and inertial properties of the respiratory system, and the pressures applied to it(13).

From a mechanical point of view, the design of mammalian respiratory systems appears to be subject to two major sets of constraints.

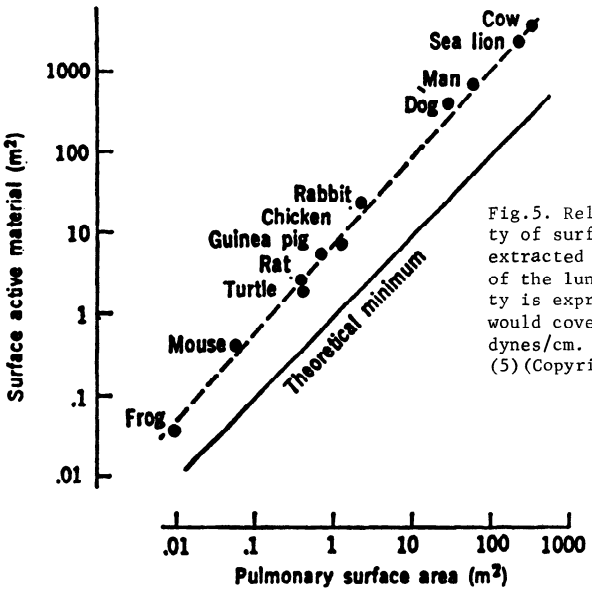

Fig.5. Relation of the quantity of surface active material extracted to the alveolar area of the lung. Surfactant quantity is expressed as the area it would cover at a tension of 12 dynes/cm. From Clements et al. (5) (Copyright 1970 AAAS.)

First is the need to satisfy the function of gas exchange. This requires provision for diffusion between gas and blood; we've discussed the considerations of surface area. It also requires mechanisms for appropriate matching of the distributions of ventilation and perfusion within the lung. Finally, it requires provision for adequate lung ventilation, for all the diffusing capacity in the world is useless unless the gas in the lung can be exchanged with the environment. What are the limits of lung ventilation, and by what mechanisms are they set? Can they be usefully measured in animals, and do they vary, as one might guess with metabolic rate?

The second major set of constraints on mechanical design of the respiratory system arises from the need to satisfy other physiological, environmental, and behavioral demands. For example, do osmotic or gravitational forces set limits? In lungs with small airspaces, is the tendency to closure by surface forces more marked? Is reopening more difficult? Are there related adaptations? Do diving or flying animals have special needs? How are they integrated with the influences of size and metabolic rate?

Let's start with human design, since it is most familiar to many. Figure 6 presents static volume-pressure curves for the lung and relaxed chest wall of a normal young upright human; a Rahn diagram. On such plots, the pressures are transmural pressures, and by convention a positive sign denotes a pressure difference between inside and outside which tends to inflate the structure in question.

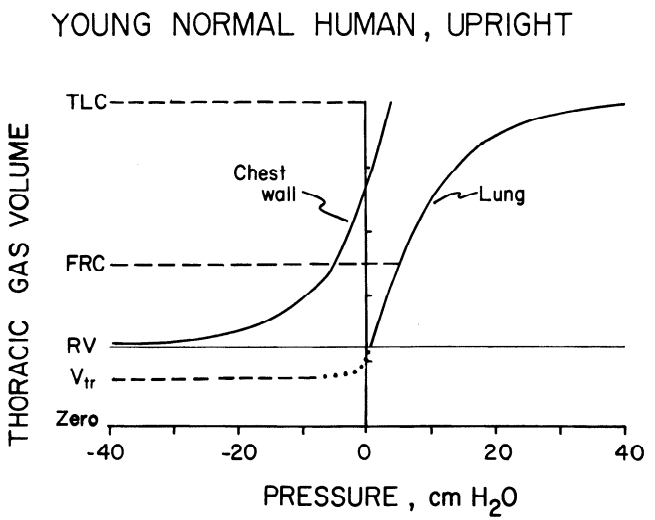

Fig.6. Diagram of quasistatic volume-pressure curves of lung and chest wall in human. For explanation, see text.

Over most of its volume range, the lung is recoiling inward - that is, trying to empty itself; it can be held at any given volume only by the application of a positive, or inflating, pressure equal and opposite to its recoil pressure. Allowed to collapse freely, that is when transpulmonary pressure (P_L) is zero, it empties to minimal air volume (MAV), and if a negative transpulmonary pressure is applied, a little more gas can be withdrawn. But then all the airways are closed, trapping a volume of gas (V_{tr}) which is perhaps 10%-15% of the total lung capacity (TLC).

The volume at which young normal human lungs have all their airways closed is less than the voluntary maximum expiratory position - i.e., V_{tr} is less than residual volume (RV) - so that at RV, most of the lung is still open.

Note that the lung becomes stiff near TLC, and the chest wall near RV. In fact, during voluntary excursions to the volume extremes, those two structures may be thought of as using up the available muscle forces at TLC and RV, respectively, and in that sense, determining the voluntary volume extremes.

In relaxed individuals with the airway open, the respiratory system seeks a static equilibrium volume at which the tendency of the lung to collapse is just balanced by an equal and opposite tendency for the chest wall to spring outward. This is referred to as the functional residual capacity, FRC. You can see, then, that if allowed to do so, the chest

wall by itself would passively spring out to a higher volume; but then further increases in volume would require an inflating pressure to be applied to the chest wall.

Let's examine the volume extremes in more detail, and compare them with the situation in other mammals.

Voluntarily inspiring to TLC, man normally applies transpulmonary pressure (P_L) of about 30-40 cmH_2O to his lungs; this may range from 25 to 50 cmH_2O depending on age, strength, and other factors. In order to measure P_L, the pressure difference across the lung, we must measure not only pressure at the airway opening, Pao, but also the pressure at the lung surface, or pleural pressure (P_{pl}). Pressure varies from place to place within the pleural space because of the effects of gravity and the different shapes of lung and chest wall, but for some purposes, to a useful approximation, pleural pressure can be treated as having a single value estimated by measuring the pressure within a thinwalled balloon in the thoracic esophagus.

Now when is the last time your dog ever inspired to TLC? Never, is the answer, because it is an unphysiological maneuver. Then how shall we define TLC, or full inflation of the lungs, in relaxed animals passively driven to high volumes during an experiment? Fortunately, this question has not caused much anguish among most investigators, who customarily select some arbitrary maximum transpulmonary pressure, usually about 25-30 cmH_2O, sometimes more or less.

It has been argued that the flatness of the deflation volume-pressure (VP) curve near TLC means that only small differences in maximum volume will result, no matter what peak inflation pressure is chosen. I think that's not quite true, as the diagram shown in Figure 7 suggests, for the deflation curves originate from different points much influenced by the shape of the inflation VP curve (which is quite variable depending on the starting conditions) and do not immediately become congruent. Here I have started deflation VP curves from peak inflation pressures of 20, 30 and 40 cmH_2O, assuming the same inflation curve in each case. Extrapolating the deflation curves to some maximum volume asymptote, for example by fitting exponential curves, would not bring one to the same maximum volumes.

Nevertheless, Stahl can give us a value of about 54 ml/kg body weight for TLC, varying only slightly with body weight. Let me cite two departures from this "normal" value.

Sea otters (Figure 8) are sort of like those 8-door airport limousines; they look as if they'd been sawed in half and welded back together with an extra section in the middle. They float high, but that is partly because they have a lot of air trapped in their fur for insulation; they lack the thick fat layer of many other marine mammals.

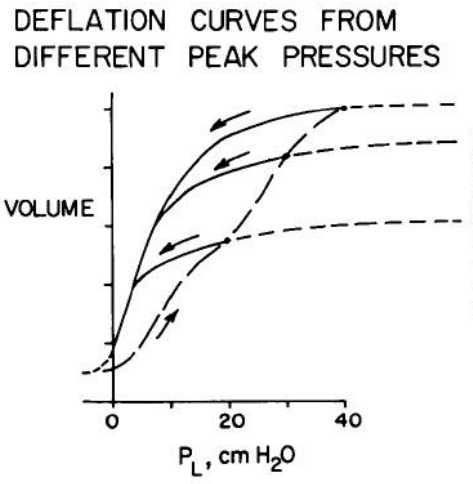

Fig.7. Relationship of maximum lung volume and quasistatic deflation VP curves to peak inflation pressures of 20,30, and 40 cmH_2O. Dashed line represents inflation VP curve. Dotted lines represent extrapolation of deflation curves to maximum volume asymptotes.

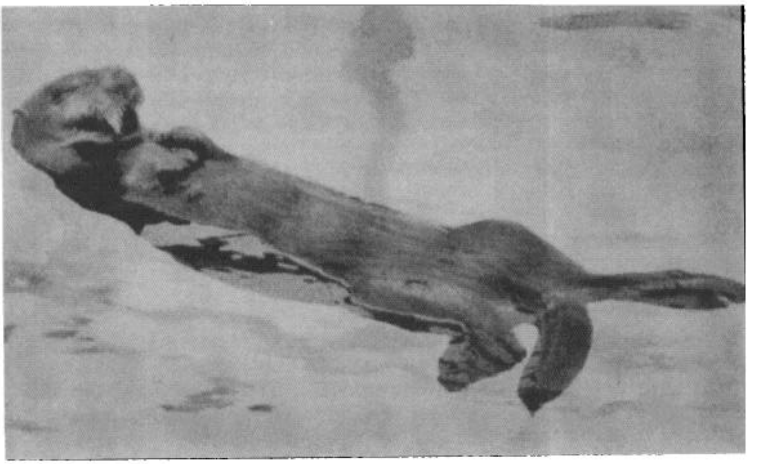

Fig.8. Sea otter at ease.

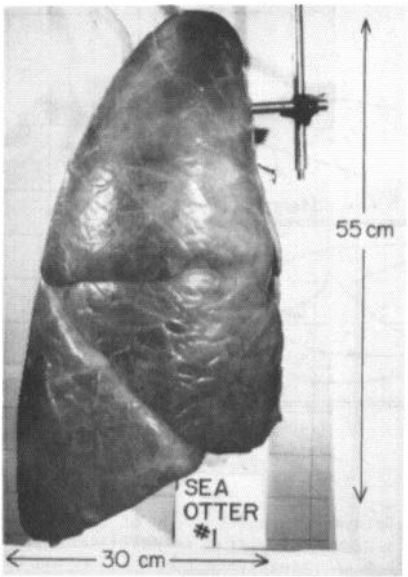

Fig.9. Freshly excised lungs of sea otter #1, inflated to a pressure of 30 cmH_2O.

Figure 9 gives body weight and lung volumes for 3 sea otters, made on board the R/V Alpha Helix. You have to choose some upper limit for P_L, to define TLC, so I used 30 cmH_2O here. An 80-lb sea otter has a TLC twice that of an adult man. That is, their TLC's are 5 to 8 times the predicted values! You may imagine that Dr. Joseph Brain and I looked for calibration errors when we made these measurements; fortunately we photographed all three sets of excised lungs, and still have one set, air-dried in the inflated state (Figure 9). Both confirm the volume measured in the field. This nearly incredible departure is an extreme, in my experience. It must be signal, not noise. What can we make of it? The sea otter has a high metabolic rate; he is also a breath-hold diver in frigid waters. Presumably he would like to take advantage of oxygen stores in the lung during diving, and because he is a shallow diver, uptake of nitrogen from the lung is not a threat. That is, he is not likely to suffer from decompression sickness even if he continues to exchange gas between blood and large stores of O_2 and N_2 in the lung.

Let's consider some other unusual mammals: bats. Figure 10 is a diagram of a pressure plethysmograph suitable for use with small mammals. In such animals, esophageal pressure must be measured with small water-filled catheters instead of the air-filled balloon-catheters used in larger mammals. Their static and dynamic accuracy, while documented by several investigators in animals down to the size of hamsters, may still be regarded as uncertain. I believe artefacts occur when tracheal pressure is less than pleural pressure.

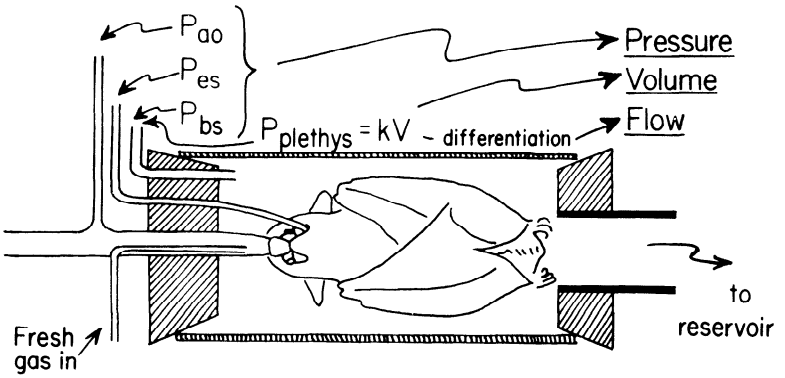

Fig.10. Arrangement of pressure plethysmograph for study of respiratory mechanics in small mammals. It is connected with a larger reservoir stuffed with copper sponge so that plethysmographic compression and expansion is nearly isothermal. Pao, Pes, Pbs, and $P_{plethys}$ are respectively, pressure at airway opening, thoracic esophagus, body surface, and plethysmograph.

Using these methods, I sought to make quasistatic volume-pressure curves of the lung in some bats. In an 82 gram fruit bat, inflation pressures of 30 cmH_2O resulted in curves like those in Figure 11. The vital capacity (VC) of 3 ml compares with a predicted value of 4.3 ml; not too bad. Then the anesthetized animal took a breath (Figure 12). Here the VC was 4.2 ml. The 3 ml value measured above was, at best, about 70% of the "truth." I pursued the question up to a transpulmonary pressure of 60 cmH_2O without any clear indication of a limit (Figure 13). The VC then was 6.6 ml, more than 150% of the value predicted by Stahl's equations. One can speculate that normal mammalian surface tensions are associated with high recoil pressures in small alveoli, and that "full inflation" of the lungs requires high transpulmonary pressures. What is the "true" maximum pressure and volume? Given this kind of uncertainty, what good are Stahl's regression equations?

What criteria, then, can one suggest for full inflation, or TLC, in experimental animals? Nothing very satisfactory, I'm afraid.

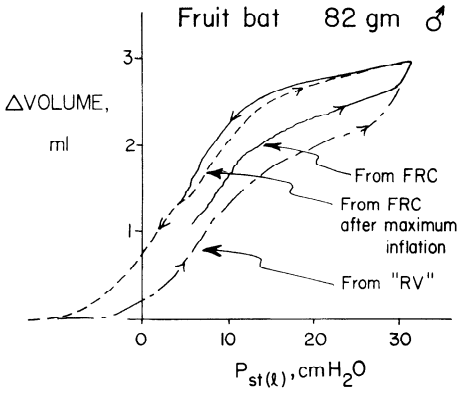

Fig.11. VP curves of lung during passive maneuvers. Static transpulmonary pressure, Pst(L), is the difference between Pao and Pes during very slow volume change.

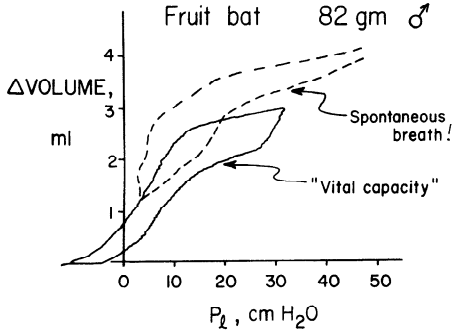

Fig.12. VP curves during rapid voluntary maneuver (dashed line). Note peak transpulmonary pressure and volume greater than those applied in passive maneuvers.

First, it seems reasonable that it should be at least as great as the biggest spontaneous breath. It should not be enough to cause lung disruption. The inflation limb of the VP curve should be flattening off, according to current thinking, but that can be misleading because many species show a double-humped inflation curve, like those shown in Figure 14 for a mouse. Only the topmost line here represents a deflation volume-pressure curve for the lung. It is always the same, starting from the same peak inflation pressure. All the rest of the curves are during inflation, and their differences reflect different initial conditions.

You can see that inflating the lung is generally more difficult, (that is, requires higher pressures at any given volume) the lower the starting volume. The solid lines were made during air-breathing; the dashed lines during oxygen breathing, which allows one to start from volumes below RV, even from the gas-free state, by occluding the airway while gas is taken up from the lung by the circulation.

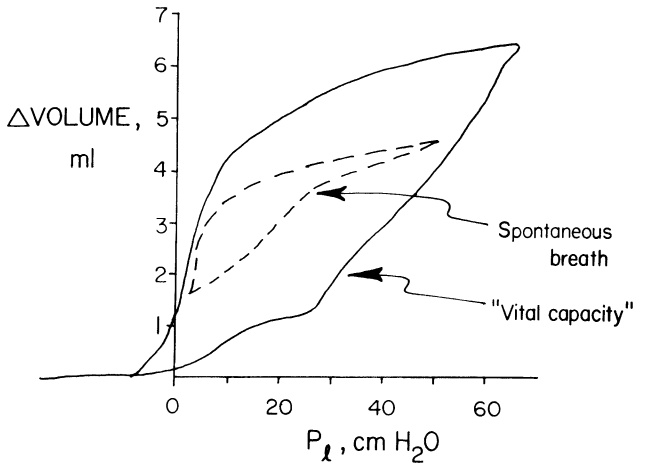

Fig.13. When slow passive maneuvers are extended to higher pressures, greater volumes are achieved. What is the "true" maximum lung volume of this animal?

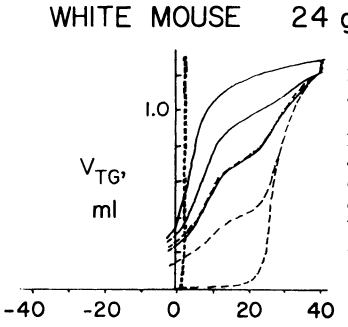

Fig.14. Quasistatic VP curves of lung in anesthetized white mouse breathing air (solid lines) or oxygen (dashed lines). Deflation from peak pressure of 40 cmH_2O always follows top line, but many different inflation curves are seen depending on the "volume history" of the lung. Lowest line is inflation from gas-free state in vivo.

If we had simply accepted downward concavity of the inflation VP curves as an index of full inflation, we might have stopped at a pressure of 20 cmH_2O, or so. The "full inflation" volume so determined would have had many values. Such double curves are seen in animals at least up to the size of dogs; the "knee", or upturn in the curve at higher pressures, may involve recruitment of lung units, changes in surface tension, and complicated changes in geometry of airspace walls (3, 6, 17).

These curves demonstrate another behavior which might lead to a criterion for full inflation of the lung, though you will note that "full inflation" remains undefined. If, at some volume or distending pressure, all the inflation VP curves have converged, relatively independent of the prior volume history, then we might be able to say that all of the lung's units, or surface, had been recruited and full inflation was achieved. That convergence occurs, in this mouse, when P_L is 35-40 cmH_2O.

Note also, on these curves, that the initial pressure required to open the gas-free lung is over 20 cmH_2O. In other mammals it is lower, and in the great whales it is only about 5 cmH_2O. This difference is at least partly attributable to the smaller size of the airspaces in the mouse, being opened in the presence of similar surface tension.

Let's consider residual volume (RV) next. To reach RV in normal young humans, muscle forces or pressure equivalent to about -40 cmH_2O must be applied to the respiratory system, balanced mostly by the chest wall which is quite stiff at this volume (Figure 6).

At RV in humans, as at most lung volumes, the lung may be thought of as sagging within the chest because of its own weight. So it is not uniformly inflated, and dependent regions are less distended than upper regions. In fact, the lowermost regions reach such low volumes that their airways close. If, at RV, one inhales a small bolus of a tracer gas, none of it goes to the closed regions. Appropriate subsequent measurements of expired tracer gas concentration can detect the effects of this non-uniformity, and indicate, during a slow expiration from TLC, the overall lung volume at which airways first start to close. Measurement of the so-called "closing volume" promises to become a clinically useful test of small airway behavior. It is under intensive study.

By lowering pressure at the airway opening, humans can be forced to volumes below RV. The sensation is very uncomfortable. Because the chest wall is so stiff, intrathoracic pressure must be very low to cause even modest volume decrements below RV.

When intrathoracic pressure reaches values of -80 to -100 cmH_2O with respect to atmospheric, circulatory problems apparently can occur. The left heart is loaded, blood shifts into the thorax, and the heart and pulmonary circulation are distended with blood. Pulmonary edema and perhaps cardiac arrhythmias can result. This set of events is referred to as "lung squeeze" or "thoracic squeeze" by divers.

Figure 15 shows VP curves of lung and chest wall in an anesthetized, apneic, upright horse, made during studies with Dr. Jerry Gillespie. Unlike the situation in man, the chest wall is much stiffer than the lung, at FRC.

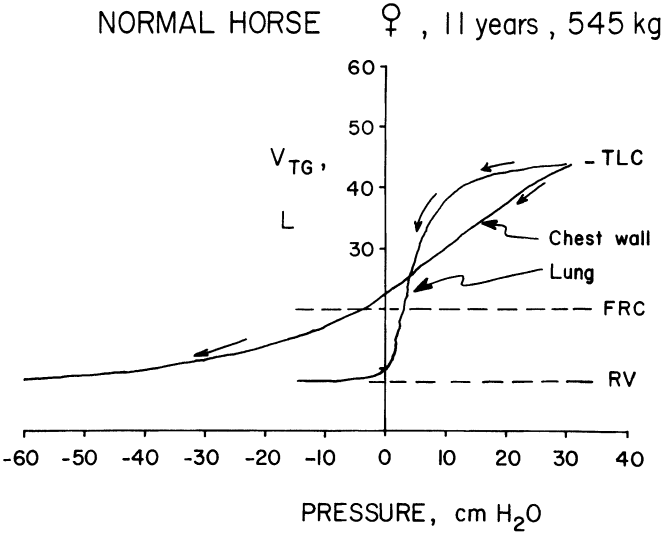

Fig.15. Quasistatic VP curves of lung and chest wall in a normal horse. At most volumes, slope of chest wall curve is much less than that of lung curve; that is, chest wall is much stiffer (less compliant) than lung. Very low intrathoracic pressures are necessary to reach low lung volumes (e.g. the volume at which P_L=0).

In order to force these animals to low volumes, intrathoracic pressure had to be lowered to -60 or even -80 cmH_2O. Most of our experimental animals tolerated this maneuver, but two died abruptly during this part of our study. In another similar study a sea lion died abruptly, with a massive hemothorax apparently due to a ruptured thoracic vena cava.

But some mammals need to go to extremely low thoracic gas volumes, not by expiration but by gas compression. Weddell seals dive to 1600 feet, toothed whales to twice that depth. At a pressure of 50 to 100 atmospheres absolute, the gas in their lungs occupies one 50th to one 100th of its original volume, even neglecting gas exchange. How do they avoid circulatory catastrophe?

Though there are several other logical possibilities, the answer I accept was suggested years ago by Scholander (12): a flexible chest wall allows the thoracic gas volume to diminish without setting up intolerable pressure differences. In fact, some seals' chest walls are not only very

compliant, but they also actually appear to recoil inward at all lung volumes, as shown in Figure 16. That is to say, in the relaxed anesthetized animal, not immersed in water, pleural pressure is positive over the whole vital capacity volume range.

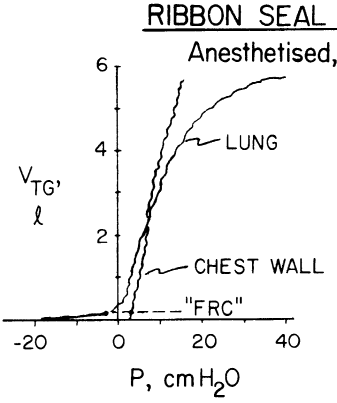

Fig.16. VP curves of a phocid seal. Note that lung can be deflated (via the airway) to an essentially gas-free state, and that relaxed chest wall is very compliant and recoils inward at all lung volumes.

These animals show another interesting difference from "normal" mammalian respiratory mechanics (Figure 16). The lung, when freely collapsed, is essentially gas-free. It looks like liver and sinks in water. Since both lung and relaxed chest wall recoil inward at all volumes, and since the lungs do not trap gas, the relaxed volume of this seal's respiratory system is close to zero, and there is little difference between what might be called FRC and the RV, MAV and V_{tr}. Probably the failure of these lungs to trap gas at low volumes is explainable on the basis of the cartilage rings which encircle and support their airways as far out as respiratory bronchioles. Scholander, observing these characteristics many years ago, suggested that deep-diving mammals avoid excessive nitrogen uptake during dives when the gas in their lungs is compressed into the conducting airways; gas exchange in the collapsed parenchyma then ceases (12).

The flexible chest wall of some deep-diving mammals therefore apparently is an adaptation to environmental stresses. But it appears to raise another problem. If seals relaxed between breaths, with an open airway, like terrestrial mammals, the FRC would be nearly at zero thoracic gas volume. Immense swings in arterial gas concentration would probably occur. But seals breathe differently. Even when ashore, they breathe with long inspiratory breath-holds, interrupted at intervals by brief rapid expiration and immediate inspiration of three-quarters of the VC or more. Thus there is an efficient behavioral solution for the problems resulting from the structural adaptation of the chest wall and lungs to deep diving. The glottis and nasal sphincters are a much less costly way to maintain high lung volumes than is inspiratory muscle activity. The usefulness of the term "FRC" in these animals is limited,

of course, so a more descriptive term like "end-expiratory volume" should be used.

Surely these highly specialized and adapted mammals are much different from most terrestrial mammals. Let us look, if we can, at mechanisms determining residual volume in more familiar mammals. Is it a stiff chest wall, as in man and horse, or is it finally the impossibility of getting any more air out of the lung, as in the seal?

As indicated in Figure 17, many published VP curves suggest that it is the latter. These are from a paper by Agostoni and coworkers (2). Each curve represents five animals. Though the authors were not explicit about it, it appears that the RV was considered to have been reached when no further change in volume could be accomplished. The airway pressures necessary to achieve this state were never more negative than about -10 cmH_2O. When no change in lung volume occurs in spite of big changes in airway pressure one can conclude that any air remaining in the lung is trapped behind closed airways. There is evidence that closure occurs in bronchioles about 1 mm in diameter.

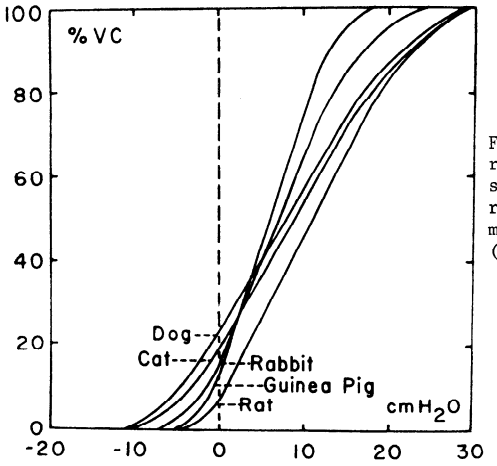

Fig.17. Mean VP curves of the respiratory systems of several species. Note the low expiratory reserve volumes, related to animal size. From Agostoni et al. (2).

Thus the mechanism determining residual volume in many familiar mammals including laboratory animals is qualitatively different from that operating in man. I'll give one practical example of the interpretive difficulty this can cause. Several groups of investigators have been attempting to measure closing volume in dogs. At first, all defined RV - the starting point for the inspiration of the tracer bolus - as the thoracic gas volume at a Pao of about -30 cmH_2O. But under those circumstances, the distribution of the gas in the lungs of these animals was probably nearly uniform, determined by airway closing mechanisms. Thus the initial gravity-determined non-uniformities in volume and closure which occur in man at RV and which are necessary in the measurement of the CV were not present, and satisfactory

measurement of CV was not possible. In one recently published paper, the authors neatly got around the difficulty by starting the maneuver at Pao of only -5 cmH_2O.

Last in our consideration of static lung volumes is the functional residual capacity (FRC). We've already observed that in man and horse, this resting position of the respiratory system is determined by a static balance of forces, the lung tending to collapse and the chest wall to spring out (Figure 6). We've seen that this passive mechanism is replaced by an active, behavioral one in seals. Let's consider one more mammal.

Figure 18 shows quasistatic VP curves of lung and chest wall in an anesthetized white mouse, made with the methods described above.

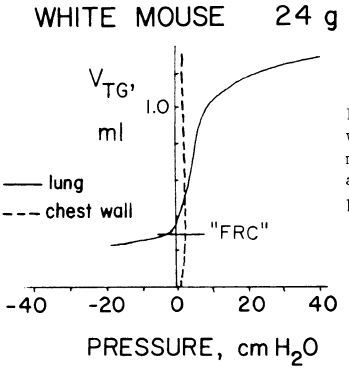

Fig.18. Rahn diagram for lungs and chest wall of anesthetized laboratory white mouse. P_L and Pcw are equal and opposite at FRC but P_L is negative and Pcw is positive. ERV is about 4% of the VC.

Like the seal, this mouse's chest wall is almost infinitely compliant, and again like the seal's, it recoils inward over most of the range of lung volumes. You may challenge the value of the esophageal pressure measurement, but the measurement of volume is secure. Here we see that the volume of air which can be withdrawn by applying a negative pressure to the airway opening was small. In a group of 30 white mice, the expiratory reserve volume (ERV) averaged 4% of the vital capacity, and in many mice was essentially zero. What does this mean?

When the FRC, RV, and V_{tr} are all the same (equal to about 17% TLC, in these mice) we can say that FRC is probably determined by airway closure. Several authors have confirmed the finding of Cavagna et al (4) that negative transpulmonary pressures of about 2 cmH_2O were necessary to cause airway closure. If mouse lungs behave in that fashion, we may infer that pleural pressure in relaxed anesthetized mice must be positive by about 2 cmH_2O at FRC, which is just what we observed. Thus this relaxation volume in anesthetized white mice appears to be a static balance of forces between lung and chest wall, but the situation is reversed from man and most other mammals: the chest wall is resting on the lung, which resists further collapse, because its airways are

closed. Do any other animals do this? Anesthetized hamsters appear to behave the same way (9). Bats, however, do not, and awake guinea pigs apparently don't.

Two interesting consequences flow from this mechanical arrangement. First is that these animals tolerate repeated in-vivo gas-freeing of the lungs by occlusion of the airway after nitrogen washout with 100% O_2, a laboratory analog to a deep breath-hold dive, mechanically. Absolute volume of the thoracic gas can be measured this way, and so can inflation VP curves of the lung from volumes below RV, including the gas-free state.

A second consequence of the low FRC, in conjunction with the relatively high metabolic rate, is that the breath-holding time of the air breathing animal is very short. One can easily calculate that lung stores of oxygen are used up in about 5 or 6 seconds; this is obvious and probably well-known, but Ms. Lynda White and I "discovered" it for ourselves during the 20-second quasistatic maneuvers we were using to make VP curves in mice.

Do unanesthetized mice breathe at such low volumes? We don't know yet; but the observation of the floppy chest wall in the relaxed anesthetized animal has pointed to the possibility that other mechanisms normally operate to maintain higher lung volumes, for example reflexly controlled inspiratory muscle activity.

We now turn to the only topic I will discuss which deals with dynamics of the respiratory system. The lung's capacity to exchange gas depends, as I said before, not only on diffusion but also on bulk flow. So we expect the capacity for ventilation to match an animal's metabolic demands. At first it looks very difficult to get any idea about the upper limits to ventilation, if one supposes that they are set by ventilatory muscle capacities or by the ventilation required during the heaviest exercise.

Fortunately we can bypass those difficulties, at least for a first approximation of the upper limits to lung ventilation. This is because there are well-defined limits to the expiratory flow rates achievable during forced emptying of the lungs. A flow-limiting mechanism involving compression of intrathoracic airways operates in the lung, in a way analogous with a Starling resistor or the so-called vascular waterfall. The result is that maximum expiratory flow rates are independent of expiratory effort; the maximum flows in effect are dependent instead upon the lung volume at which they are measured.

Therefore plotting instantaneous maximum expiratory flow against lung volume - a maximum expiratory flow-volume (MEFV) curve - outlines a domain within which all expiratory events must lie. Inspiratory flows may be plotted on the same axes, though their limiting mechanisms are not comparable. Figure 19 diagrams a set of flow-volume curves for a normal young human. Curves are shown for two breathing cycles in addition to maximum values; resting breathing, and the 15" maximum voluntary ventilation. During heavy exercise, fit individuals may ventilate at about 50 to 75% of the MVV.

Note that peak expiratory flows here are about 10 L/sec, in an individual whose VC is about 5 liters. Since the VC is nearly a constant function of body weight, we can take size out of our MEFV curves by plotting volume in units of VC and flow as $\overline{VC}$/second; this person's peak expiratory flow is 2 VC/sec.

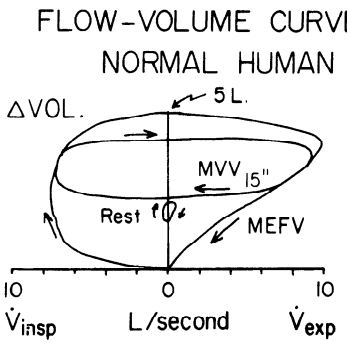

Fig.19. Flow-volume diagram with three sets of curves: maximum inspiratory and expiratory vital capacity maneuvers, resting breathing, and a single cycle during a maximum voluntary ventilation (MVV) maneuver.

How can we get experimental animals to do forced expiratory vital capacity maneuvers in order to measure MEFV curves? We can't. But lowering pressure in the airway is mechanically equivalent, for this purpose, to raising pressure at the lung surface. So with due cautions about the effects of the airway cannula and other problems, one can record MEFV curves by abruptly connecting the airway of an inflated lung (even in the excised state) with an evacuated reservoir, and measuring the resulting volume and flow events plethysmographically.

The method is applicable to mammals from bat to whale, at least. In the latter case the equipment assumes unusual proportions.

Robert Lowe, Jerry Gillespie and I studied excised lungs from medium-sized baleen whales, such as that shown in Figure 20 inflated at a pressure of 30 cmH_2O. Some readers may be interested to note the small amount of deformation resulting from the support of the lung's entire weight where it touches the ground. Perhaps that is why Dr. Hoppin is so pleased. His assistant is Mr. Michael Kosicki.

We used an integrated-flow plethysmograph, in which flow was measured by an array of linear resistors on the end of the box, and integrated to provide volume information. The evacuated reservoir for the forced expirations consisted of a bank of twenty-four 55-gallon drums, manifolded down to an 8-inch butterfly valve in the airway. Apparently ordinary MEFV curves resulted (Figure 21), with peak flows a bit over 2 VC/sec, the same range as man.

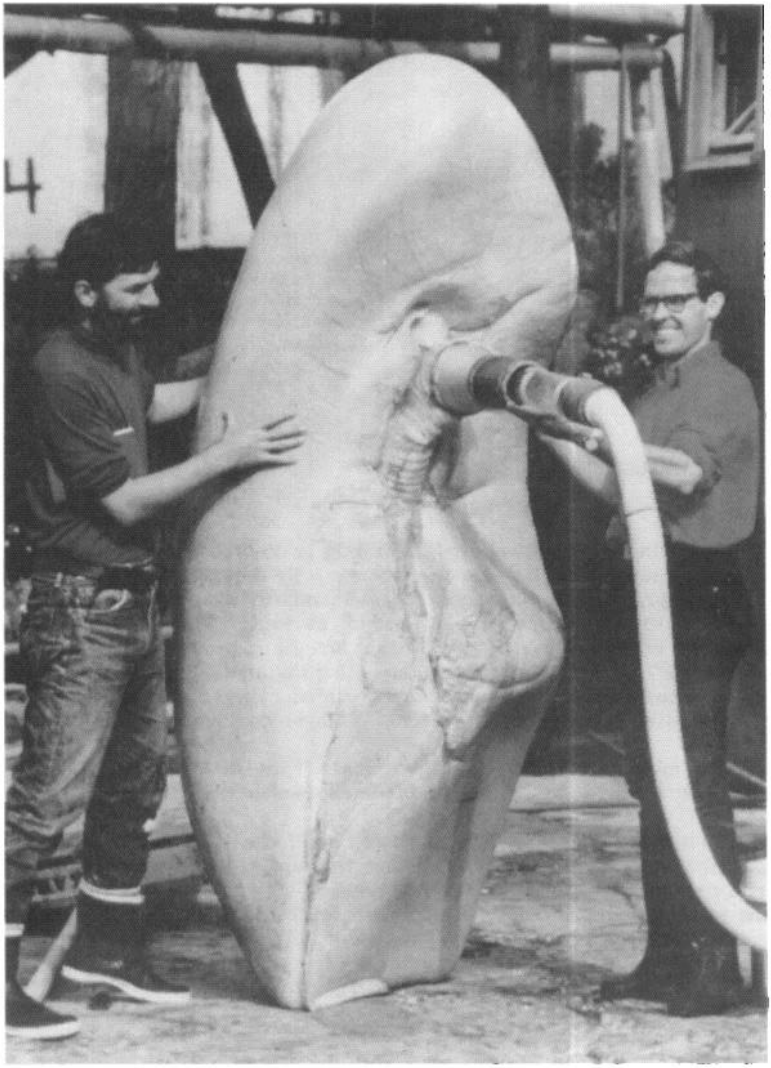

Fig.20. Lung from a sei whale, inflated at a pressure of 30 cmH_2O. Volume about 900 liters.

Other animals do better, as shown in Figure 22. You will appreciate that when a lung empties at 40 VC/sec., the event is over quickly; I am not certain that the little pressure plethysmograph used here was fast enough to do justice to the bat.

We see that humans and whales are near the low end of the scale of ventilatory capacity. But they are also near the lower end of the scale metabolically. So some index of ventilatory capacity, drawn from MEFV curves, might be more interesting if it were compared with metabolic demands. I've tried to do that in the following way.

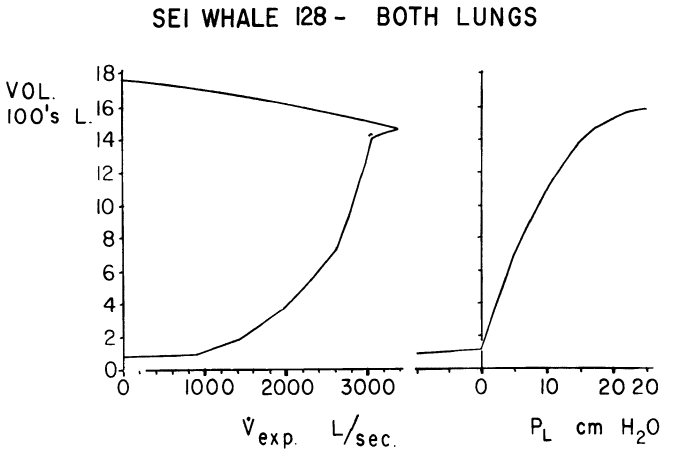

Fig.21. Quasistatic VP curve and maximum expiratory flow-volume (MEFV) curves for both lungs of a mid-sized sei whale. Peak flow is about 2 VC/sec.

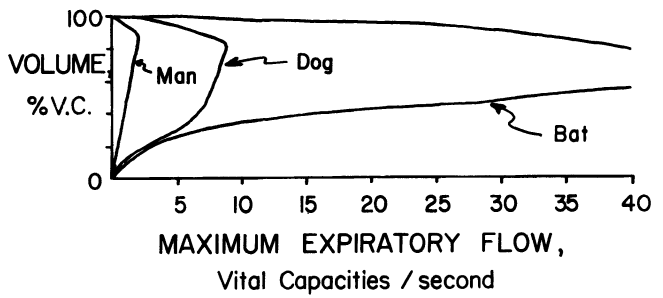

Fig.22. MEFV curves show big differences in upper limits to lung ventilation among species.

Like Tenney and Remmers, I would have liked data about maximum exercise $\dot{V}o_2$ in mammals. Something close may soon be available from remarkable work on animal locomotion being done by C. R. Taylor and others (15). But for now I used the resting oxygen consumption data from Tenney and Remmers.

If we assume, for the moment, that the ratio of maximal exercise to resting oxygen consumption is about 20: 1 for all mammals - the relationship which Hemmingsen (7) has called the "metabolic scope" - then we would expect a rough proportionality between resting $\dot{V}o_2$ and some index of the lungs' maximum capacity for ventilation.

Figure 23 shows a log-log plot of resting metabolic rate against peak expiratory flows, both expressed in units intended to take size out of the comparison. (The dashed line is not a regression line, but simply a reference line with a slope of 1.)

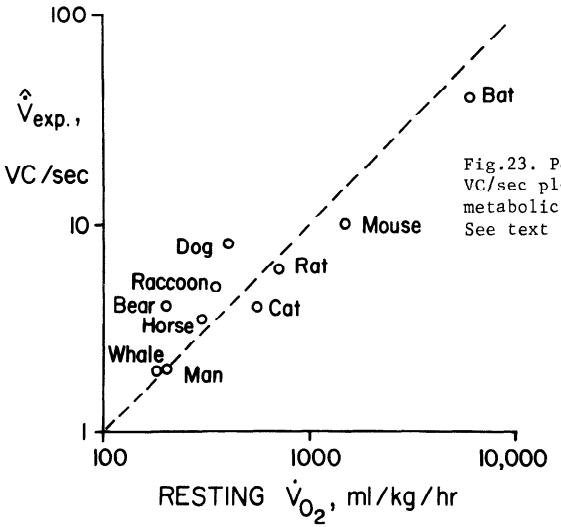

Fig.23. Peak expiratory flows in VC/sec plotted against resting metabolic rate for several mammals. See text for explanation.

If this index of lung turnover capacity (peak expiratory flow in VC/sec) varies directly with metabolic demand as expressed by resting $\dot{V}o_2$, a regression line should have a slope 1. If our assumption is false that all animals have similar metabolic scopes, then those with higher exercise capacities should lie above the regression line, and those with lower exercise capacities should lie below.

There aren't enough good data here to allow any confidence in a regression line. It may be that its slope will be less than one, which would make us guess that the smaller, more metabolically active animals have a somewhat lower metabolic scope than others; and it also appears that dogs would lie above such a line and cats below it, so that

their metabolic scopes may differ, though their sizes, and resting metabolic rates, are not very different.

Now let's try to extract some other generalizations, insights, and questions.

Implicit in much of the data we've seen is the fact that lungs which span 7 orders of magnitude in size all are operated over the same range of transpulmonary pressures. One can speculate that lungs designed to operate at lower transmural pressures would be subject to excessive deformation by gravity, the tendency increasing with the vertical height of the lung. But getting around that by lung redesign seems feasible, and Agostoni and his colleagues appear to have established, by careful work, that the total difference in pleural pressure from top to bottom is the same for large and small lungs (1). So the influence of gravity may not be a problem.

Operating lungs at much higher transpulmonary pressures would influence circulatory mechanics, including venous return and the afterloads of both right and left ventricles. Again, redesign should circumvent all the problems I can see, except one: the necessity for keeping the pleural space free of fluid, which depends upon osmotic forces, among other things.

Next, though we don't yet know whether any normal animals really do run very low FRC's with closed lung units, we wonder what kinds of behavioral mechanisms - e.g. reflexly controlled inspiratory muscle activity - may be used to adjust this volume. Or do some animals indeed shut down airspaces, as they shut down capillaries, only recruiting them at times of increased gas exchange need?

We wonder whether there is a tendency for the chest wall to be stiffer in large mammals, and if so, why? Is it related to a need to stabilize the FRC in the face of big gravity effects, for example in recumbency or during immersion? Let's summarize some of the points raised in this selective review of comparative mammalian mechanics.

1) Mechanical design of mammalian respiratory systems must meet constraints haveing to do with their gas exchange function and with other considerations such as osmotic forces and circulatory mechanics, gravity, and habitat and life style.

2) In general, size-related properties vary with body weight to the first power, while function-related properties vary with body weight to the 0.75 power.

3) Departures from "normal" mammalian design specifications represent either signal (that is, true departures due to adaptive specialization) or noise (that is, departures due to measurement errors, either in the species in question or in the studies used to establish the norm).

4) Definition of lung volumes and the mechanisms which set them are different in animals and man. Some of the differences are significant in experimental settings.

5) The maximum expiratory flow-limiting mechanism is a tool not yet widely applied in comparative physiology.

6) The need for, and the actual physiology of, the FRC in small and large mammals could stand closer examination.

7) It is not clear why lungs which range over 7 orders of magnitude in size are all designed to operate with similar pressures.

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STUDIES ON THE MECHANISM OF TUBULAR ACIDIFICATION[1]

by

GERHARD GIEBISCH[2] and GERHARD MALNIC[3]

The narrow range of the pH of body fluids underscores the importance of homeostatic control mechanisms acting on hydrogen ions. The pH of extracellular fluid is stabilized within a rather narrow range of 7.35 to 7.45 despite acid and alkaline challenges that originate from dietary intake and metabolic degradation of food. Besides extracellular and intracellular buffers which represent the first line of defense against acid-base challenges it is generally accepted that 1) the metabolic production of nonvolatile organic acids from an acid-ash diet, 2) the respiratory control of CO_2 tension, 3) the renal regulation of plasma bicarbonate levels and 4) the renal excretion of hydrogen ions in the form of titratable acid at a rate equivalent to that of endogenous acid production are key factors in the maintenance of a stable blood pH (Rector, 1973; Pitts, 1952/53; Malnic and Giebisch, 1972a; Malnic and Steinmetz, 1976; Rector, 1971). The crucial role of the bicarbonate-CO_2 system derives from the unique physiological properties of this buffer pair. First, the bicarbonate-CO_2 system operates as an "open" system since the CO_2 tension in the body fluids is regulated by ventilation and pulmonary gas exchange. Secondly, the maintenance of appropriate bicarbonate levels is achieved by adjustments of the rate of bicarbonate reabsorption by the renal tubules.

In the following, some recent work dealing with some kinetic aspects of tubular acidification will be discussed, in particular (with) the role of hydrogen ion secretion in tubular acidification, and the coupling of hydrogen ion secretion to the transport of sodium and chloride. Much of this work is based on the application of microperfusion methods to the study of acidification by single mammalian tubules.

By way of introduction we might briefly review some of the main features of the mechanism of tubular acidification (Rector, 1973; Pitts, 1952/53; Malnic and Giebisch, 1972a; Malnic and Steinmetz, 1976; Rector, 1971). Figure 1 depicts the "classical" view of the transport operation underlying bicarbonate reabsorption. Cellular hydrogen ions, generated by carbonic anhydrase-stimulated hydration of CO_2, are pumped by an active extrusion process across the luminal membrane, interact with filtered bicarbonate and form carbonic acid. The latter breaks down to H_2O and CO_2. Cellular bicarbonate ion derived from carbonic acid, leaves the cell with sodium and is thus retrieved from the filtrate. This process is central to the maintenance of a constant

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[1]Taken from the introductory remarks given at the session on Renal Electrolyte Transport at the 1976 Federation Meetings. Supported by grants from NIH, NSF, American Heart Assoc., and Fundacao de Amparo a Pesquisa de Est. Sao Paulo, Brasil.

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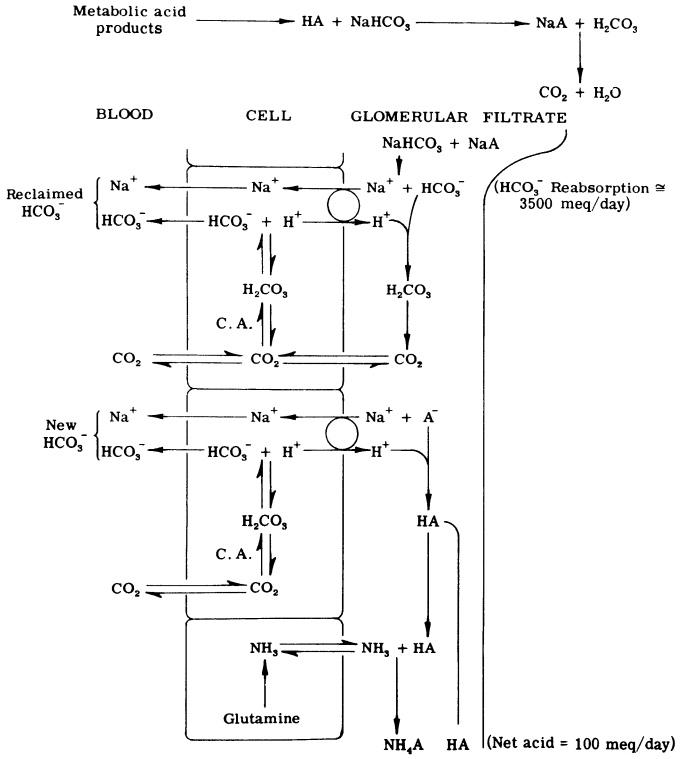

Fig.1. Cell model showing interaction of secreted hydrogen ions with different luminal buffers. Hydrogen ions, formed within tubule cells, are pumped across the luminal cell membrane and react with filtered bicarbonate. Such titration of bicarbonate generates carbonic acid which decomposes into $H_2O + CO_2$. In addition, hydrogen ions can also interact with such non-volatile buffers as phosphate (A^-) to form acid salts (HA), or with NH_3 to form ammonium. The latter two operations generate titratable acid. Note that net acid excretion amounts to only a small fraction of the amount of hydrogen ions consumed in the reabsorption of the filtered bicarbonate. (From ref. Rector, 1971).

plasma bicarbonate levels but does obviously not constitute a mechanism for net acid excretion. The luminal titration of bicarbonate ions is not, however, the sole operation involving hydrogen ion secretion. If, as shown in the middle and lower section of Figure 1, the buffer species is a non-volatile species such as phosphate, secretion of hydrogen ions leads to the formation of titratable acid. The latter is largely excreted into the urine. Similarly, conversion of NH_3 to NH_4 effects net excretion of hydrogen ions. Hence, in a way, volatile and non-volatile buffers

compete for hydrogen ions and as Rector has pointed out, the distribution of the secreted moiety of hydrogen ions depends critically on the decline of luminal pH along the nephron (Rector, 1973; Rector, 1971). As bicarbonate is reabsorbed along the nephron, a progressively larger fraction of hydrogen ions will interact with non-bicarbonate buffers to form titratable acid. Similarly, the amount of ammonia trapped in the urine as ammonium ions will increase. Clearly, as the bicarbonate concentration in the filtrate is reduced, the efficiency of restoring acid-base balance is augmented by a shift towards luminal titration of non-volatile buffers.

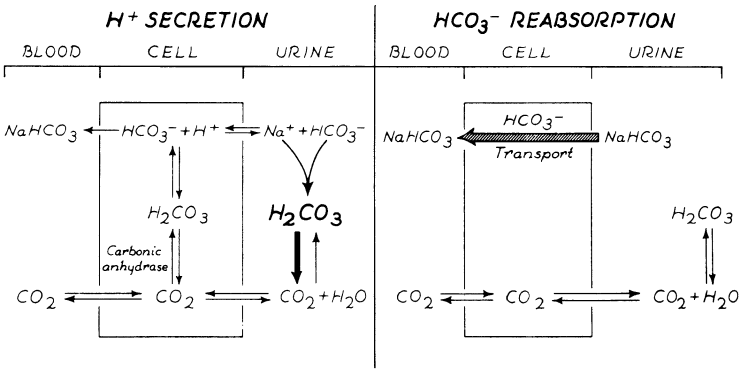

Fig.2. Cell models portraying the effects of hydrogen ion secretion versus bicarbonate reabsorption. (From ref. Rector, 1973).

It has been recognized for some time that tubular hydrogen ion secretion is not the sole possible mechanism of tubular acidification. Figure 2, also taken from Rector's work, illustrates that either hydrogen ion secretion, as shown before, or bicarbonate reabsorption in its ionic form, could account for tubular acidification. As stressed by Rector, the consequences of these two operations upon the "in-situ" pH after carbonic anhydrase inhibition will differ (Rector, 1973; Rector, 1971). With hydrogen ion secretion, an acid disequilibrium pH in the lumen might be present in vivo, that is, a pH lower than that observed after in vitro equilibration with the animal's pCO_2. This is due to the inherently low rate of uncatalyzed H_2CO_3 dehydration compared to the rate of hydrogen ion secretion necessary to achieve tubular bicarbonate reabsorption at the actually observed rates (Rector, 1973; Rector, 1971; Walser and Mudge, 1960). In contrast, an alkaline disequilibrium pH might result from bicarbonate reabsorption per se, particularly if titration of non-bicarbonate buffers were to consume H_2CO_3 at a rate exceeding that of its generation. Hence, a lower carbonic acid concentration may be present for the existing CO_2 level than expected at equilibrium. An alkaline "disequilibrium" pH would result.

The development of glass- and antimony microelectrodes has made it possible to measure the pH of tubular fluid in situ, and several groups of investigators have shown that after carbonic anhydrase inhibition, an acid disequilibrium pH obtains in proximal tubules (Rector, Carter and Seldin, 1965; Vieira and Malnic, 1968; Malnic, Mello Aires and Giebisch, 1972a). In the distal tubule, an acid disequilibrium pH obtains spontaneously, even in the absence of carbonic anhydrase inhibition. Hence, the finding of an acid disequilibrium pH in both proximal and distal tubule indicates that H-ion secretion participates in the process of bicarbonate reabsorption. In our view, it is highly unlikely that the following criticism of Brodsky and Schilb invalidates this conclusion (Brodsky and Schilb, 1974). These investigators argued that in a limited region like the tubular lumen an elevation of luminal pCO_2 may be due to a high cell pCO_2 and its subsequent equilibration with the luminal fluid. Making reasonable assumptions of cellular CO_2 permeability and CO_2 production, it can be calculated that the expected cell pCO_2 could, at best, exceed the venous or luminal pCO_2 only by a few mm Hg (Malnic and Giebisch, in preparation). These values are much too low to account for the observed magnitude of the proximal disequilibrium pH (ΔpH between 0.4 to 0.8 pH units).

However, the generally held view that luminal pCO_2 is always equal to that of the arterial blood may need revision. If CO_2 flow out of the tubule were to encounter a diffusion barrier, its luminal level could be higher during bicarbonate reabsorption than that in blood. This could also lead to an acid disequilibrium pH (Karlmark and Danielson, 1974). Hence, both an increased carbonic acid concentration or an elevated tubular pCO_2 level may account for acid disequilibrium. Sohtell and Karlmark have developed a micro pCO_2 electrode and reported that proximal tubular pCO_2 in rats in normal acid-base conditions may exceed arterial pCO_2 values by some 16 mm Hg (Sohtell and Karlmark, 1976). These observations confirm indirect calculations of tubular CO_2-permeability based on measurements of the time course of pH changes in initially CO_2-free bicarbonate droplets in proximal tubules (Malnic and Giebisch, in preparation; Malnic and Mello Aires, 1971). Such measurements have indicated proximal luminal pCO_2 levels in excess of that in arterial blood. The magnitude of such a transepithalial CO_2 gradient will depend on and be proportional to the rate of bicarbonate reabsorption. It is probably safe to suggest that by the time fluid has reached the middle of the proximal tubule, and bicarbonate concentrations have dropped to below some 10 mEq/L, the pCO_2 disequilibrium is quite small, and does not invalidate calculations of bicarbonate concentrations based on equilibration of luminal fluid samples with pCO_2 levels similar to that of the animal's arterial blood (Malnic and Giebisch, 1976; Malnic and Mello Aires, 1971).

While it is thus generally acknowledged that hydrogen ion secretion plays a key role in bicarbonate reabsorption and titratable acid formation, it is more difficult to assess the possible role of additional bicarbonate reabsorption "as such" (Maren, 1967; 1974).

This problem as well as some kinetic aspects of luminal buffer titration have been approached by stationary microperfusion of single

rat tubules with bicarbonate or phosphate buffers and following their pH changes with a carefully calibrated antimony electrode system (Malnic and Giebisch, 1972a; Malnic and Steinmetz, 1976; Malnic and Giebisch, 1976; Malnic and Mello Aires, 1971; Malnic, Mello Aires and Giebisch, 1972b; Malnic, Mello Aires and Giebisch, 1976). Figure 3 shows the experimental stationary perfusion method employed; two double-barrelled micropipettes are used. One, shown on the left, is used to isolate the test-buffer solution from the remainder of the tubular contents. A second one, shown on the right, serves to monitor luminal pH-changes with time. Not shown here but also possible is the simultaneous perfusion of both the lumen and peritubular fluid with perfusion fluids of known content. This permits one to assess the effects of peritubular changes in fluid composition on luminal acidification (Malnic and Giebisch, 1976; Mello Aires and Malnic, 1975). Figure 4 shows acidification rates of 100 mM bicarbonate (left) and alkaline phosphate buffers in control acid-base conditions and after diamox administration. The approach of luminal buffer to its steady state levels is plotted as a function of time. Values on the ordinate are the difference between the luminal HCO_3^- or H_2PO_4 concentrations and their respective steady state levels. One obtains from such plots 1) half-times of acidification, which can readily be converted into rate coefficients since the plot of log (buffer) with time is linear, and 2) steady-state pH levels. Net acidification rates can be calculated from the rate coefficient, the difference between initial luminal buffer concentration and its steady-state level, and tubular geometry (Malnic and Giebisch, 1972a; Malnic and Mello Aires, 1971; Malnic, Mello Aires and Giebisch, 1972b).

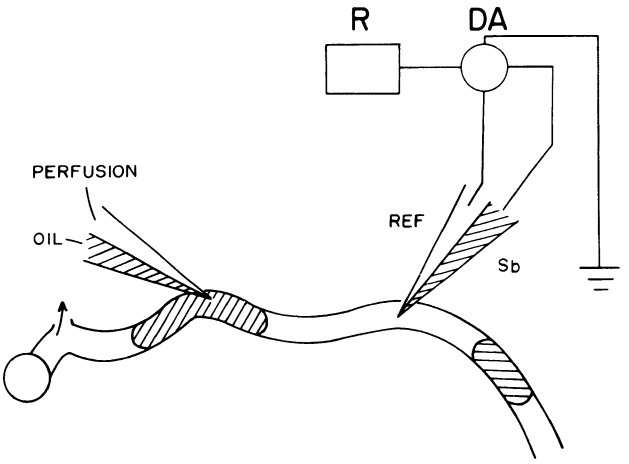

Fig.3. Stopped-flow microperfusion method for kinetic evaluation of tubular acidification using double-barrelled antimony(Sb)-reference electrode and double-barrelled (colored oil-perfusion fluid) perfusion pipette. DA: differential amplifier, R: recorder. (Modified from ref. Malnic and Giebisch, 1972a).

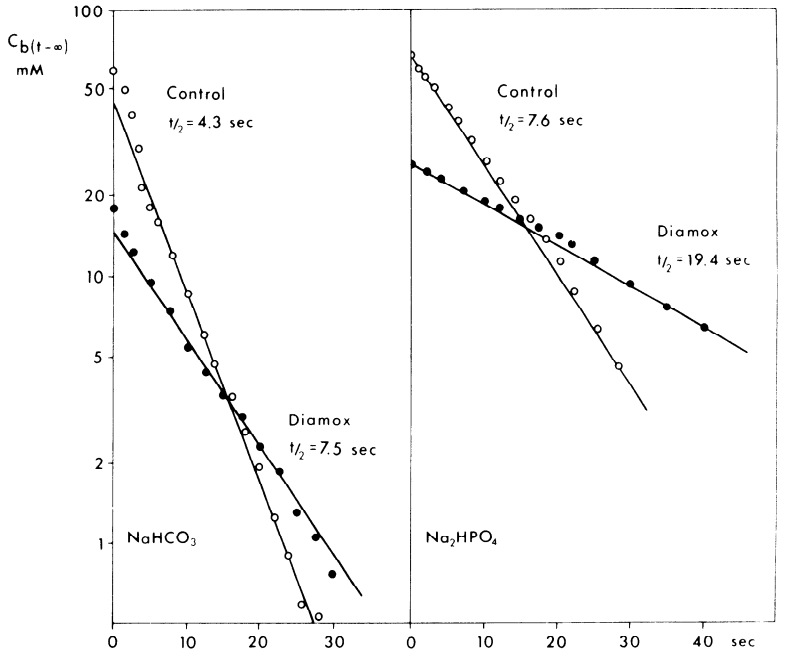

Fig.4. Approach of luminal buffer base (C_b) to its steady-state level (∞) in proximal tubule of control and acetazolamide-infused rats during perfusions with bicarbonate and alkaline phosphate solutions. Half-times of acidification are given for the different experimental conditions. (Modified from ref. Malnic and Mello Aires, 1971; Malnic, Mello Aires and Giebisch, 1972b).

Some aspects of this method of approach need validation. The semi-logarithmic plot of the approach of both luminal buffers to their respective steady-state pH values yields a single exponential. Since initially large transepithelial concentration gradients for bicarbonate and alkaline phosphate are present in a direction favoring diffusional loss from the lumen such passive buffer loss could mimic hydrogen ion secretion. However, it can be seen that the rate coefficient of acidification is similar over the whole luminal concentration range, particularly also over the lower concentration range of bicarbonate, for instance, when the transepithelial concentration gradient reverses at plasma concentrations of some 25 mEq/L (Malnic and Giebisch, 1972a; Malnic and Steinmetz, 1976; Malnic and Mello Aires, 1971; Malnic, Mello Aires and Giebisch, 1972b; Malnic, Mello Aires and Giebisch, 1976). Since the rate of acidification is not decreased below this concentration range, it is unlikely that passive bicarbonate reabsorption importantly contributes to the observed rate of acidification.

Some additional sources of errors have to be considered. Anion flux into the lumen such as that of either chloride or bicarbonate into initially chloride-free bicarbonate or bicarbonate-free phosphate droplets have to be considered. The fluid movement associated with such ion fluxes into the test-droplets could have unspecific effects by diluting luminal buffers and thereby change pH. In addition, bicarbonate entry into phosphate samples might provide an additional buffer source. Most of these potential sources of errors are small. Thus, perfusion of peritubular capillaries with cyclamate instead of chloride has only a small effect on luminal acidification. However, chloride influx into bicarbonate acidification does exert a finite effect on the apparent rate coefficient of acidification (Malnic and Giebisch, 1976; Malnic, Mello Aires and Giebisch, 1972b; Cassola, Giebisch and Malnic, 1976) for which corrections can be applied.[4] When bicarbonate is replaced by phosphate buffers in the peritubular fluid, no significant change in acidification was seen. Hence, transepithelial bicarbonate leakage into phosphate droplets does not significantly affect the observed rates of acidification. Finally, it is also unlikely that the reabsorptive loss of phosphate anions could affect the apparent acidification constants since it has been shown that the rate of loss of phosphate from the proximal lumen is much slower, by almost an order of magnitude, than that of acidification. Obviously, this potential source of error can be avoided altogether when acidification rates are expressed in terms of initial values at time zero when the total amount of phosphate is present in the lumen.

If we accept then the interpretation that these experiments provide a reasonable estimate of bicarbonate reabsorption and, in the case of phosphate perfusion, of tubular hydrogen ion secretion we may conclude that: 1) there is no evidence of saturation of either bicarbonate reabsorption or of hydrogen ion secretion up to luminal buffer concentrations as high as 100 mM. This conclusion is based on the observation that a single exponential obtains when the approach of either bicarbonate or acid phosphate concentrations from initial concentrations as high as 100 mM to their respective steady-state values is plotted semilogarithmically against time. Hence, other variables remaining unchanged, the luminal buffer load thus emerges as a major determinant of the tubular rate of buffer titration. As the buffer concentration rises buffer reabsorption and hydrogen ion secretion are proportionately stimulated.

This behavior could be due to a pump-leak system such that the back leak of either hydrogen or bicarbonate ions depends on the luminal H or buffer concentration. With increasing pH such passive fluxes would fall: net hydrogen and bicarbonate transport would then be expected to increase. An alternative mechanism would be a hydrogen pump in the luminal cell

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[4]The effects of buffer dilution by chloride influx upon luminal pH changes differ in bicarbonate and phosphate droplets. Dilution of phosphate buffers will not affect pH since the conjugate buffer pair is equally diluted as the total phosphate remains virtually constant over the time period of acidification ("closed" system). In contrast, bicarbonate is titrated at nearly constant H_2CO_3 level ("open" system). Hence, water influx, by diluting bicarbonate, mimics acidification.

membrane whose activity is sensitive to the electrochemical potential gradient against which it operates. It's activity would increase with a decline in the transmembrane H-ion difference. It is possible that in the proximal tubule, an inherently highly leaky nephron segment, the first mechanism is present while in the distal tubule the second mechanism is operative (Malnic and Giebisch, 1972a; Malnic and Steinmetz, 1976; Cassola, Giebisch and Malnic, 1976). Calculations based on relaxation curves of imposed transepithelial hydrogen ion gradients indicate that the hydrogen ion conductance of the proximal tubule is higher than that of the distal tubule (Cassola, Giebisch and Malnic, 1976). This would be consistent with the proposed site of the pump-leak model in the proximal, and the gradient-sensitive model in the distal tubular epithelium. However, it is clear that both types of operations could be present at a given nephron site.

The absence of a clearcut transport maximum of both bicarbonate and hydrogen ion transport in stationary microperfusion studies has found support in recent studies in which it was shown that the bicarbonate titration curve, relating plasma bicarbonate levels to tubular bicarbonate transport fails to plateau when care is taken to minimize extracellular volume expansion during the elevation of plasma bicarbonate levels (Kurtzman, 1970a; Purkerson, 1969). When the concentration of bicarbonate in plasma is raised without volume expansion, reabsorption rates of bicarbonate rise in a similar fashion to that observed in single nephron perfusion studies.

Similarly, the inherently unsaturated character of distal bicarbonate and hydrogen ion transport is reflected by the fact that with an increase in distal bicarbonate delivery bicarbonate reabsorption rises proportionately. Figure 5 represents a summary of free-flow micropuncture studies in a wide variety of acid-base conditions in which the distal bicarbonate load was assessed by measurements of inulin and bicarbonate concentrations and compared to the amount of bicarbonate reabsorbed along the distal tubule (Giebisch, 1974). Clearly, there is no transport maximum. With increased delivery of buffer, bicarbonate reabsorption rises, and with it, almost certainly also hydrogen ion secretion.

If we accept that the rate of acidification of phosphate represents hydrogen ion secretion, a comparison can be made with the rate of bicarbonate reabsorption in similar experimental conditions (Cassola, Giebisch and Malnic, 1976; Malnic and Steinmetz, 1976). The rate of total bicarbonate reabsorption can be assessed in microperfusion experiments using bicarbonate buffers as test buffer in the lumen. The rate of catalyzed hydrogen ion secretion can be derived from the difference between bicarbonate reabsorption in control and diamox-treated animals. Total hydrogen ion secretion, calculated as the sum of catalyzed and uncatalyzed hydrogen ion secretion, can also be obtained. The rate of uncatalyzed hydrogen ion secretion is calculated from acidification rates of initially alkaline phosphate droplets after diamox. The comparison of the total hydrogen ion secretion rate so calculated, with total bicarbonate reabsorption indicates that a sizeable fraction of proximal tubular bicarbonate reabsorption, some 46%, is not mediated by either catalyzed or uncatalyzed hydrogen ion secretion. With respect to the distal tubule,

a similar analysis shows that a larger fraction of bicarbonate reabsorption is mediated via carbonic anhydrase-catalyzed hydrogen ion secretion than in the proximal tubule. The fraction of bicarbonate reabsorption not accountable for by hydrogen ion secretion, amounts to only some 13% of total bicarbonate reabsorption.

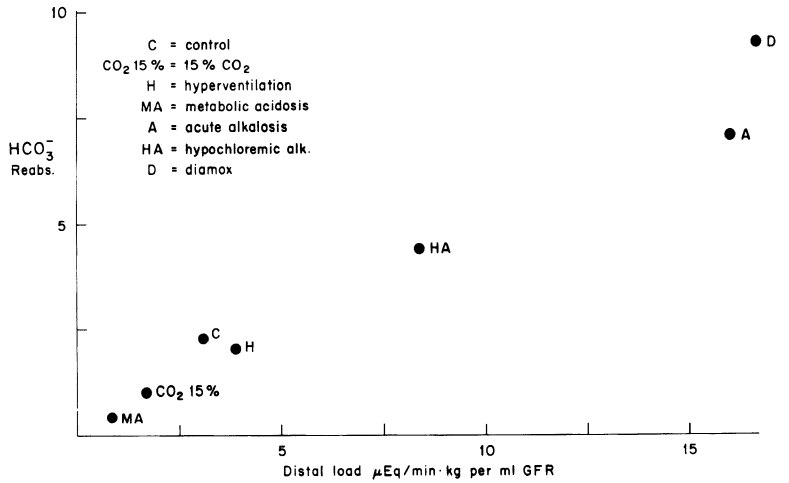

Fig.5. Summary of data depicting the relationship between distal tubular bicarbonate reabsorption and bicarbonate load entering the distal tubule in different acid-base conditions. (From ref. Giebisch, 1974).

As to the sizeable portion of bicarbonate transport that remains intact in the proximal tubule after diamox in control animals, two possibilities arise: first, this remainder could represent bicarbonate transport as such, a view held by Maren (1967;1974). Alternatively, Rector (1973, 1971) has proposed a schema shown in Figure 6. Here it is assumed that carbonic acid recirculation could sustain hydrogen ion secretion by non-ionic diffusion from lumen back into the cell, thereby supplying hydrogen ions independently of carbonic anhydrase. This mechanism clearly depends on the presence of a diffusible acid species in the lumen. We favor this view over bicarbonate transport as such for three reasons: First, a significant disequilibrium pH is maintained after diamox, evidence in favor of continued hydrogen ion secretion after carbonic anhydrase inhibition. Secondly, Ullrich and his associates have shown that glycodiazine reabsorption from the lumen, before and after diamox, closely resembles that of bicarbonate. If it is assumed that this buffer is mainly transferred out of the lumen in the form of its lipid-soluble non-ionized form, its rate of reabsorption closely mimics that of hydrogen ion secretion. The fact that glycodiazine transfer after diamox continues at a rate similar to that of bicarbonate, is compatible with continued hydrogen ion secretion. The latter persists due to recirculation of undissociated glycodiazine buffer acid. The fact that acidification of phosphate

buffer after diamox is more depressed than that of bicarbonate or glycodiazine is consistent with the notion that recirculation of undissociated acid plays a key role in acidification since the acid phosphate anion is less permeant than either carbonic acid or glycodiazine (Ullrich, Rumrich & Baumann, 1975). Finally, it appears from a study of the components of bicarbonate and phosphate acidification that in rats in metabolic acidosis hydrogen ion secretion can fully account for bicarbonate reabsorption. A relatively larger fraction of acidification remains intact after diamox treatment in phosphate perfused tubules. This finding of a reduced sensitivity of carbonic anhydrase inhibition in acidosis may be related to the lower cell pH in acidosis. In acidosis then there is no evidence supporting bicarbonate reabsorption as such. Further studies in other acid-base disturbances would be of interest.

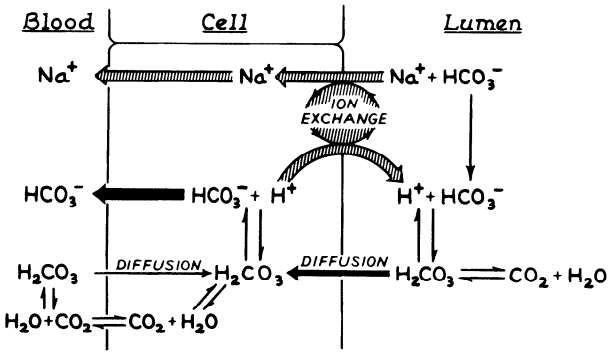

Fig.6. Cell schema showing recirculation of carbonic acid from the tubular lumen to cell, generating hydrogen ions without carbonic anhydrase catalysis. (From ref. Rector, 1973).

By using luminal and peritubular perfusion methods simultaneously it has also become possible to gain information concerning the coupling of hydrogen ions to the movement of other ions. Figure 7 shows a cell model showing that hydrogen ion secretion is directly coupled to sodium reabsorption by an Na-H exchange mechanism. Translocation of sodium from lumen into the cell is thought to be coupled to hydrogen ion movement in the opposite direction. The strongest direct support of this hypothesis is based on experiments on vesicles isolated from renal brush border membrane in which addition of sodium to the medium induces proton movement from vesicles into the incubation medium (Murer, Hopfer and Kinne, 1976). Since coupled transport processes involving cotransport of sodium with glucose and amino acids have been convincingly demonstrated in the luminal membrane of proximal tubules the possibility has been considered that the concentration difference between lumen and cell that exists for sodium, maintained by the activity of a peritubular sodium-potassium exchange pump, could even provide the driving force for hydrogen ion secretion. At least two predictions follow for such a mechanism of acidification. First, if the luminal and peritubular sodium concentration is lowered to that of the cell water, i.e. to some 40mEq/L,

net transport of sodium and hydrogen ion secretion should fall sharply. Secondly, one might also expect that the deletion of potassium from the peritubular perfusion fluid should abolish net sodium transport. As a consequence of inhibition of peritubular Na-K exchange, cellular sodium would rise and hence depress hydrogen ion secretion as the driving force for sodium entry across the luminal cell membrane decreases.

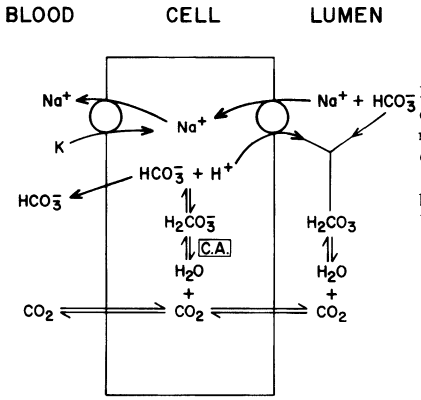

Fig.7. Cell schema depicting Na-K exchange across the peritubular cell membrane of renal tubule cell and coupled Na-H exchange across the luminal cell membrane. Carbonic anhydrase stimulated formation of carbonic acid serves to supply hydrogen ions to the Na-H exchange pump.

Data from perfusion experiments of Dr. Chan in our laboratory (unpublished observations) on rat proximal tubules indicate that partial replacement of sodium to some 40 mEq/L by choline in the lumen and in peritubular capillaries led to almost complete cessation of net sodium reabsorption. In sharp contrast, tubular bicarbonate and acidification of phosphate buffers remained at near normal levels. Analysis of luminal chloride indicated that the fall in bicarbonate was fully matched by a rise in tubular chloride. Hence, if sodium in the lumen is reduced, the tubular epithelium has the ability of HCl secretion. This observation indicates that sodium and hydrogen ion movement may be uncoupled.

Experiments in which sodium transport was abolished by removal of potassium from the peritubular perfusion fluid are also of interest. As expected from the presence of peritubular Na-K exchange pump, this ionic deletion leads to a dramatic, almost complete abolishment of net fluid and sodium transport. Again, only small changes in hydrogen ion secretion were observed. That the rate of hydrogen ion secretion can be dissociated from sodium transport is further shown in experiments in which peritubular alkalinization significantly reduced bicarbonate transport. In sharp contrast, sodium transport was only altered in a minor fashion by this maneuver. The relative insensitivity of tubular hydrogen ion secretion to sodium was also demonstrated in perfusion experiments in which even at such low levels of luminal and peritubular sodium as 1 mEq/L, hydrogen ion transport continued at a level approaching two-thirds of control rates (Malnic, unpublished). Recent evidence obtained in cortical collecting tubules, turtle and toad bladder are in full agreement with the view of only loose coupling or

no direct coupling between sodium and hydrogen ion transport (Machen, 1975; Ludens, 1975; Steinmetz, Omachi and Frazier, 1967; Stoner, 1974).

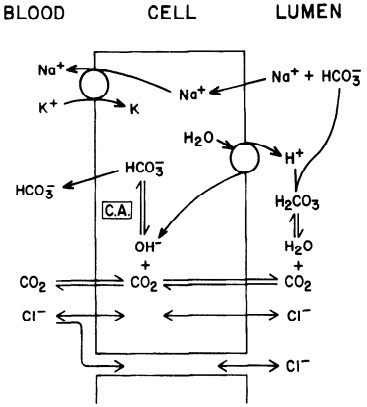

Fig.8. Cell schema depicting Na-K exchange across the peritubular cell membrane of renal tubule cell and uncoupled, possibly electrogenic hydrogen ion secretion across the luminal cell membrane. Carbonic anhydrase is visualized to catalyze the buffering of OH by CO_2.

In view of these results we favor the following view of the mechanism underlying renal tubular mechanism of acidification as summarized in Figure 8. Hydrogen ions are generated by decomposition of water into OH and H ions. The latter are pumped into the lumen, and OH ions neutralized by CO_2. The secretion of hydrogen ions could be electrogenic and generate small electrical potentials that promote either sodium reabsorption - (which normally predominates) - or chloride secretion. Since acidification may continue at near normal levels in the absence of either luminal sodium or of peritubular chloride (peritubular perfusions with cyclamate), it is clear that the coupling of hydrogen ion secretion to sodium or chloride movement must be variable and that, in some situations at least, hydrogen ion secretion can be uncoupled from sodium reabsorption. Coupling of hydrogen ion movement to sodium and chloride would be expected to depend on the electrochemical potential of these counterions and the conductance of the respective transport paths involved. In our view such a flexible and unspecific mode of coupling is quite satisfactory to explain the wide spectrum of transport ratios of sodium to hydrogen that is observed when primarily either tubular acidification or sodium transport are varied.

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SODIUM-CALCIUM EXCHANGE AND THE REGULATION OF CELL CALCIUM IN MUSCLE FIBERS*

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It is now widely recognized that low concentrations of calcium ions play a fundamental role in triggering muscle contraction (10). Most muscle fibers contract when the intracellular (sarcoplasmic) free calcium concentration ($(Ca^{2+})_i$) exceeds about 10^{-7}M (cf. Figure 8, below). In some types of muscle, such as invertebrate "skeletal" muscle and vertebrate cardiac muscle a considerable fraction of the inward ionic current across the sarcolemma, during excitation, may be carried by Ca^{2+} ions (29); the entering Ca^{2+} ions may therefore play a critical role in excitation-contraction coupling in these muscle fibers. Furthermore, even in vertebrate twitch-type skeletal muscle, where virtually all of the Ca^{2+} required to activate the contractile machinery can be supplied from the sarcoplasmic reticulum (cf. 9, 10), there is evidence for increased ^{45}Ca uptake from the extracellular medium during activation (4). While relaxation may be effected by rapid sequestration of Ca^{2+} (e.g., in the sarcoplasmic reticulum; 10), in the long run the extra Ca^{2+} which enters during activity must be extruded from the fibers in order to maintain a steady Ca^{2+} balance.

The fact that, at rest, sarcoplasm is at a negative potential means that positively, charged Ca^{2+} ions ought to be more concentrated in the sarcoplasm than in the surrounding medium. Instead, $(Ca^{2+})_i$ in relaxed muscle is less than 10^{-7}M- only a small fraction of the concentration in the extracellular fluid (about 10^{-3}M in vertebrates and 3-4 x 10^{-3}M in marine invertebrates; 5). Clearly, if a steady Ca^{2+} balance is to be maintained, Ca^{2+} must be extruded against a large electrochemical gradient. The purpose of this article is to review briefly the evidence which indicates that a counterflow exchange of Na^+ ions for Ca^{2+} ions may be involved in this "uphill" extrusion of Ca^{2+}. The data suggest that energy from the Na electrochemical gradient may be used to power Ca^{2+} transport. It should be noted that this type of transport mechanism is not limited to muscle; numerous studies support the view that a very similar, if not identical, Na-Ca exchange mechanism may be involved in Ca^{2+} transport in vertebrate and invertebrate nervous tissue, various secretory tissues, and intestinal and renal epithelia (5).

The hypothetical models diagrammed in Figure 1 illustrate the main features of the Na-Ca exchange mechanism: it is assumed that a "carrier" molecule (X), intrinsic to the sarcolemma, can bind either Na^+ or Ca^{2+}, and can translocate these ions across the membrane. For example, two (or three) Na^+ ions may combine with a carrier at the outside and be transported across the membrane to the sarcoplasmic face, where they are exchanged for a Ca^{2+} ion, which is then carried to the outside face.

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*Taken from the introductory remarks given at the session on Nerve-Muscle Membranes at the 1976 Federation Meetings.

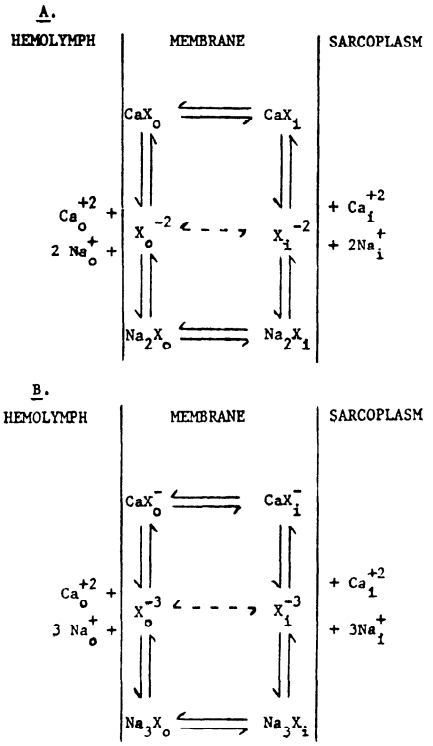

Fig.1. Two models of sodium-calcium countertransport carrier mechanisms.(A) Model for an electrically neutral exchange of two Na^+-for-one Ca^{+2}.(B) Model involving the exchange of three Na^+-for-one Ca^{+2} and one free negative charge. The free carrier (X^{-2} or X^{-3}) is assumed to be a divalent or trivalent anion, respectively, with specificity for Na^+ or Ca^{2+} ions. The chemical reactions between carrier and counter ions are assumed to be very rapid, while the diffusion of the carrier-cation complexes (CaX or Na_2X in the case of the divalent carrier, and CaX^- or Na_3X for the trivalent model) across the membrane are rate limiting; free carrier presumably diffuses very slowly, if at all. The subscripts, i and o, refer to the sarcoplasm and hemolymph, or internal and external surfaces of the membrane, respectively (from ref. 32, with permission).

Alternative models, involving neutral carrier molecules, or simultaneous translocation mechanisms (as opposed to the sequential mechanisms depicted in Figure 1), may also be considered (6). Furthermore, ATP may play a role in this process (cf. 21), although it need not necessarily directly provide the energy for Ca transport (6).

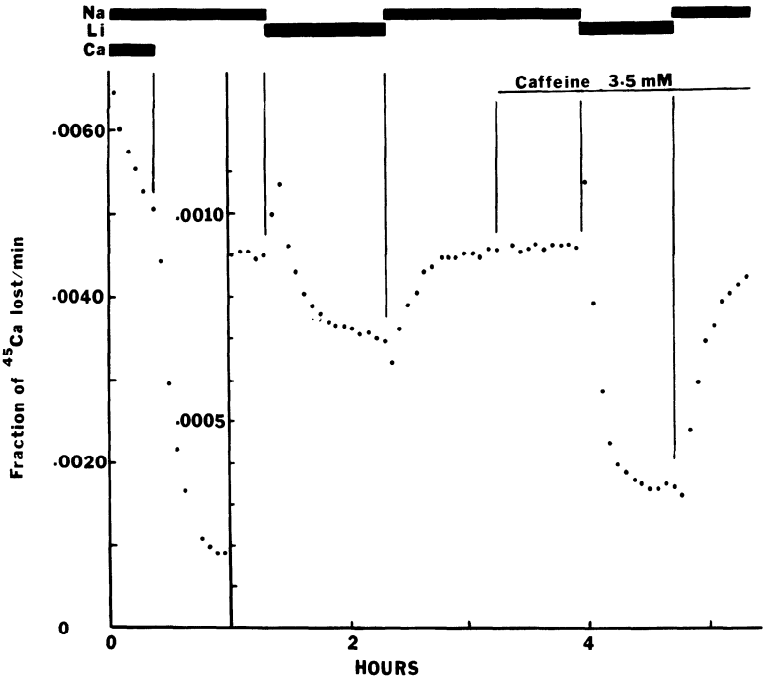

Fig.2. Effects of external cations on the rate constant of ^{45}Ca efflux from a barnacle muscle fiber before & during caffeine treatment. The bars at the top of the graph indicate the periods during which $CaCl_2$ (11 mM) and NaCl (440 mM) or LiCl (440 mM) were present in the external medium; the $MgCl_2$ concentrations, 32 mM in the Ca-containing fluid, was increased to 43 mM in the Ca-free solutions. This fiber was injected with ^{45}Ca 40 min before the first point on the graph. No contracture was visible in the muscle during the exposure to caffeine. Fiber diameter, 1.28 mm; temperature, 21°C (from ref. 32, with permission).

Crustacean Muscle

Certain crustaceans, most notably some species of Pacific Coast barnacles, have giant muscle fibers (1-2 mm diameter x 20-30 mm length) which can be directly injected with ^{45}Ca, and are therefore particularly suitable for certain types of transport studies. Ca efflux data from a ^{45}Ca-injected barnacle muscle fiber are shown in Figure 2 (see also ref. 1). The main point is that a significant fraction of the Ca efflux is sensitive to removal of external Na (in this case, replaced

by Li, a change which does not affect the resting membrane potential; Russell and Blaustein, unpublished data). This Na-dependent fraction presumably represents the Na-Ca exchange (cf. 6). There is also an external Ca-dependent Ca efflux (Figure 2); this may represent Ca-Ca exchange, and will not be considered in the subsequent discussion. Low doses of caffeine (insufficient to induce contracture) reduce the "residual" (Na- and Ca-independent) Ca efflux and significantly enhance the Na-free effect (figure 2); the explanation for this effect is not yet clear, but may be related to a slight increase in $(Ca^{2+})_i$.

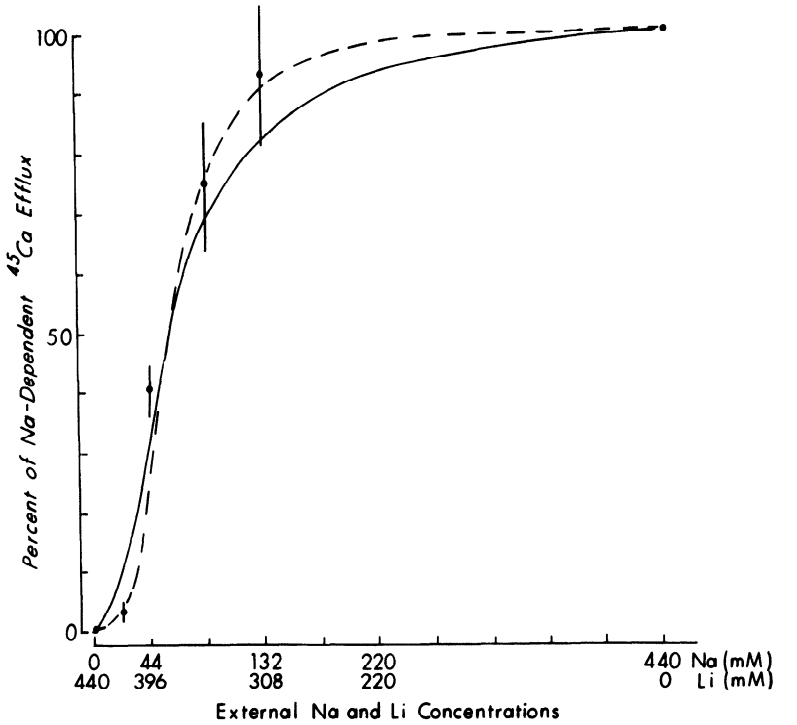

Fig.3. Percent of the maximal Na_o-dependent ^{45}Ca efflux in Ca-free seawaters plotted as a function of the external Na and Li concentrations; the Na_o-dependent Ca efflux into Ca-free Na SW is taken as 100%. The graphed points are the mean values from three ^{45}Ca-injected barnacle muscle fibers; the vertical bars through the points represent the standard errors. All experiments were conducted at temperatures of 18 ± 1°C. The data have been fitted to an equation of the form, $J_{Ca} = J_{Ca}^{Max} \{1 + (\bar{K}_{Na}/(Na)_o)^n\}$, where J_{Ca} is the Na_o-dependent ^{45}Ca efflux at any external Na concentration ($(Na)_o$), relative to that in Ca-free Na SW (J_{Ca}^{Max}); $\bar{K}_{Na}$ is the mean half-saturation value for Na_o. The mean rate constant for the Na_o-dependent ^{45}Ca efflux in Ca-free Na SW (i.e. k in Ca-free Na SW minus k in Ca-free Li SW) for the three experiments was 5.3 ± 0.4 x 10^{-4} min^{-1}. The exponent (n) had a value of 2 (solid line) or 3 (dashed line); $\bar{K}_{Na}$ was 60mM in both cases (from ref. 32, with permission).

The relationship between the external Na concentration, $(Na)_o$, and the magnitude of the Na-dependent fraction of the Ca efflux is illustrated in Figure 3. Note that the curve is sigmoid, and that a cubic relationship (dashed line) fits the data best. This may indicate that three external Na^+ ions are required to activate the efflux of one Ca^{2+}; a 3 Na^+-for-1 Ca^{2+} exchange model (e.g., Figure 1B) would be consistent with this observation. In this case, energy from the Na electrochemical gradient, alone, could in principle maintain $(Ca^{2+})_i$ at about 7 x 10^{-8}M (within the physiological range; 18) according to the equation (cf. 5, 6):

$$1) \qquad \frac{(Ca^{2+})_o}{(Ca^{2+})_i} = \frac{(Na^+)_o}{(Na^+)_i}^3 \exp \frac{-V_m F}{RT}$$

where $(Ca^{2+})_o$ is 3-4 mM (31), $(Na^+)_o$ is 460 mM, $(Na^+)_i$ is about 25 mM (15), and the resting membrane potential, v_m, is about -55 mV at 15°C (12). R, T and F are the gas constant, absolute temperature and Faraday's number, respectively.

An important corollary of the Na-Ca exchange models, such as those shown in Figure 1, is that altering the internal or external Na concentration should also affect Ca influx. Muscle contraction may serve as a convenient assay for (net) Ca entry. The contracture records in Figure 4 show that the barnacle muscle shortens when external Na is removed; this response is increased in rate and magnitude in Na-loaded muscle fibers. These data correspond to Di Polo's (11) observation on ^{45}Ca influx in dialyzed barnacle muscle fibers, and indicate that lowering $(Na^+)_o$ and/or raising $(Na^+)_i$ tends to increase Ca entry.

The significance of external Na for net Ca extrusion is indicated by the contracture record in Figure 5. In this case the Na-loaded fiber went into contracture when transferred to an Na-free solution (Na replaced by Li). Although external Ca is required to induce the contracture, shortening could be maintained in a Ca- and Na-free medium; reintroduction of external Na, with or without Ca, caused prompt relaxation (also see ref. 26). Presumably, sufficient Ca entered during the exposure to the Li + Ca solution to overwhelm the intracellular Ca sequestration mechanism, and external Na was then required to activate net Ca extrusion (by Na-Ca exchange).

Vertebrate Skeletal Muscle

It is somewhat surprising that the mechanism for Ca transport has been least well characterized in the most frequently studied of muscle types, vertebrate skeletal muscle. It has long been known that Ca entry into frog skeletal muscle increases during activity (4); thus, according to the considerations outlined above, we would certainly expect that the muscle fibers possess a mechanism to extrude Ca against a large electrochemical gradient. Hints about the nature of this mechanism are limited to the study by Cosmos and Harris (8). These authors showed that conditions which led to net Na gain by the muscle fibers, also caused net Ca gain; when the Na was re-extruded, Ca followed pari passu. Also,

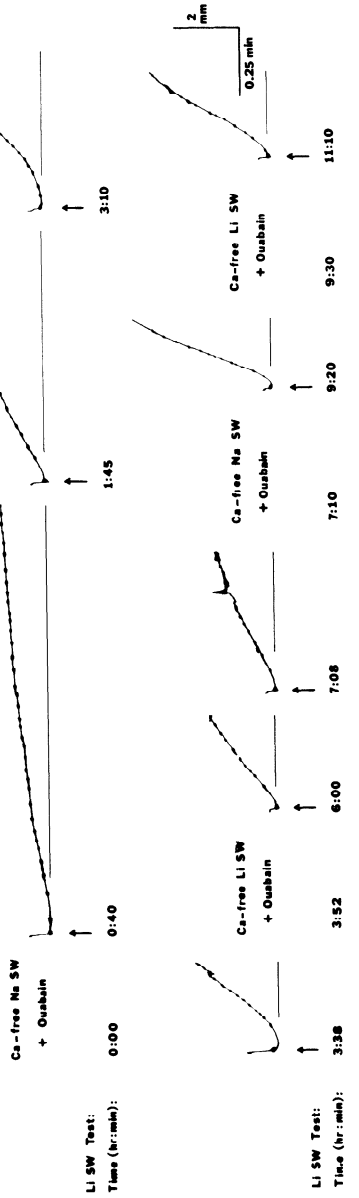
Ca-free Na SW
+ Ouabain
Li SW Test:
Time (hr:min): 0:00
0:40
1:45
3:10
Ca-free Li SW
+ Ouabain
3:38
3:52
6:00
7:08
Ca-free Na SW
+ Ouabain
7:10
9:20
Ca-free Li SW
+ Ouabain
9:30
11:10
2 mm
0.25 min

Fig.4

reduction of $(Na)_o$ enhanced ^{89}Sr uptake (in other experiments, ^{89}Sr appeared to be handled like ^{45}Ca), and net Sr loss followed reintroduction of the external Na - despite continued presence of ^{89}Sr in the medium. Although these findings may implicate an Na-Ca exchange mechanism in Ca transport in frog skeletal muscle, the data are far from conclusive.

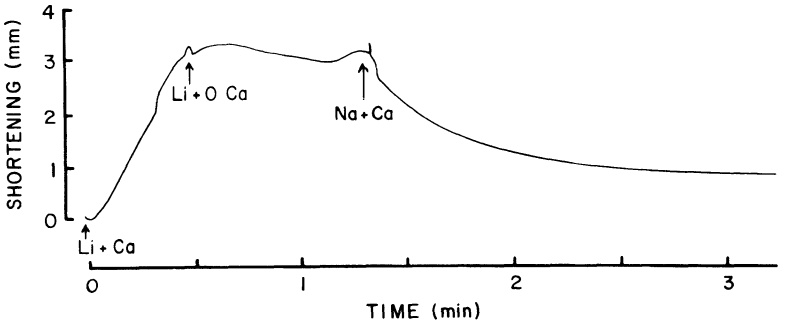

Fig.5. Effect of external cations on the relaxation of a barnacle muscle fiber. Recording is from the same experiment as are those of Fig.4, and was obtained 10 min before the 6:00 record of Fig.4. The relaxed, Na-loaded fiber was exposed to Ca-containing Na-free (Li) sea water at the beginning of the record, and rapidly went into contracture. The contracture was maintained despite removal of external Ca (at "Li + 0 Ca"), but relaxation was promptly initiated when the "control" Na + Ca-containing fluid was added back (Blaustein, unpublished experiment).

Fig.4. Effect of internal Na concentration on the shortening velocity of a barnacle muscle fiber. A fresh muscle fiber was placed in Ca-free Na SW (sea water) for 20 min to wash out external Ca. It was then attached to one end of the lever of a heart/smooth muscle transducer; a 125 mg counter-weight was attached to the other end of the lever, equally-distant from the fulcrum. When the fiber was initially tested with Li SW (after 40 min in Ca-free Na SW), it did not shorten (record not shown). Forty-five minutes after starting the washout in Ca-free Na SW, incubation in 2 mM Ca-Na SW containing 5×10^{-4}M,ouabain was begun (this is indicated as "zero-time" in the figure). Periodically, thereafter, the fiber was exposed to Li SW for brief periods, and then returned to the ouabain solution; the shortening records are shown in the figure. At 3:52, incubation in Ca-free Li SW containing 5×10^{-4}M ouabain was started in an effort to reduce the intracellular Na. The records at 6:00 and 7:08 indicate the response of the fiber to short exposures to Li SW (with 20 mM Ca). Re-loading with Na was started at 7:10, and the subsequent response to a Li SW test (at 9:20) is shown. Again, at 9:30, the fiber was returned to the Ca-free Li SW containing ouabain, to reduce the cell Na content; at 11:00, the fiber was again tested with Li SW. Fiber resting length was 35 mm; mean diameter, 0.80 mm; weight, 18.8 mg; temperature, 19.5°C (Blaustein, unpublished experiment).

Smooth Muscle

Much more information is available regarding Ca transport in various types of vertebrate smooth muscle. For example, as is the case in barnacle muscle (Figure 2), a considerable fraction of the Ca efflux from ^{45}Ca-loaded arterial muscle (but not from adventitia) is dependent upon external Na (Figure 6). Furthermore, lowering $(Na)_o$ causes net Ca entry (30) and induces contractures in aortic strips (e.g., see Figure 7). These (low Na-induced) contractures occur only in the presence of external Ca and, in contrast to those observed in crustacean muscle (Figures 4 and 5), do not require prior Na loading (Figure 7A). In fact, brief treatment with ouabain or with K-free media is sufficient to increase tension in vascular smooth muscle (23; and see Figure 7B) - presumably as a result of an increase in $(Na^+)_i$, and consequently, in $(Ca^{2+})_i$ (cf. equation 1).

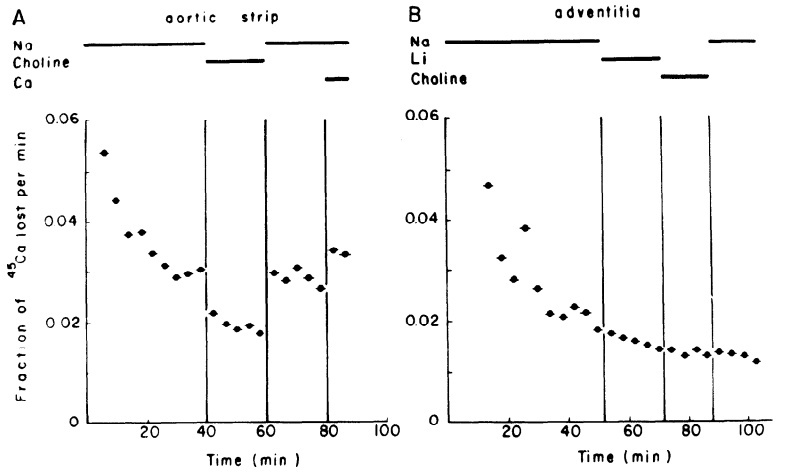

Fig.6. The effect of external Na on ^{45}Ca efflux from a rabbit aortic strip (left) and from a strip of adventitia isolated from a rabbit aorta (right). Ordinate: fraction of ^{45}Ca lost per minute from the tissue into the inactive rinsing solutions (rate coefficient); abscissa: time of ^{45}Ca efflux. The bars above the various efflux periods indicate the nature of the Na substitutes. The Ca-free rinsing solutions contained 0.5 mM EGTA; the solution during the last efflux period for the aortic strip contained 1.8 mM $lCaCl_2$. Note the marked decrease of ^{45}Ca efflux from the aortic strip when Nacl in the rinsing solution was replaced by choline chloride and the subsequent increase when Na was readmitted; no such effect occurred with the adventitia (from ref. 30, with permission).

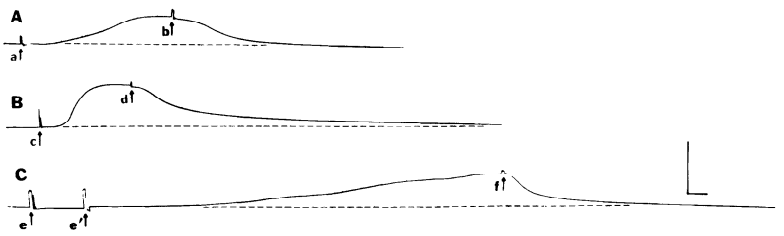

Fig.7. Effect of cations on tension of rabbit aortic strip. The resting load was 0.5 gm in all cases. A. Increase in tension due to exposure (at "a") to Na-free Li Tyrodes solution. The tissue relaxed promptly, when returned to standard (Na-containing) Tyrodes (at "b"). B. Between records A and B, the aortic strip was incubated for 30 min in K-free Ca-free Na-containing Tyrodes to load the muscle with Na. Exposure to K-free Na-free Li Tyrodes (with 1.8 mM $CaCl_2$), at "c", caused a more rapid and greater rise in tension than seen in A. The standard Tyrodes was reintroduced at "d". C. Data from another aortic strip showing the effect of external K removal (at "e" and "e") on tension; the solutions all contained 1.8 mM $CaCl_2$. The strip promptly relaxed when external K was added back (at "f"). Temperature, 37°C. Calibration: vertical (tension) = 2 gm (A and B) or 1 gm (C); horizontal (time) = 1 min (Blaustein and Reuter, unpublished experiment).

The influence of external cations on relaxation has also been investigated in several types of vertebrate smooth muscle. As in invertebrate muscle (26 and Figure 5), relaxation following a contracture is markedly slowed or incomplete in the absence of external Na in the ileum (20), in taenia coli (22), and in arterial (7, 30) and venous (3) smooth muscle. Again, these observations implicate Na-Ca exchange in net Ca extrusion from these muscle fibers.

In contrast to twitch-type skeletal muscle, which may relax completely between contractions when stimulated at a low frequency, some steady tension ("tone") is normally maintained at all times in arterial smooth muscle. This means that the steady ionized $(Ca^{2+})_i$ in these fibers must exceed 10^{-7}M, the threshold for contraction (Figure 8). Since intracellular stores (e.g., in the sarcoplasmic reticulum, see Figure 9) cannot serve as an infinite source or sink for Ca, it is difficult to escape the conclusion that, in this tissue, the plasma membrane (sarcolemma) has the primary control over the long-term regulation of $(Ca^{2+})_i$, and thereby, of arterial tone. For example, a "command" to raise tension by increasing $(Ca^{2+})_i$ through release of Ca^{2+} from the sarcoplasmic reticulum (via "P_{Ca}" in Figure 9) would normally only result in a transient tension increase - unless the sarcolemmal Ca "pump" (Na-Ca exchange?) were reset to maintain the new, higher $(Ca^{2+})_i$ level.

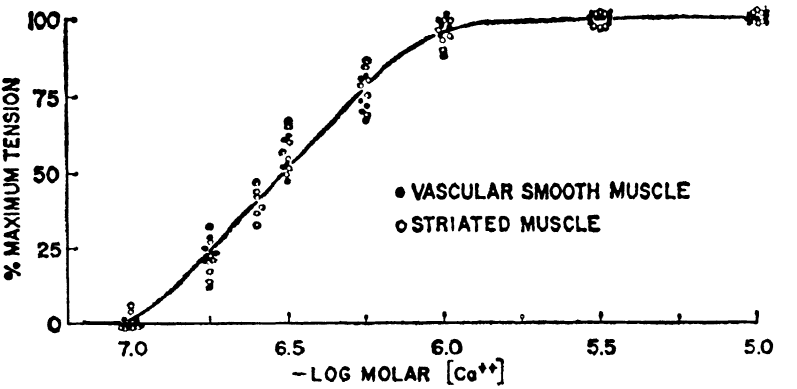

Fig.8. Effect of the concentration of free Ca^{2+} on the tension developed by individual glycerinated psoas (striated) and vascular (smooth) muscle fibers. Conditions: temperature, 20°C; 150 mM KCl; 20 mM histidine buffer (pH 6.6); 5 mM ATP and 5 mM Mg; 4 mM EGTA $_{total}$. Free (Ca^{2+}) was varied by changing the ratio $Ca_{total}/EGTA_{total}$ appropriately. The calcium requirements for contraction of these two preparations are virtually identical (from ref. 13, with permission; copyright 1972 by the American Association for the Advancement of Science).

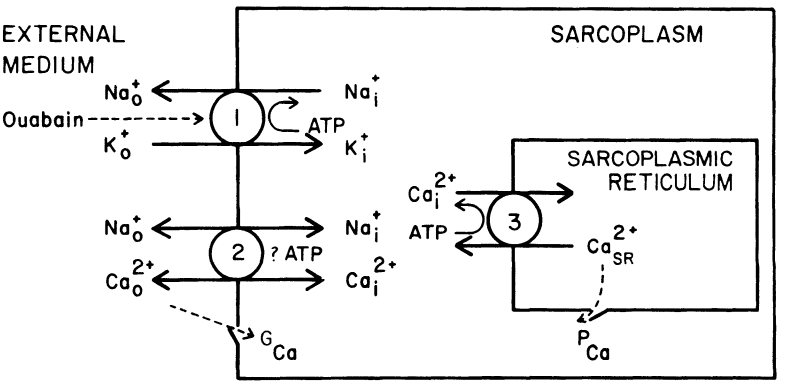

Fig.9. Diagram of the compartmentalization of Ca in muscle fibers. The ATP-dependent, ouabain-sensitive Na-K exchange pump (1) and some of the main pathways involved in Ca redistribution are shown: 2, the sarcolemmal Na-Ca exchange; 3, the sarcoplasmic reticulum (SR) ATP-dependent Ca pump; P_{Ca}, the pathway through which Ca^{2+} moves from SR to sarcoplasm as a consequence of muscle excitation; G_{Ca}, the voltage-sensitive Ca conductance pathway in the sarcolemma through which a Ca current may enter. Mitochondrial storage sites and Ca binding sites (e.g. proteins) in the sarcoplasm and SR have been omitted for the sake of simplicity.

The striking sensitivity of vascular smooth muscle to changes in $(Na)_o$ and $(Na)_i$, noted above, could be accounted for if $(Ca^{2+})_i$ (and tension; Figure 8) is controlled through Na-Ca exchange (cf. equation 1). This concept may be explored further by considering the (hypothetical) consequence of a small rise in $(Na^+)_i$. Assuming a 3 Na^+-for-1 Ca^{2+} Na-Ca exchange stoichiometry (see above; there are no data regarding the stoichiometry in vascular smooth muscle), the values in Table I indicate that a three per cent increase in $(Na^+)_i$ may increase $(Ca^{2+})_i$ sufficiently to raise tension by about twenty per cent (Figure 8). In view of the well-documented inhibitory action of cardiac glycosides on the sodium pump (e.g., 17), this sequence of events could explain the increase in peripheral vascular resistance which results from administration of low doses of cardiac glycosides (doses without effect on cardiac output; 19, 24). The same Na-Ca exchange mechanism may be invoked to explain how, in some hypertensives, natriuretic agents and a low sodium diet can, by slightly lowering tissue Na^+ concentrations (since plasma Na^+ is relatively invariant) lead to a reduced $(Ca^{2+})_i$ and therefore, to lower vascular wall tension and reduced blood pressure (cf. 14).

TABLE I.

Hypothetical Values for $(Na^+)_i$ and $(Ca^{2+})_i$ Calculated from Equation 1

Assumed	Calculated*		Percent of
$(Na^+)_i$	$(Ca^{2+})_i$	pCa_i	Maximum
(mM)	(M)	$(-\log(Ca^{2+})_i)$	Tension**
17.0	1.78×10^{-7}	6.75	25
17.6	1.95×10^{-7}	6.70	30

*From equation 1, assuming: $(Na^+)_o$ = 145mM, $(Ca^{2+})_o$ = 1.2mM, and V_m = -60 mV.

**From Figure 8.

Cardiac Muscle

The first evidence for Na-Ca interaction was obtained in cardiac muscle, when Wilbrandt and Koller (34) showed that the force of ventricular contraction depended upon the ratio, $(Ca)_o/(Na)_o^2$. Niedergerke and his colleagues (cf. 25) observed contractures in ventricular muscle exposed to Na-depleted solutions; this was associated with a net gain of Ca. The muscle lost Ca and relaxed upon return to control Ringer's fluid.

Reuter and his colleagues (16, 21, 31) examined the effects of internal and external Na on Ca fluxes in mammalian cardiac muscle and demonstrated that in these preparations, too, lowering $(Na)_o$ and/or raising $(Na)_i$ tends to reduce Ca efflux and enhance Ca entry. Their observation that the Ca efflux is, in part, Na-dependent, is illustrated

by the data in Figure 10. It therefore seems reasonable to conclude that the Na electrochemical gradient also helps to maintain the $(Ca^{2+})_o/(Ca^{2+})_i$ ratio in cardiac muscle.

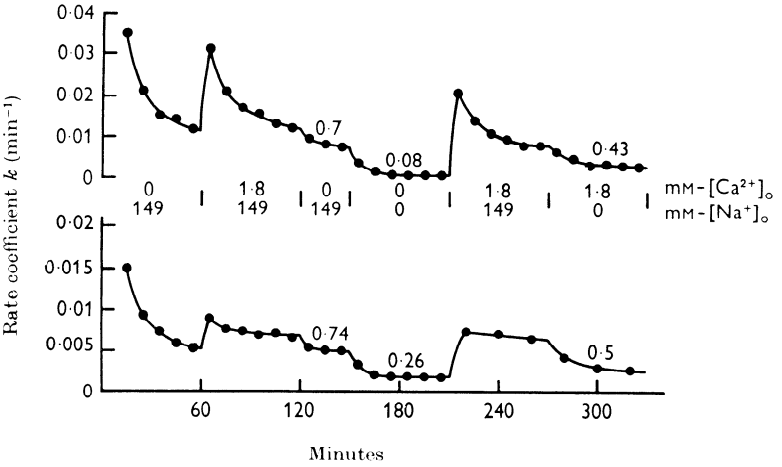

Fig.10. The effects of removing $(Ca^{2+})_o$ and $(Na^+)_o$ on Ca efflux from guinea-pig auricle (upper curve) and a ventricular trabecula of a sheep (lower curve). The numbers below the upper curve indicate the Na and Ca concentrations in the bathing solutions. In Na-free solutions NaCl was replaced by sucrose. The numbers immediately above each curve indicate the fractions of the preceding control efflux to which Ca efflux was reduced by removing external Na and/or Ca (from ref. 31, with permission).

On the Cardiotonic Action of Cardiac Glycosides

The only reproducibly demonstrated action of cardiac glycosides is inhibition of the sodium pump (e.g., 17), and it has been repeatedly suggested that cardiac glycosides may induce a positive inotropic response as a consequence of this inhibition (e.g., 27,28). The foregoing considerations raise the possibility that Na-Ca exchange may be the link between sodium pump inhibition and the inotropic response, and the diagram in Figure 9 can be conveniently employed to illustrate this inter-relationship. To facilitate this description, it will be convenient to make several simplifying assumptions and approximations:

a. The voltage-dependent Ca inward current (through "G_{Ca}" in Figure 9, cf. ref. 29), which may normally help to activate contraction (e.g.2), is assumed to be unaffected by cardiac glycosides and will be ignored. The "activator" Ca^{2+} will be assumed to come directly from the sarcoplasmic reticulum (through "P_{Ca}" in Figure 9), as in skeletal muscle.

b. Then, since the myocardium is relaxed between beats, if the log $(Ca^{2+})_i$-versus-tension curve of Figure 8 also applies to cardiac muscle

(35), $(Ca^{2+})_i$ at rest will be less than 10^{-7}M; lacking knowledge of the precise value, let us assume that resting $(Ca^{2+})_i = 0.32 \times 10^{-7}$M ($-\log (Ca^{2+})_i$, or "$pCa_i$" = 7.5).

c. To achieve 60% activation of contraction pCa_i will have to fall to 6.4 (i.e., $(Ca^{2+})_i$ will increase to about 4.0×10^{-7}M).

d. The sarcoplasmic reticulum (SR) will be assumed to constitute 10% of the total fiber volume and, at rest, to have a Ca^{2+} concentration of 3.2×10^{-4}M. Thus, the rate constant for Ca^{2+} uptake by the SR (k_{S-SR}) will be 10^4 times the rate constant for Ca loss from the SR (k_{SR-S}), in order to maintain the 10^4-fold Ca^{2+} concentration gradient between the SR and the sarcoplasm.

e. During activation, the muscle fiber action potential is assumed to cause the Ca permeability (P_{Ca}) of the SR membrane to increase by a fixed amount and for a fixed time period - sufficient to allow 1 per cent of the SR Ca^{2+} (i.e., 1% of the 3.2×10^{-4}M Ca^{2+}) to flow into the sarcoplasm. Because of the difference in volumes of SR and sarcoplasm (and ignoring the Ca buffering effect of sarcoplasmic proteins; cf. 9, 10), this Ca will be sufficient to raise (Ca^{2+}) in the sarcoplasm by 3.6×10^{-7}M; thus, the final pCa_i will fall to about 6.4 ($(Ca^{2+})_i = 3.6 \times 10^{-7} + 0.32 \times 10^{-7} = 3.92 \times 10^{-7}$M). According to Figure 8, this will give about 60% of maximal tension.

Now, suppose that a small dose of cardiac glycoside is given - sufficient to increase $(Na^+)_i$ by a few per cent (see above), and because of the re-setting of the Na-Ca exchange gradients (cf. equation 1), to lower resting pCa_i from 7.5 to 7.4 ($(Ca^{2+})_i$ will increase from 0.32×10^{-7}M to 0.40×10^{-7}M. Assuming that the SR Ca pump is not directly affected by the glycoside (there is little experimental support for such action), the ratio of the rate constants, k_{S-SR}/k_{SR-S}, will be unchanged, and the (Ca^{2+}) in the SR will now increase to 4.0×10^{-4}M. (Note that the Ca content of the fiber, as a whole, would only increase by about 0.5% in this case; cf. 16). If, during an action potential, P_{Ca} increases to the same extent as before, and for the same length of time per beat, 1% of the SR Ca^{2+} will again be lost to the sarcoplasm. But now, the $(Ca^{2+})_i$ will be increased by 4.4×10^{-7}M, so that the final value will be about 4.8×10^{-7}M ($pCa_i = 6.3$), which corresponds to a tension of about 72% (Figure 8) - an 18% increase over that prevailing in the absence of the glycoside. In other words, the length of the step along the abscissa of the pCa_i-tension diagram (Figure 8), during activation, will not be changed; however, as a consequence of the slight rise in resting $(Ca^{2+})_i$, the entire step will be shifted to the right by a small increment. Thus, a small change in $(Na^+)_i$ may, with the Na-Ca exchange mechanism as an intermediary, lead to the accumulation and availability of sufficient extra Ca^{2+} in the SR, to significantly enhance contractile force.

Conclusion

In sum, the aforementioned observations support the idea that the Na electrochemical gradient plays a critical role in the regulation of fiber Ca in most, if not all, types of muscle. Na-Ca exchange is not

an exclusive property of muscle, however: many other tissues apparently possess similar, if not identical, Ca transport mechanisms (5). Moreover, Na-Ca exchange may be only one example of a large class of transport mechanisms which employ energy from the Na electrochemical gradient to transport other solutes against their gradients (cf. 33).

Acknowledgement

I am grateful to Drs. P. De Weer, S. Lang, and R. Rakowski for helpful discussion. Research from the author's laboratory described above was supported by research grant 74-806 from the American Heart Association, and a Jerry Lewis Neuromuscular Research Center Grant from the Muscular Dystrophy Associations of America (to Washington University).

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FLEISCHNER SOCIETY MEETING

The Fleischner Society, a multidisciplinary international organization devoted to the study of the chest, announces its 7th annual symposium on diseases of the chest to be held at the Americana of Bal Harbour in Miami Beach, Florida, from February 27th to March 2nd, 1977. The content of the symposium will be divided about equally into lectures and a selection of refresher courses. Registrants also may enroll for small group sessions with individual faculty members at lunch. Commercial and scientific exhibits will also be course innovations this year. Approved for 20 hours Category I Credit AMA Physicians Recognition Award. Fee $225. Resident or Fellow $150. Make checks payable to The Fleischner Society, c/o Mrs. Lucy Kelley, Department of Radiology, Jackson Memorial Hospital, Miami, Florida - 33154.

REFRESHER COURSE IN CARDIAC RADIOLOGY

A refresher course in cardiac radiology will be presented by the North American Society for Cardiac Radiology, March 20 to 24, 1977 at the Hyatt Regency Phoenix in Phoenix, Arizona. The program will include didactic and seminar presentations of topics dealing with the radiology of pediatric and adult heart disease, as well as discussions of new techniques in cardiac diagnosis and a scientific session for all participants. For further information, please write to: Dr. M. Paul Capp, Dept. of Radiology, Arizona Medical Center, Tucson, AZ 85724.

PERIPHERAL FACTORS IN IRREVERSIBLE HEMORRHAGIC SHOCK*

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Department of Surgery and Bioengineering
University of California, San Diego

I would like to discuss and summarize some controversial aspects of what is known in the experimental literature as irreversible hemorrhagic shock, the condition in which a replacement of the blood originally withdrawn is no longer an effective restorative procedure.

Before proceeding with the discussion of mechanisms and the organ systems involved in the development of the irreversible phase of shock, I would like to point out certain aspects of experimental shock related to the type of method used. I apologize for bringing up the old-new topic of experimental technique which is so important, especially in evaluation of pathogenetic factors active in the irreversible phase of shock.

An ideal experimental model should fulfill several requirements: reproducibility, predictable outcome, economic feasibility, and reasonable similarity to clinical reality. Few, if any, of the currently known models fulfill all of these requirements, and the investigator has to weigh both the advantages and disadvantages of the model selected for a given shock investigation. I do not plan to discuss a number of important factors, such as the type of anesthesia or the absence of anesthesia, selection of the species, age, previous history, but I would like to attract your attention to the basic type of hemorrhagic shock model, which, with some simplification, can be subdivided into two types: one is the classical fixed hypotension model, and the second is a single volume withdrawal type of hemorrhagic shock. As it is well known, the classical Wiggers type of shock model (1) has introduced a high degree of reproducibility into experimental shock studies. However, its disadvantage is rather significant since the hypotensive period which is profound and lasts for two to three hours, is remote from clinical reality. Even worse, it distorts a very important pathophysiologic mechanism: the mechanism of compensation. Under clinical conditions, even with severe shock, the preferential areas such as the cerebral and coronary vascular beds are enjoying the preferential treatment by the circulatory system. In the Wiggers type of shock, the coronary and cerebral vascular circulatory system are exposed to the same hypotension as all other vascular beds. On the other hand, the single withdrawal hemorrhage model (2, 3, 4) which utilizes basically the withdrawal of a certain amount of blood during a relatively short and uninterrupted period of time, does offer the animal the opportunity to compensate. Blood is withdrawn at a given rate until the blood pressure (Fig. 1) reaches a certain level, and then all connections with the reservoir are removed. Usually a spontaneous increase in blood pressure is observed. The arterial pressure does not remain at compensated values, but starts to drop slowly.

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*Taken from the introductory remarks given at the session on Shock I at the 1976 Federation Meetings. Supported by NHLI Grant HL 12690-07A1.

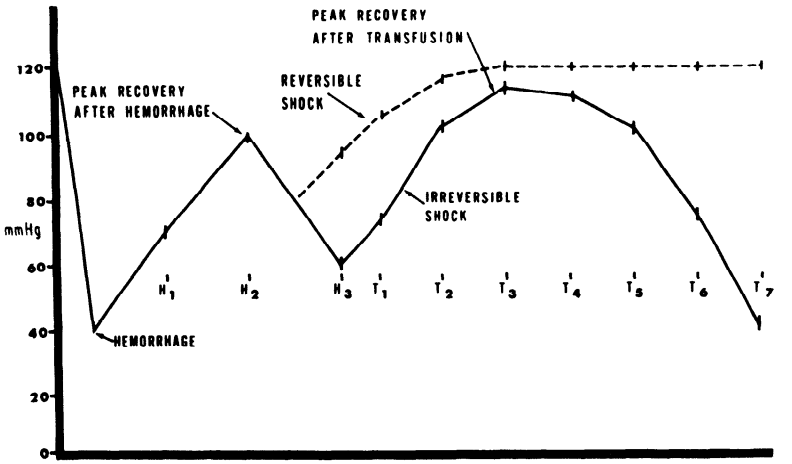

Fig.1. Schematic time course of the "reversible and irreversible" shock experiments (broken line, "reversible", unbroken line "irreversible"). (By permission from A. Fronek and T. Witzel: Hemodynamics of the terminal vascular bed in canine hemorrhagic shock. Surgery 75: 408, 1974.)

When the pressure reaches a certain percentage of the peak recovery pressure, all the shed blood is re-transfused. Under these conditions we can decide whether we want to produce reversible or irreversible shock conditions, depending on whether retransfusion takes place at a 20 or a 40% drop of maximum compensated pressure. The advantages we view with this single withdrawal type of shock are these: 1) during the crucial time of hypovolumia, the animal is permitted to compensate and 2) the investigator has an opportunity to monitor the development of the compensatory mechanism of the circulatory system. On the other hand, the preferential circulatory vascular beds are not exposed to such a drastic hypotension as it is the case with the continuous or graded hypotension Wiggers-type hemorrhagic shock model.

Figure 2 shows in diagrammatic form, the major sequelae believed to be involved in the breakdown of the circulation during the shock syndrome. In essence, the contribution of the heart directly must be weighed against factors which interfere with the return of blood from the periphery and, thereby, interfere with cardiac output indirectly. A major involvement of cardiac insufficiency in the phase of irreversibility has a number of strong proponents. On the other hand, there is an impressive array of evidence favoring peripheral vascular mechanisms as the principle or triggering cause of the declining venous return responsible for the irreversible or decompensatory phase of the syndrome. In a diagrammatic fashion, the various peripheral factors which come into consideration, can be summarized as follows: An impairment of capacitance

function, microcirculatory disturbances, circulatory changes at the level of the terminal vasculature, intercellular metabolic and other pathophysiologic derrangements, and finally, rheological factors -all these may lead to a decline in venous return, leading to a decline in cardiac output. The diagram identifies the declining cardiac performance, as one of the possible primary factors leading to a declining cardiac output. This relationship is illustrated in a more detailed way in Fig. 3 which summarizes various alternatives leading to a decrease in cardiac output.

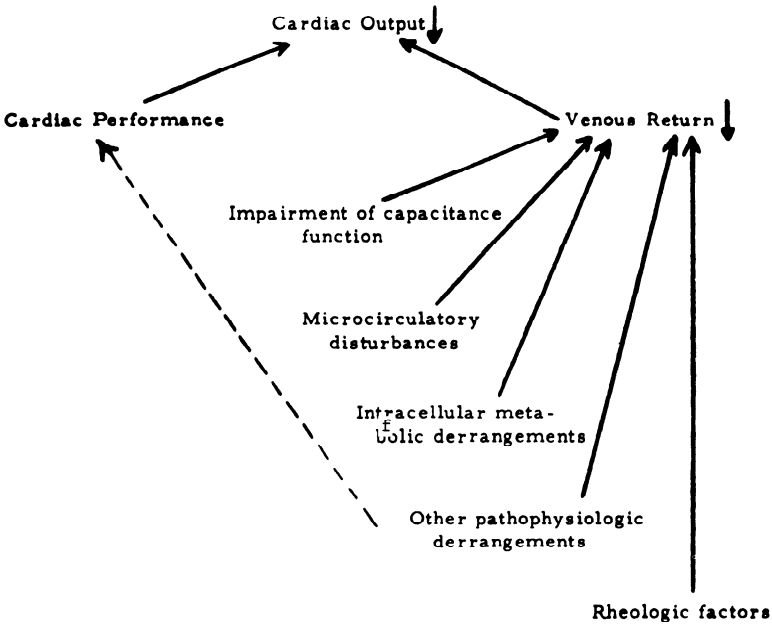

Fig.2. Factors influencing cardiac output in hemorrhagic shock. (By permission from B.W. Zweifach and A. Fronek. The Interplay of Central and Peripheral Factors in Irreversible Hemorrhagic Shock. Progress in Cardiovasc. Dis. 18: 147, 1975).

In view of the fact that it is accompanied by an increased heart rate, it must be caused by decreased stroke volume. In this case, there are two possibilities: either a decrease in diastolic volume, or decreased cardiac contractility. The upper part of the diagram which is related to a decreased venous return will be discussed later. If we turn now our attention to the decreased cardiac contractility, we can theoretically assume two alternatives: A declining or decreasing sympathomimetic support, or beginning cardiac depression. However, recent observations seem to downgrade the importance of the first possibility: catecholamine levels were not found to decrease below control levels (10)

although declining sensitivity to sympathomimetic stimulation cannot be ruled out. On the other hand, many studies have reported declining cardiac performance synchronous with the overall deterioration of the circulatory system (5-9). It should be pointed out that practically in all of these experiments, the Wiggers severe hypotension procedure was used and it is difficult to differentiate primary cardiac depression from that induced by accompanying coronary hypotension. It is well established that coronary hypoperfusion will lead ultimately to a depression of cardiac performance (11-13).

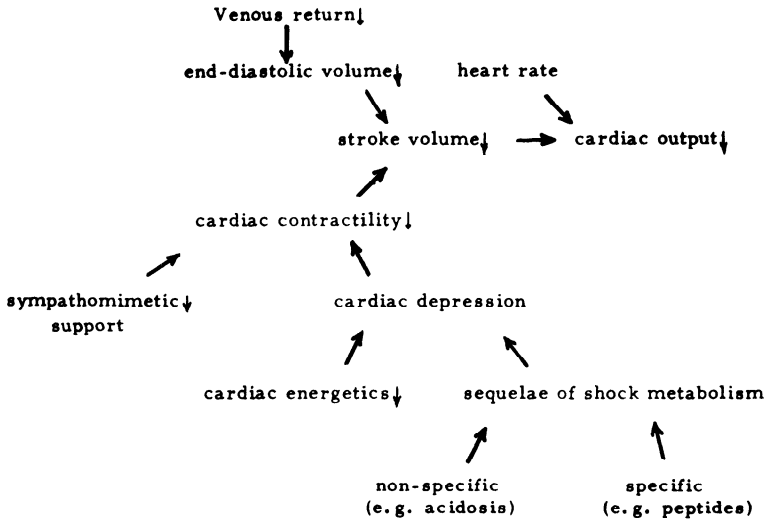

Fig.3. Pathways of cardiac output decline in hemorrhagic shock. (By permission from B.W. Zweifach and A. Fronek. The Interplay of Central and Peripheral Factors in Irreversible Hemorrhagic Shock. Progress in Cardiovasc. Dis. 18: 147, 1975.)

On the other hand, a number of investigators could not confirm a substantial cardiac participation in the ultimate circulatory deterioration (14-18). It is beyond the scope of this discussion to analyze in detail the possible reasons of these discrepancies. We would like to emphasize only that a number of authors (18, 19) using indices insensitive to changes of end-diastolic volume, could not detect any depression of myocardial contractility in spite of a 40 mm Hg hypotension which lasted on the average 1-1/2 hour.

In returning to the main theme of our discussion, the peripheral factors, Fig. 4 presents the chain of events which may lead to a decreased venous return. The first factor which we may consider is the change in compliance of the capacitance vessels. The ideal answer would be to obtain direct evidence of the behavior and change in compliance

of the capacitance system. However, these studies are technically very difficult, and demanding. Some reports which have been published in this direction indicate that sympathomimetic stimulation leads not only to veno-constriction and to a decreased venous initial volume, but to an increased venous compliance (20, 21). These seemingly paradoxical results can be reconciled if it is assumed that the volume-pressure relationship is nonlinear and that there is a hysteresis-like shift of the curve.

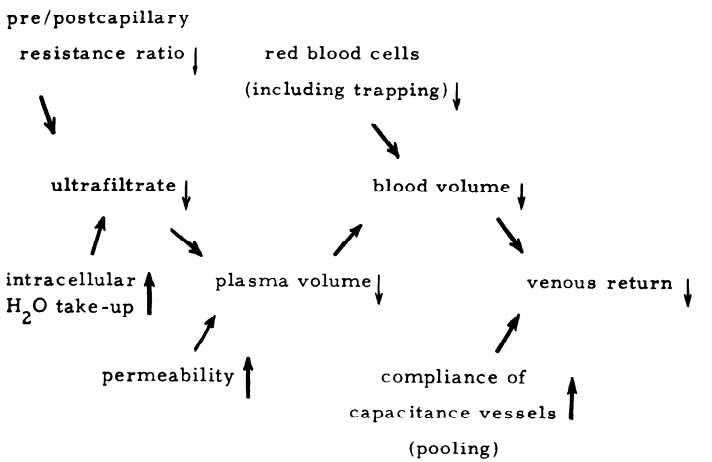

Fig.4. Alternative mechanisms leading to a decreased venous return to the heart. (By permission from B.W. Zweifach and A. Fronek. The Interplay of Central and Peripheral Factors in Irreversible Hemorrhagic Shock. Progress in Cardiovasc. Dis. 18: 147, 1975).

It can be hoped that with development of better techniques, the role of capacitance function perhaps will be answered in a more reliable way. The next possibility is a change in blood volume - decrease of blood volume. Abel and Wolfe (22) showed a decrease in blood volume following retransfusion in irreversible shock in which there was a loss of both fluids and protein, suggestive of some change in capillary permeability. On the other hand, Chien and co-workers (23) who also found a decrease of plasma volume concomitant with a drop in total plasma proteins point out that this drop is proportional to a red blood cell volume drop. They concluded that sequestration was a more acceptable explanation of such a phenomenon.

It would seem that regional blood volume determination would give an answer as to the site of blood volume decrease. However, regional blood volume measurements, particularly under low flow conditions, present many difficulties. The indicator dilution technique is one of the oldest approaches but its validity has been challenged on the basis of unreliable mean transit time determination. The arguments usually raised (24) are that there is an unreliable mixing and possibly artificially

shortened mean transit time, especially if non-nutritional channels are open. Such experiments have not served to clarify the nature or even the unequivocal existence of fluid losses. In classical microcirculation experiments in which the hydrodynamic conductivity of the capillary and venule walls in omentum and mesentery was measured, it was found that the K factor, the hydrodynamic conductivity, is unchanged even when arterial blood pressure was kept 40 to 50 mm Hg for periods up to 2-1/2 hours (25). With more severe hypotension, 35 mm for 90 minutes or longer, there was only a moderate increase in permeability. Coming back to our flow chart, we have to consider ultrafiltration. This assumption has been actually made by a number of authors, among others by Mellander and Lewis (26). They have found that the resistance and capacitance vessels have a different sensitivity to sympathetic stimulation, and they assumed that this will give rise to a decreased pre-postcapillary resistance ratio and, therefore, favor filtration. In our recently completed experiments (4), pre-and postcapillary resistance and its ratio were determined. We observed a proportional increase in pre-and postcapillary resistance, but a similar change was observed during the post-transfusion failure as is shown in Figs. 5 and 6.

These experiments of course relate only to the vascular system of the hind limb and the question remains whether similar changes occur for example in the splanchnic system. The need for such an information is apparent in view of the number of reports according to which the intestinal vascular system seems to play an important role in the irreversibility of hemorrhagic shock.

If we return to our original flowchart (Fig. 4), there is another alternative for a decreased ultrafiltrate: increased intracellular water uptake. As we discussed earlier, experimental evidence points to a progressive decrease in circulating plasma volume during the late oligemic and irreversible post-infusion phase. Much of the research has been directed towards the identification of the site of fluid leakage. The amount of fluid recovered from the lumen of the intestinal system cannot fully account for the decreased volume. In recent years, a number of reports analyzing different aspects of metabolic changes during hemorrhagic shock are offering new data. It is well established that cellular hypoxia can lead to an impaired membrane activity with an ensuing change in the electrolytic balance (27-29). Indirect evidence for such a phenomenon was obtained in muscle preparations operating under hypoxic conditions (30, 31), and in hemorrhagic shock experiments (32, 33). Campion and co-workers (34) measured the resting transmembrane potential difference in muscle cells of various animals, rats, dogs, and baboons. They found consistently a significant decrease during the deep shock phase (34-37). Along with these functional changes, there was an increase in intracellular sodium and a decrease in intracellular potassium (35, 36). Kovách and Rosell (38, 39) using the subcutaneous adipose tissue preparation of Rosell, found a substantial decrease in metabolic activity during the oligemic phase which, in contrast to other tissues, is not restored by retransfusion. One of the effects of this decrease in available energy source of adipose tissue is an increase in the water content of these cells as shown in some of our recent experiments on cats (40) during the post-transfusion irreversible phase.

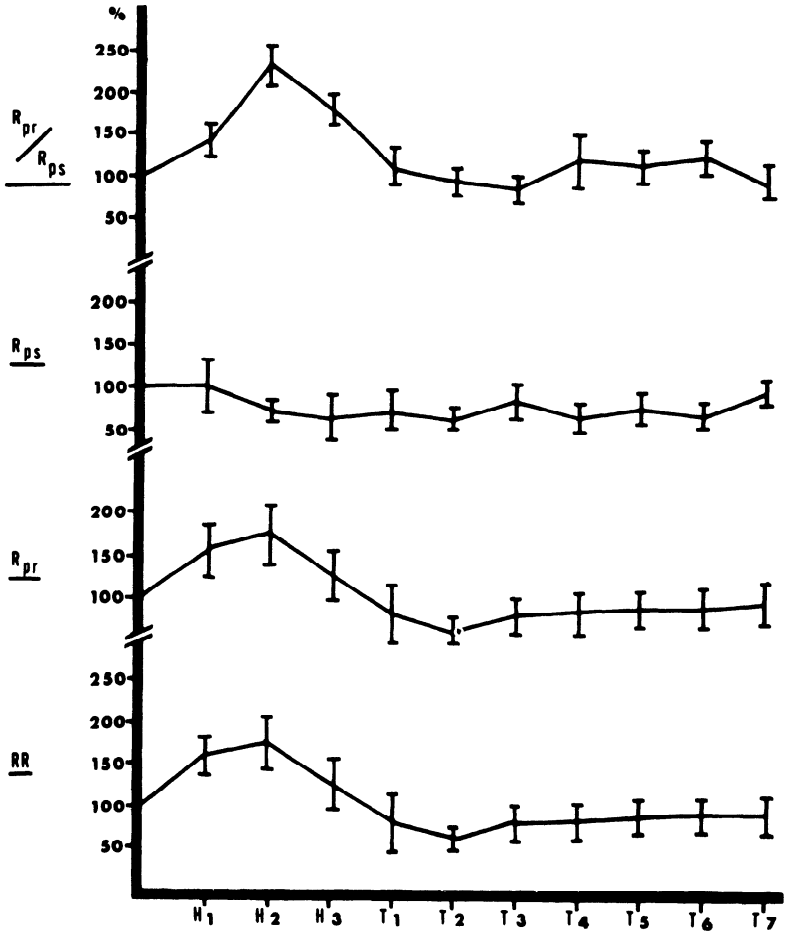

Fig.5. "Reversible" shock, calculated values (percent changes). Rpr/Rps precapillary/post-capillary resistance ratio; Rps, postcapillary resistance; Rpr, precapillary resistance; RR, regional resistance. (By permission from A. Fronek and T. Witzel. Hemodynamics of the terminal vascular bed in canine hemorrhagic shock. Surgery 75: 408, 1974).

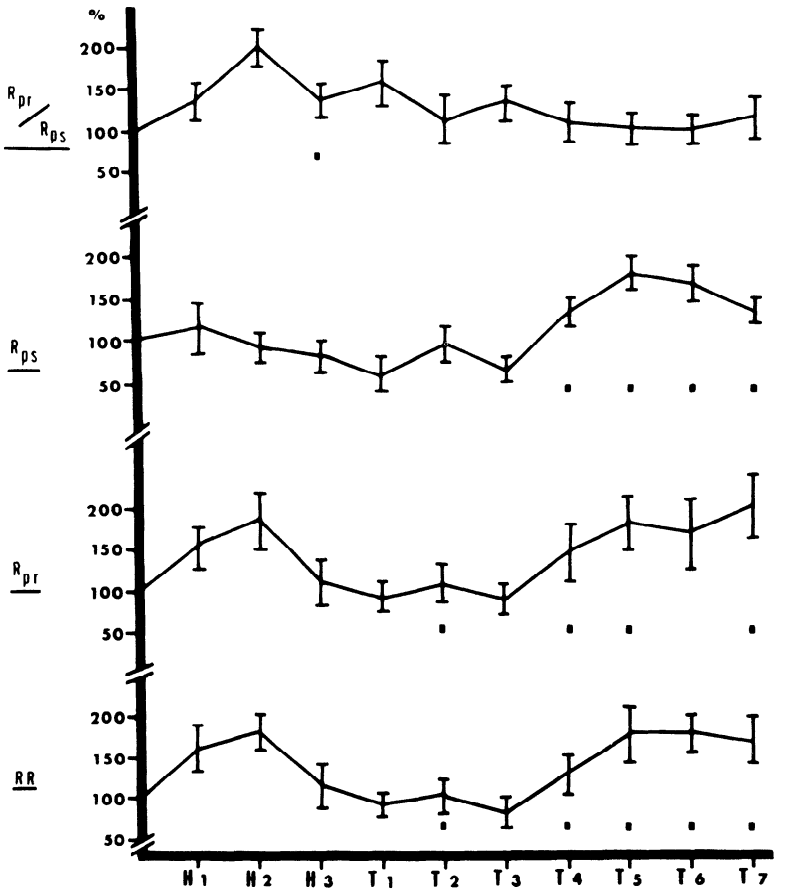

Fig.6. "Irreversible" shock, calculated values (percent change). Rpr/Rps precapillary/postcapillary resistance ratio; Rps, postcapillary resistance: Rpr, precapillary resistance; RR, regional resistance. The square (■) indicates statistically significant difference ($p < 0.05$ or better) as compared to corresponding values in Figure 5. (By permission from A. Fronek and T. Witzel. Hemodynamics of the terminal vascular bed in canine hemorrhagic shock. Surgery 75: 408, 1974).

Summarizing our discussion, the following sequence of events and working hypothesis can be postulated. During the initial low perfusion state, there is a decrease in available energy-rich resources, mainly ATP. The ensuing intracellular acidosis resulting from the switch to nonaerobic energy pathways together with a declining efficiency of the sodium pump mechanism causes an efflux of potassium from the cell accompanied by the increasing intracellular sodium concentration which will attract more water to the cell. Such a derrangement could act in a positive feedback mode to depress the already strained membrane pumping and function.

Two major questions pertinent to the pathogenesis of irreversible shock can be raised: 1) are these intracellular fluid movements of such an order of magnitude as to explain the progressive reduction in intravascular fluid volume during the post-transfusion period? 2) Are these phenomena applicable generally to all tissues, or as it seems more likely, different tissues may present different degrees of susceptability to hypoxia, and especially to cell membrane pump derrangement, for instance in intestine, kidney, adipose tissue, as opposed to the skeletal muscle cells?

Difficulties in unraveling the relative importance of the various pathogenetic pathways can be ascribed to a number of contingencies. 1) Inadequate techniques, especially as it concerns compliance measurements in intact animals, fluid fluxes and permeability determination. 2) Many otherwise carefully designed experiments have yielded seemingly contradictory results since the basic hemorrhagic shock model produced protracted coronary and cerebral hypotension as well. 3) It is highly probable that the breakdown of homeostatic mechanism does not follow a single pathway as schematically sketched in Fig. 4, but that two or more pathogenetic pathways are involved either simultaneously or are interrelated in a cause-effect relationship, operating on the basis of local positive feedback loops.

We have examined several possible mechanisms which have been suggested as contributory factors under particular experimental conditions. We assume mainly on the basis of indirect evidence that it is the impairment of basic fluid flux mechanisms between the various fluid compartments which is at the core of the problem of the irreversibility of hemorrhagic shock.

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COUNCIL OF ACADEMIC SOCIETIES BRIEF

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RECENT CONGRESSIONAL ACTION. As the 94th Congress drew to a close a large number of bills, some of them months in preparation, were hastily passed. The fate of several bills and a look ahead at the work of the next legislative session will interest the biomedical community.

Health Manpower Bill. H.R. 5546, the Health Professions Educational Assistance Act of 1976, was substantially modified in the House-Senate Conference Committee and signed by the President on October 12, 1976. The requirements medical schools must meet in order to receive capitation are: On July 15, 1977, 35% of filled first-year graduate (GME-1) positions in direct and affiliated hospitals must, in the national aggregate, be in the primary care specialties of family practice, internal medicine, and pediatrics (ob-gyn was excluded in Conference); on July 15, 1978, 40% must be in primary care; and on July 15, 1979, 50%. If these national percentages for primary care positions are not met, then only schools meeting or exceeding these percentages in their own direct and affiliated hospitals will receive capitation. The Act requires that in counting GME-1 positions in primary care, the Secretary shall discount from the total, the number who enter other training programs in their second graduate year.

A provision for U.S. citizens studying medicine abroad, which was not in either the House or Senate bills, was generated in the Conference. This provision requires that to receive capitation, schools must admit a number of students (the number to be apportioned equitably among all schools) who have successfully completed two years in a foreign school, have passed NBME Part I, and have applied to the Secretary for apportionment to a school. Specific individuals will not be assigned to schools, but schools may not deny admission on academic grounds to students who have passed Part I, NBME. This highly controversial provision encroaches on the right of faculties to select students. It is anticipated that because the provision was inserted into the Act without prior discussion or public hearings, legislative review and modification may be possible in the next Congress.

Among the other provisions, the Act authorizes special project grant support for the development of graduate programs in the primary care specialties of family practice, internal medicine, and pediatrics. It also extends the National Health Service Corps and increases the authorization levels for the Corps.

After three years of debate through two sessions of Congress, the final bill, with the exception of the U.S. foreign medical student provision, is reasonable and provides for federal support for medical education in a satisfactory manner.

1977 Labor-HEW Appropriations Bill. This $56.5 billion bill, the first appropriations bill in recent memory to be completed before the start of the fiscal year, was vetoed by President Ford at the last possible moment. Congress responded in one day with a resounding override vote. The NIH budget is thus assured with, as usual, a comfortable increase for the Cancer Institute, a lesser one for the Heart, Lung, and Blood Institute, and allowances which barely keep up with inflation for most of the rest of NIH. Training grants suffered severely in FY 1976 due to late renewal of their authorizing legislation and will continue down in 1977. For example, the National Institute of Arthritis, Metabolism, and Digestive Diseases (NIAMDD), which funds most clinical training grants, received a training appropriation of about $9 million (down from $15 million in fiscal 1975) but because of specially earmarked new programs such as the Arthritis and Diabetes Advisory Boards, NIAMDD may have less than $7 million available for training.

Other Bills. The statutory Diabetes and Arthritis Boards were created at the end of the session. Authority for emergency medical services was renewed with much more emphasis on physician and allied manpower training than in the previous law. The Clinical Laboratories bill failed despite much work and agreement as to a need for its antifraud provisions. Clinical research laboratories would have been affected by this bill and by regulations still proposed by HEW.

WHAT'S AHEAD IN 1977. Next year will be a banner year in Congress for biomedical research legislation. The Cancer Act, the Cardiovascular, Lung, and Blood authority, the Research Training Act, and HEW Appropriations must be renewed in 1977. Also, the Senate Health Subcommittee has served notice it intends to conduct a thorough review of the mission of NIH with special emphasis on ways to increase applied research, clinical trials, and the transfer of research ideas to patient care. These "technology transfer" functions will likely be the main theme for the coming year if recent hearings are indicators of the trend. The Congress will undoubtedly attempt again to increase the scientific expertise of the Food and Drug Administration. Clearly, the biomedical research community must labor skillfully and persistently to justify stable funding, basic research, and research training in the coming year. Common goals must be emphasized and partisan concerns must be played down in support of the basic policies of importance to the total endeavor.

Although, as noted above, the Clinical Laboratory Improvement Act of 1976 failed to pass, the Administration held hearings August 26, 1976 to discuss possible regulations under the Clinical Laboratory Act of 1967. The Administration believes that the best way to assure that the output of laboratories meets high standards is to require that laboratory technicians be well trained and, usually, graduates of clinical laboratory programs. Laboratories must be headed by board-certified directors. These requirements will apply to all clinical laboratories including those which are performing clinical research. Clearly, such requirements would impede clinical research. CAS/AAMC are working to modify these rules.