CONTENTS

ACTIONS TAKEN AT SPRING MEETING
April 15-20, 1968

ELECTIONS - C. Ladd Prosser was elected to the position of President-Elect. A. Clifford Barger was elected to a full four-year term on Council.

Daniel C. Tosteson was elected to fill the unexpired term of C. Ladd Prosser on Council.

All candidates nominated by Council were elected to membership. (See Newly Elected Members).

All elections are effective July 1, 1968.

NEXT ELECTION OF MEMBERS - The 1968 Fall Meeting of the Society has been cancelled due to the International Physiological Congress being held in Washington, D. C. August 25-31, 1968. Since new members are generally elected at the Society's Fall Meeting Council decided to have a mail ballot. A list of nominations recommended by Council will be sent to all voting members. Any voting member can vote against a nominee in the usual manner, by crossing a line through his name. These are to be returned to the APS Office. If a member does not wish to vote against anyone he need not return the marked ballot. Bylaws state that a two-thirds majority vote shall be necessary for election. No return of the ballot will be considered a vote for the enture list of nominees. Bylaws also state that members must be informed of who the nominees are at least one month prior to final election. The mail ballot will carry a deadline date, at least one month after mailing, probably August 1. Newly elected members will be informed sometime in August, their membership being effective January 1, 1969.

ABSTRACTS FOR 1969 SPRING MEETING - The Society agreed to follow the same rules that were authorized for the 1968 Spring Meeting - limiting the number of papers accepted for oral presentation to approximately 850. If more than 850 abstracts are received, every n^{th} paper will be excluded from oral presentation, but the abstracts will be published. No sponsored abstracts will be accepted. A person's name can appear only once on the program. An APS regular, retired or honorary member must be one of the authors.

In 1968 only 803 abstracts were received, therefore, the above rule did not have to be invoked.

STUDENT RATES FOR PHYSIOLOGICAL REVIEWS - Council approved for a three-year trial period beginning January 1969 a plan of offering Physiological Reviews to students at a reduced rate of $10 per year. Students are defined as those registered for credit toward a degree as well as those holding official appointments as interns, residents or post-doctoral fellows in North America. Certification and validity of student status, as defined above, is to be attested to by the inclusion of the signature of a regular member of APS on the

subscription order. Certification also will be necessary for renewals of student subscription orders.

The reduced student rate does not apply to any of the other APS journals.

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HANDBOOKS OF PHYSIOLOGY

During the past nine years the Society has published thirteen volumes in six sections in the Handbook series.

Section 6, Alimentary Canal, is now in production. Volume I (Food and Water Intake) and Volume II (Secretion) were published in 1967. Volume III (Intestinal Absorption) was published in January 1968. Volume IV (Motility) and Volume V (Bile; Digestion; Ruminal Physiology), which complete the series on the Alimentary Canal will be published in the Fall of 1968. C. F. Code is the Section Editor and W. Heidel is Executive Editor. Members of the Editorial Committee are J. R. Brobeck, R. K. Crane, H. W. Davenport, M. I. Grossman, H. D. Janowitz, C. L. Prosser, and T. H. Wilson.

Forthcoming sections, now in the planning stage are:

Section 7, Renal and Electrolyte Physiology. Editors are R. W. Berliner and J. Orloff.

Section 8, Endocrinology. Editors are R. O. Greep and E. B. Astwood.

Also in the planning stage is a revision of the three volumes of the Neurophysiology Section.

Physiology Society members receive a discount on all volumes and should place their orders through the Society Office, 9650 Rockville Pike, Bethesda, Maryland 20014. Non-members should send orders to The Williams and Wilkins Company, 428 East Preston Street, Baltimore, Maryland 21202.

MEMBERSHIP STATUS

April 1, 1968

Active Members	2860
Retired Members	159
Honorary Members	18
Associate Members	218
	3255

SUSTAINING ASSOCIATES

Abbott Laboratories, Inc.
Ayerst Laboratories
Burroughs Wellcome & Co.
CIBA Pharmaceutical Products
Gilford Instrument Laboratories
Gilson Medical Electronics
Grass Instrument Co.
Harvard Apparatus Co.
Hoffman-LaRoche Laboratories
Lakeside Laboratories
Eli Lilly & Co.
Merck Sharp & Dohme Laboratories
The Norwich Pharmacal Co.
Chas. Pfizer & Co.
Riker Laboratories, Inc.
The Squibb Institute
The Upjohn Co.
Warner-Lambert Research Institute
Wyeth Laboratories

DEATHS SINCE FALL MEETING 1967

Chester W. Darrow - 4/7/67
Virginia D. Davenport - 3/24/68
Daniel M. Green - 3/16/68
John Haldi - 12/4/67
Henry N. Harkins - 8/12/67
Carl G. Hartman - 3/1/68
Charles L. Hess - 2/25/68
Kenneth N. Ogle - 2/22/68
Harold F. Pierce - 5/6/63
J. Paul Quigley - 11/21/67
Carlos I. Reed - 12/6/67
Stanley P. Reiman - 2/21/68
Wayne G. Rohse - 10/25/67
Ferdinand J.M. Sichel - 4/11/68
Henry W. Schoenborn - 9/2/67

50-YEAR MEMBERS

Walter C. Alvarez
Samuel Amberg
Aaron Arkin
George A. Baitsell
Olaf Bergeim
Harold C. Bradley
Thorne M. Carpenter
Percy M. Dawson
George Fahr
Mabel P. Fitzgerald
Maurice H. Givens
Charles M. Gruber
Addison Gulick
Frank A. Hartman
Harold L. Higgins
Paul E. Howe
Andrew C. Ivy
Dennis E. Jackson
Edward C. Kendall
Benjamin Kramer
Henry Laurens
Edward Lodholz
David Marine
Jesse F. McClendon
Franklin C. McLean
Frederick R. Miller
Victor H. K. Moorhouse
Sergius Morgulis
Eugene L. Opie
Julius M. Rogoff
George B. Roth
Andrew H. Ryan

Benjamin H. Schlomovitz
Charles D. Snyder
George H. Whipple
Rosalind Wulzen

NEWLY ELECTED MEMBERS

The following, nominated by Council, were elected to membership in the Society at the Spring meeting, 1968.

ABILDGAARD, Charles F.: Assoc. Prof. Ped., Univ. of Illinois
ADOLPH, Robert J.: Dir. Bioelectronics Lab., Cincinnati Gen. Hosp.
AGERSBORG, Helmer P. K., Jr.: Asst. Dir., Res. Div., Wyeth Labs.
AKUTSU, Tetsuzo: Assoc. Prof. Surg., Univ. of Mississippi Med. Ctr.
ALVARADO, Francisco: Assoc. Prof. Pharmacol., Univ. Louisville
ANDREOLI, Thomas E.: Asst. Prof. Med. & Physiol., Duke Univ.
ANDREWS, Richard V.: Assoc. Prof. Biol., Creighton Univ.
BAILE, Clifton A.: Instr. Nutrition, Harvard Sch. Public Health
BASHOUR, Fouad A.: Assoc. Prof. Med., Univ. Texas Southwestern
BAUMAN, John W., Jr.: Chief Endocrinol., Bur. Res., Princeton, N.J.
BIBER, Thomas U. L.: Asst. Prof. Physiol., Yale Univ. Sch. Med.
BOWMAN, Robert E.: Assoc. Prof. Psychol., Wisconsin Reg. Primate Ctr.
BRANSOME, Edwin D., Jr.: Asst. Prof. Exptl. Med., Mass. Inst. Tech.
BUSH, Ian E.: Sr. Sci., Worcester Fndn. Exptl. Biol.
CHERNICK, Victor: Assoc. Prof. Physiol. & Ped., Univ. of Manitoba
CHEZ, Ronald A.: Asst. Prof. Ob-Gyn., Univ. of Pittsburgh
CLARKE, Neville P.: Chief, Biodynamics Div., Brooks AFB, Texas
CRONIN, R. F. Patrick: Asst. Prof. Med. & Physiol., Montreal Gen. Hosp.
DAVIDSON, John K. III: Assoc. Prof. Physiol., Univ. of Toronto
DAVIS, Larry Dean: Asst. Prof. Physiol., Univ. of Wisconsin Med. Sch.
DEL GUERCIO, Louis R. M.: Assoc. Prof. Surg., Albert Einstein Coll. Med.
DE MELLO, Walmor C.: Assoc. Prof. Pharmacol., San Juan, Puerto Rico
DEREN, Julius J.: Dir. G.I. Research, Maimonides Hosp.
DUNSON, William A.: Asst. Prof. Biol., Pennsylvania State Univ.
EARLEY, Laurence E.: Assoc. in Med., Harvard Med. Sch.
EBERSTEIN, Arthur: Asst. Prof. Rehabil. Med., Inst. Rehabil. Med.
FAULKNER, John A.: Assoc. Prof. Physiol., Univ. of Michigan
FINN, Arthur L.: Asst. Prof. Physiol. & Med., Yale Univ. Sch. Med.
FIORICA, Vincent: Res. Physiologist, Fed. Aviation Admin., Oklahoma City
FIRSCHEIN, Hilliard E.: Asst. Prof. Biochem., Hosp. for Spec. Surgery
FRANK, Morton H.: Asst. Prof. Physiol., New York Med. Coll.
FROMMER, Peter L.: Acting Chief, Myocard. Infarction Br., NIH
FUNG, Yuan-Cheng B.: Prof. Bioengr. & Appl. Mechanics, Univ. of California
GALLAGHER, Neil I.: Chief of Staff, Dir. St. Louis Med. Serv., VA Hosp.
GARFINKEL, David: Assoc. Prof. Biophysics, Univ. Pennsylvania
GIAMMONA, Samuel T.: Assoc. Prof. Ped., Univ. Miami Child Devel. Ctr.
GILBOE, David D.: Asst. Prof. Surg. & Physiol., Univ. Hosps., Madison
GILLESPIE, Jerry R.: Asst. Prof. Cardiopul. Lab., Univ. Calif., Davis

GINSKI, John M.: Assoc. Prof. Physiol. & Biophys., Univ. Tennessee
GLOOR, Pierre: Assoc. Prof. Neurol. & Neurosurg., Montreal Neurol. Inst.
GOLDBERG, Martin: Assoc. Prof. Med., Univ. of Pennsylvania
GOLDRING, Roberta M.: Asst. Prof. Med., New York Univ.
GOLDSMITH, Harry L.: Asst. Prof. Exptl. Med., Montreal Gen. Hosp.
GRUPP, Gunter: Prof. Exptl. Med., Univ. of Cincinnati
HAMMEN, Carl S.: Assoc. Prof. Zool., Univ. of Rhode Island
HANSON, Kenneth M.: Asst. Prof. Physiol., Ohio State Univ.
HARMISON, Charles R.: Asst. Prof. Physiol. & Pharmacol., Wayne State Univ.
HART, Benjamin L.: Asst. Prof. Anat. & Psychol., Univ. California, Davis
HEGYELI, Andrew F.: Sr. Res. Pathologist, Battelle Mem. Inst., Columbus, Ohio
HERMANN, Howard T.: Dir. Neurophysiol. Res. Lab., Mass. Gen. Hosp.
HIGGINS, E. Arnold: Res. Physiologist, Civil Aeromed. Inst., Oklahoma City
HONRUBIA, Vicente: Asst. Prof. Physiol. & Surg., Vanderbilt Univ.
HRUZA, Zdenek: Res. Prof., Dept. Pathol., New York Univ. Sch. Med.
INESI, Giuseppe: Asst. Prof. Pharmacol., Univ. California, S.F.
JANE, John A.: Asst. Prof. Neurosurg., Western Reserve Univ.
KAHN, Norman: Asst. Prof. Pharmacol., Columbia Univ. Coll. P & S
KAPLAN, Manuel E.: Asst. Prof. Med., Washington Univ.
KASHGARIAN, Michael: Asst. Prof. Pathol., Yale Univ. Sch. Med.
KNAPP, Francis M.: Asst. Prof. Biol. Sci., Duquesne Univ.
KRAUSS, Stephen: Res. Assoc. Dept. Hematology, Mt. Sinai Hosp.
LARSON, Charles P., Jr.: Asst. Prof. Anesthesia, Univ. California, S.F.
LIPICKY, Raymond J.: Asst. Prof. Pharmacol., Univ. Cincinnati
LITTLE, John B.: Asst. Prof. Rad. Biol., Harvard Sch. Public Health
LIU, Frank T.Y.: Assoc. Prof. Physiol., Univ. of Pittsburgh
LOURENCO, Ruy V.: Assoc. Prof. Med., New Jersey Coll. Med.
MARCINIAK, Ewa J.: Res. Assoc. Physiol. & Pharmacol., Wayne State Univ.
MAUDE, David L.: Asst. Prof. Physiol., New York Med. Coll.
McDONALD, Robert H., Jr.: Asst. Prof. Med. & Pharmacol., Univ. of Pittsburgh
McILWAIN, James T.: Asst. Prof. Physiol., Univ. of Cincinnati
McKENZIE, Jess M.: Chief, Stress Physiol., Aeromed. Res. Br., Oklahoma City
MELMON, Kenneth L.: Asst. Prof. Med. & Pharmacol., Univ. California, S.F.
MOORHOUSE, John A.: Assoc. Prof. Physiol., Univ. of Manitoba
MOSESSON, Michael W.: Asst. Prof. Med., State Univ. New York, Downstate Med. Ctr.
NAIR, Kappiareth G.: Asst. Prof. Med. & Physiol., Univ. of Chicago
NELSON, Darren M.: Assoc. Res. Prof. Ob-Gyn., Univ. of Oklahoma
NICOLL, Charles S.: Asst. Prof. Physiol., Univ. California, Berkeley
NYHUS, Lloyd M.: Prof. Surg., Univ. of Illinois
OAKLEY, Bruce: Asst. Prof. Zool., Univ. of Michigan
OLSSON, Ray A.: Res. Internist, Dept. C.V. Dis., Walter Reed Army Inst. Res.

ORKAND, Richard K.: Asst. Prof. Physiol., Univl of Utah Med. Ctr.
PHILLIPS, Richard D.: Res. Physiologist, U. S. Naval Rad. Def. Lab., San Francisco
PILAR, Guillermo R.: Asst. Res. Prof. Physiol., Univ. of Utah Med. Ctr.
PITTMAN, James A., Jr.: Prof. Med., Dir. Endocrinol. & Metabolism, Univ. of Alabama
POLLAY, Michael: Asst. Prof. Neurosurg., Univ. of New Mexico
QUINLIVAN, William L. G.: Assoc. Prof. Gyn-Obstet., UCLA
RAMSAY, Allan G.: Assoc. Prof. Physiol., Univ. of Alabama Med. Ctr.
RAMWELL, Peter W.: Sr. Scientist, Worcester Fndn. for Exptl. Biol.
REYNOLDS, Leslie B., Jr.: Assoc. Prof. Physiol., Univ. Tennessee
SCHERLAG, Benjamin J.: Res. Physiologist, USPHS Hosp., Staten Island
SCHEUER, James: Asst. Prof. Med., Univ. of Pittsburgh
SCHILDER, Donald P.: Dir. Pulmonary Physiol., VA Hosp., West Haven, Conn.
SEN, Amar K.: Assoc. Prof. Pharmacol., Univ. of Toronto
SILEN, William: Prof.Surg., Harvard Med. School
SOELDNER, John S.: Instr. Med., Harvard Med. School
SPANN, James F., Jr.: Sr. Invest., Cardiology Br., NIH
SPARKS, Harvey V.: Asst. Prof. Physiol., Univ. of Michigan
SUGIOKA, Kenneth: Prof. Surg., Div. Anesthesiol., Univ. North Carolina
SULLIVAN, Francis J.: Res. Physiol., Arctic Aeromed Lab.
SULLIVAN, Maurice F.: Mgr. Physiol. Sect., Battelle Mem. Inst., Richland, Wash.
SURKS, Martin I.: Res. Invest., Montefiore Hosp. & Med. Ctr.
SUSSMAN, Karl E.: Asst. Prof. Med., Asst. Dir. Univ. Colorado Med. Ctr.
TAYLOR, Aubrey: Postdoctoral Fellow, Biophys. Lab., Harvard Med. School
THEIL, George B.: Assoc. Prof. Med., Univ. of Iowa
THIES, Roger E.: Assoc. Prof. Physiol., Univ. of Oklahoma Med. Ctr.
VAN HUSS, Wayne D.: Prof. Health & Phys. Ed., Michigan State Univ.
VEITH, Frank J.: Assoc. Prof. Surg., Albert Einstein Coll. Med.
VESSELL, Elliot S.: Head, Sect. Pharmacogenetics, NIH
VOGEL, John H. K.: Asst. Prof. Med., Univ. of Colorado Med. Ctr.
von BAUMGARTEN, Rudolf J.: Prof. Physiol., Univ. of Michigan
WALLACE, Andrew G.: Asst. Prof. Med., Duke Univ.
WAYLAND, Harold: Prof. Engr. Sci., California Inst. Technology
WEINER, Daniel E.: Asst. Prof. Physiol., Univ. of Virginia
WENNEMARK, James R.: Assoc. Prof. Med., Univ. of Tennessee
WILLIAMSON, John R.: Assoc. Prof. Biophys. & Phys. Biochem., Univ. of Pennsylvania
ZIMMERMAN, Arthur M.: Prof. Dept. Zool., Univ. of Toronto

ASSOCIATE MEMBERS

BASSETT, Arthur L.: Postdoctoral Fellow, Columbia Univ., Pharmacol.
BENNETT, Marvin, H.: Instr. Anatomy, Louisiana State Univ. Med. Ctr.
BIGGER, John T., Jr.: Assoc. Fellow, Pharmacol., Columbia Univ.
BUNCH, Wilton H.: Med. Fellow, Orthopedics, Univ. of Minnesota
CRILL, Wayne E.: Asst. Prof. Physiol. & Biophys., Univ. Washington

DETAR, Reed L.: Grad Student, Instr. Physiol., Univ. of Michigan
DOBRIN, Philip B.: NIH Predoctoral Fellow, Physiol., Loyola Univ.
GRONWALL, Ronald R.: Asst. Prof. Physiol., Kansas State Univ.
JACQUES, Felix A.: Assoc. Prof. Biol., St. Bonaventure Univ., N.Y.
LEBOVITZ, Robert M.: Doctoral Candidate, Physiol. Dept., UCLA
MAACK, Thomas M.: Adv. Res. Fellow - Physiol., Upstate Med. Ctr.
MARQUIS, Norman R.: Res. & Teaching Fellow, Biol. Chem., Harvard Univ.
MAYERLE, Joan A.: USPHS Trainee Physiol., Univ. California, S.F.
MULIERI, Louis A.: Grad Student, Physiol. & Biophys., Univ. Vermont
OVERBECK, Henry W.: Assoc. Prof. Physiol., Michigan State Univ.
PRATT, Alfred J.: Res. Physiologist, 657st Aeromed. Res. Lab.
SAYEED, Mohammed M.: Asst. Prof. Physiol., Illino s State Univ.
SOLOMON, Lura Ann: Physiologist, Res. Div., VA Hosp., Oklahoma City
STIRLING, Charles E.: Instr. Physiol., Upstate Med. Ctr.
TOWNSEND, Alexandra A.: Res. Assoc., Physiol. & Pharmacol., Chicago Coll. Osteopathy
WENDLING, Michael G.: Res. Assoc. Internal Med., Univ. of Iowa Hosps.
WORTH, William S.: Res. Physiol. Pharmacol., Univ. of Colorado
ZIMMERMAN, Irwin D.: Instr. Physiol. & Biophys., Woman's Med. Coll., Pennsylvania

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FUTURE MEETINGS

1968 - Fall - Cancelled because of IUPS Congress

1968 - IUPS - Washington, D.C., August 25-30

1969 - Spring - Atlantic City, N.J., April 13-18

1969 - Fall - Univ. of California, Davis, California, Aug. 25-29

1970 - Spring - Atlantic City, N.J., April 12-17

1970 - Fall - Indiana Univ., Bloomington, August 30-September 3

1971 - Spring - Chicago, Ill., April 12-17

1971 - Fall - Univ. of Kansas, Lawrence and Kansas City

1972 - Spring - Atlantic City, N.J., April 9-14

1972 - Fall - Council invites invitations from university groups

1967 FISCAL REPORTS

SOCIETY OPERATING FUND

INCOME

Regular Membership Dues	$40,354
Associate Membership Dues	1,065
Sustaining Associates	6,700
Interest	6,224
Reimbursement from Federation Spring Meeting	15,433
Fall Meeting (net)	3,648
Sale of Laboratory Experiments	484
Sale of Back Issues of Physiology for Physicians	437
Insurance Dividend	410
Miscellaneous Income	312
Total Income	$75,067

EXPENSES

Salaries and Benefits	$25,017
Hotel and Travel	2,685
Addressing, Mailing & Shipping	1,536
Telephone	150
Printing	2,125
Supplies and Equipment	777
Career Brochures (printing)	2,223
Rent	4,660
Dues to Federation	16,548
Dues to AIBS	750
Dues to AAAS	20
Dues to Natl. Soc. Med. Res.	250
Dues to Council Academic Societies	100
Dues to Amer. Soc. Assoc. Executives	65
Education Committee	712
Bowditch Lecture	500
Miscellaneous Expenses	415
APS Business Office (SOF share)	13,685
Total Expenses	$72,218

Excess of Income over Expenses	$2,849
Reserves in Savings and Short Term Investments	$88,505

PUBLICATION OPERATING FUND

INCOME

Subscriptions	$383,287
Sale of Reprints (net)	74,127
Sale of Back and Single Issues	16,565
Advertising (net)	25,743
Page and Article Charges	117,800
Author Alterations	690
Interest	9,909
Royalties	1,967
Insurance Dividend	1,640
Miscellaneous Income	143
Total Income	$631,871

EXPENSES

Salaries and Benefits	$103,615
Section Editors Expenses	21,284
Professional Services	2,645
Printing and Engraving	347,731
Supplies and Equipment	1,635
Addressing, Mailing & Shipping	39,829
Telephone	1,283
Hotel and Travel	7,063
Repairs and Maintenance	297
Rent	14,398
Dues and Assessments	104
Miscellaneous	46
APS Business Office (POF share)	54,741
	$594,671
Assigned to Special Publications	(11,358)
Total Expenses	$583,313

Excess of Income over Expenses	$48,558

BUSINESS OFFICE EXPENSES

Salaries and Benefits	55,335
Supplies and Equipment	2,571
Mailing	238
Telephone	225
Hotel and Travel	716
Audit and Legal Fees	2,750
Rental of Equipment	394
Insurance	179
Federation Service Charge	2,612
Rent	9,566
Repairs and Maintenance	819
Dues and Assessments	55
Printing	296

Miscellaneous Expenses	8
	$75,764
Less Overhead on Projects	(1,611)
Less APS share of dissolution of Physiol. and Pharm. for Physicians	(5,727)
Total	$68,426
Allocated to SOF	(13,685)
Allocated to POF	(54,741)

PUBLICATION CONTINGENCY AND RESERVE FUND

Balance Dec. 30, 1966 (market value)	$792,061
Dividend and Interest Paid to APS	$27,941
Balance Dec. 29, 1967 (market value)	$1,033,032
Increase in market value	$240,971

SPECIAL PUBLICATIONS (HANDBOOKS) SUMMARY

As of December 31, 1967 the Handbook operation, covering the entire period since its inception in 1959, showed a net of approximately $52,000 still to be recovered from sales in order for the Society to break even on its investment. However, in 1968 three more volumes will be published which will very substantially increase the deficit. As sales increase the deficit will decrease. Prices for the Handbooks are set to reflect an eventual break even operation and no allowance is made to show a profit. At no one time has there been an excess of income over costs. The Society considers the publication of the Handbooks as a service to Physiology and does not expect to do more than possibly break even on its investment over a period of years.

THE AMERICAN PHYSIOLOGICAL SOCIETY ANNOUNCES ESTABLISHMENT OF THE JOHN FORBES PERKINS, JR., MEMORIAL FUND IN SUPPORT OF INTERNATIONAL EXCHANGES IN PHYSIOLOGY

An important contribution to International Physiology has been made by the family and friends of John Forbes Perkins, Jr. late Professor of Physiology at the University of Chicago and long a devoted and respected member of the American Physiological Society. The Memorial has been established as a permanent Fund to aid and encourage international exchanges in Physiology. The initial program is designed to provide supplementary support for the families of foreign physiologists who have been awarded Fellowships or sabbatical leave to carry out scientific work in the United States. Preference will be given to foreign physiologists in the fields of respiratory or neurophysiology; in exceptional cases, however, the fund may be used in support of U.S. physiologists who have been invited to work in a foreign laboratory and who can demonstrate the need for additional financial assistance to include their families. It is the general purpose of the Memorial to develop the full potentialities for cultural benefit associated with this type of exchange.

This general purpose would indeed have been close to John Perkins' heart. Both he and his wife, Frances Williams Perkins, maintained a special interest in welcoming foreign scholars to their home and many a physiologist from abroad enjoyed the warm and gracious hospitality of the Perkins family.

Dr. Perkins was born February 9, 1909, eldest son of Mary Coolidge and Judge John Perkins. He attended Milton Academy, Harvard College and Harvard Medical School, receiving his M.D. degree in 1936 with the intention of training for surgery. During his internship at the Massachusetts General Hospital he fell seriously ill with rheumatic fever and was forced to give up his original plans. After a long period of convalescence he returned to Harvard as Tutor in Biochemical Sciences and later as Instructor in Physiology, in which capacity he served as a strong member of the teaching staff led by Eugene Landis and Horace Davenport. His early work at Harvard was on temperature regulation and on the visco-elastic properties of smooth muscle but at this time also he became interested in respiratory physiology. After moving to the department of Physiology at the University of Chicago in 1947 he developed his interests in respiration, first in the clinical application of oximetry to chest surgery and later to fundamental studies of the chemical control of pulmonary ventilation. He made many contributions to the physiology of the carotid bodies and he soon became a respected and warmly appreciated member of the international family of respiratory physiologists. One of the high points of his career was his symposium paper on the chemical control of breathing given at the Haldane Centennial in Oxford. Dr. and Mrs. Perkins and their three children spent a sabbatical year in Germany, France and England where they renewed and cemented friendships with foreign colleagues. During this period also Dr. Perkins collected illustrations and other material for his History of Respiratory Physiology which forms the first chapter in the APS Handbook on Respiration. It is safe to say that this

scholarly article, with its remarkable collection of illustrations, will occupy a leading place in its field for many years to come.

John Perkins had a deep interest in people and this won him many close friends from all branches of physiology and from many different sectors of the academic community at Chicago. He was unusually close to his students and remembered their names and personalities for years after they graduated from medical school.

Although Dr. Perkins suffered from illness at various times in his life, he always gave the appearance of ruggedness. He was an ardent and accomplished sailor and skiier and he thought nothing of swimming in the frigid Maine waters off the island of Vinyl Haven where he spent the summers of his childhood. He was a cousin of Alexander Forbes whom he resembled both physically and in character. Like his famous cousin, he was slightly deaf in one ear and a wonderful sight at the Spring meetings of our Society was to see Cousin Alex and Cousin Johnny shouting affectionately to each other, each with a hand cupped behind one ear.

Dr. Perkins died suddenly on August 6, 1966 shortly after returning from a Symposium at Oxford, and in the full flower of his career. He will be greatly missed by many members of our Society and especially by his intimate friends in the field of respiration. It is greatly to be hoped that the Perkins Memorial Fund, now established by his family and friends, will fulfill and support the high purposes and high standards which guided John Perkins throughout his life.

Applications for the Perkins Award

Each application for an award will be made jointly by the visiting scientist and his host. Ordinarily the joint applicants will have made financial arrangements for the visiting scientist himself before applying to the Perkins Fund for family support. The application will contain an account of these arrangements, together with a description of the proposed scientific work and a brief account of how the visitor and his family intend to make use of the cultural benefits.

The amount available for each award will be in the range $3000 - $7500 depending upon the estimated needs of the family over and above the amount available for the visiting scientist himself.

The first award from the Perkind Fund will be available for the academic year beginning in September 1968. Applications for the award may be made at any time and will be reviewed at appropriate intervals by the Perkins Memorial Fund Committee of the American Physiological Society. Application forms and further information may be obtained from Dr. Ray Daggs, Executive Secretary, American Physiological Society, 9650 Rockville Pike, Bethesda, Maryland 20014.

PERKINS MEMORIAL FUND COMMITTEE

J. R. Pappenheimer, Chairman
R. E. Forster
H. Rahn
J. R. Brobeck
R. G. Daggs, Exec. Secy-Treas.

COUNCILMAN'S TOUR

C. LADD PROSSER

During the past few months I have had the opportunity to visit seven state universities, all of which may be considered as "developing universities". Four of these have medical schools, three do not; two of the latter were teachers' colleges some ten years ago, and physiology in one of these was primarily for physical education students.

One of my objectives in visiting this type of developing institution was to observe the status of general physiology in universities with medical schools as compared to those without such schools. The sample of institutions is small, but my conclusions are strengthened by visits to similar institutions during previous years.

The physiologists in non-medical departments are usually in a zoology or biology department where they constitute a minority of the staff. Even where separate physiology departments exist, they are small compared with zoology. This inevitably leads to some insecurity and lack of ability to influence policy decisions in the life sciences. In general, teaching loads are heavier than in medical schools when computed for the entire year, although one exception to this was noted. The physiologists in non-medical departments are more dependent on institutional funds for equipment, and a majority of the general physiologists in the developing state universities have no federal grants. They may have small grants from local sources, but they are often not able to compete for NSF and NIH funds.

There is relatively little interchange between medical physiology departments and the physiologists in biology or zoology. The latter may attend seminars in the medical school, but very rarely do the medical physiologists attend a seminar in biology. Joint appointments, cross-listed courses and shared direction of graduate students are much rarer than I had expected to find them. The physiologists in medical schools have more research funds and tend to take a condescending big-brother attitude toward the physiologists in biology.

I should qualify any conclusion regarding relative quality of research by stating that I am familiar with a number of larger and older universities, both state and private, where physiology in the biology departments is of first quality. Yet even in these the exchange with the medical physiologists is minimal. In the developing schools, research output is low and quality not of first order among general physiologists.

One reason for the state of some of our colleagues in biology is that in a given discipline or subdiscipline like physiology, there needs to be a critical mass of persons for maximum effectiveness. There needs to be intellectual discourse, criticism and shared students. No biology department should be satisfied with only one or two physiologists. Where separate departments of physiology exist, or divisions within large biology departments, the situation is better than where the few physiologists are submerged.

It is my contention that all physiology is one, that the study of function has much in common for all kinds of organism. If this is true, the medical physiologists have much to learn from the general physiological approach. In fact many medical physiologists are good cellular and comparative scholars, and they would do well to cultivate their counterparts in the biology departments.

What can the American Physiological Society do to promote the unity of physiology and to help the general physiologists in developing institutions? Some joint fall meetings of the APS with the comparative and general physiological societies might be useful. A number of the teachers with whom I talked asked for a resumption of the summer workshops and the visiting lecturer program which our Education Committee formerly sponsored. A small grants program would be extremely useful, if one of the agencies would undertake it, preferably under the aegis of our Society.

The population pressure and the importance of education are forcing the development of many new institutions and the enlargement of many that were small teaching colleges a few years ago. I enjoyed visiting some of these, and I believe that it is the responsibility of our Society to help physiologists in these developing universities to become productive and reputable scholars.

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AUGUST 1968 ISSUE OF THE PHYSIOLOGIST

Normally the August issue of The Physiologist is made up entirely of abstracts to be presented at the Society Fall Meeting. Since the 1968 Fall Meeting has been cancelled due to the Physiological Congress meeting in Washington, D. C., August 25-31 the August issue of the Physiologist will contain a short history and write-up of the Society. In addition to being distributed to members and subscribers as a regular issue copies will be made available to those persons attending the Congress when they visit the APS Central Offices on the afternoons of August 27, 28 and 29 as outlined in the announcement of the Congress.

BOWDITCH LECTURE

Dr. Eugene Braunwald, Professor and Chairman of the Department of Medicine at the University of California, San Diego, has been chosen to give the thirteenth Bowditch Lecture at the XXIV International Congress of Physiological Sciences in Washington, D. C., on Friday, August 30th, at 4:00 PM in the Empire Room of the Shoreham Hotel. The title of his lecture will be "The Determinants of the Oxygen Consumption of the Heart."

SATELLITE SYMPOSIA

These symposia are initiated, organized and financed independently of the XXIV International Congress of Physiological Sciences. For further information about any satellite symposium, please write directly to the organizer whose name and address is given below.

Cerebral and Cerebellar Motor Control
Sept. 2-3, Elizabeth Seton College, Yonkers, N. Y.
Dr. V. B. Brooks, New York Medical College
New York, N. Y. 10029

Olfaction and Taste
Aug. 19-21, New York City
Dr. C. Pfaffmann, Rockefeller Univ.
New York, N. Y. 10021

Regulation of Food and Water Intake
Sept. 1-3, Haverford, Pa.
Dr. A. N. Epstein, Univ. of Pennsylvania
Philadelphia, Pa. 19104

Molecular Basis of Membrane Function
Aug. 20-23, Durhan, N. C.
Dr. D. C. Tosteson, Duke Univ.
Durham, N. C. 27706

Comparative Physiology of Excitable Membranes
Sept. 1-3, Albert Einstein Coll. of Med., New York City. Dr. M. V. L. Bennett, Albert Einstein Coll. of Med., New York, N. Y. 10461

Intestinal Transport
Sept. 4-5, Indianapolis, Indiana
Dr. W. McD. Armstrong, Indiana Univ. Med. Ctr.
Indianapolis, Ind. 46207

Biological Significance of Electrogenic Ion Pumps
Aug. 24, Bethesda, Md.
Dr. W. H. Marshall, National Institutes of Health
Bethesda, Md. 20014

Carbon Dioxide: Chemical, Biochemical and Physiological Aspects
Aug. 20-21, Haverford, Pa.
Dr. R. E. Forster, Div. of Graduate Medicine, Univ. of Pennsylvania, Philadelphia, Pa. 19104

Airway Dynamics
Aug. 22-23, Haverford, Pa.
Dr. A. Bouhuys, John B. Pierce Foundation Laboratory
New Haven, Conn. 06519

Altitude and Cold
Sept. 2-6, Aspen, Colorado
Dr. R. E. Smith, Univ. of California Sch. of Veterinary Medicine
Davis, Calif. 95616

Physiological and Behavioral Temperature Regulation
Aug. 19-23, New Haven, Conn.
Dr. J. D. Hardy, John B. Pierce Foundation Laboratory
New Haven, Conn. 06519

Conference on Depressed Metabolism
Aug. 22-23, Washington, D. C.
Dr. X. J. Musacchia, Univ. of Missouri Sch. of Medicine, Columbia, Mo. 65201

Pulmonary Circulation
Aug. 31-Sept. 2, Chicago, Ill.
Dr. A. P. Fishman, Michael Reese Medical Center
Chicago, Ill. 60616

Comparative Physiology of the Heart
Sept. 2-3, Hanover, N. H.
Dr. F. V. McCann, Dartmouth Medical School
Hanover, N. H. 03755

Dynamics of Thrombus Formation and Dissolution
Aug. 31, Washington, D. C.
Dr. M. M. Guest, Univ. of Texas Medical Branch, Galveston, Texas 77550

Exocrine Glands
Aug. 22-23, Philadelphia, Pa.
Dr. S. Y. Botelho, Div. of Graduate Medicine, Univ. of Pennsylvania, Philadelphia, Pa. 19104

Lactogenesis
Aug. 24, New Bolton Center, Pa.
Dr. M. Reynolds, Sch. of Veterinary Medicine, Univ. of Pennsylvania, Philadelphia, Pa. 19104

VISITING PHYSIOLOGISTS

There will be many foreign physiologists attending the XXIV International Congress of Physiological Sciences in Washington, D. C. August 25-31, 1968. The Organizing Committee for the Congress has set up a Visiting Physiologists Committee to coordinate visits of foreign physiologists to various institutions and laboratories. If any group wishes to have visitors before or after the Congress arrangements can be made by contacting the member of the Committee nearest to the host institution. Committee members and addresses are:

C. McC. Brooks, Chairman
State U. New York
Downstate Med. Ctr.
Brooklyn, N.Y. 11203

E. F. Adolph
U. of Rochester
Sch. of Med. and Dentistry
Rochester, N.Y. 14620

L. M. N. Bach
Tulane U. Sch. Med.
New Orleans, La. 70112

A. C. Barger
Harvard U. Med. Sch.
Boston, Mass. 02115

J. R. Brobeck
U. of Pennsylvania Sch. Med.
Philadelphia, Pa. 19104

C. F. Code
Mayo Fndn., U. of Minnesota
Rochester, Minn. 55901

P. J. Cordeau
U. of Montreal
Montreal, Quebec, Canada

C. Eyzaguirre
U. of Utah Coll. Med.
Salt Lake City, Utah, 84112

L. Irving
Inst. Arctic Biol.
U. of Alaska
College, Alaska 99701

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U. Faculty Medicine
Mexico, D.F., Mexico

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Vancouver, B. C., Canada

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Los Angeles, Calif. 90024

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Gainesville, Fla. 32601

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Nashville, Tenn. 37203

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Seattle, Wash. 98105

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Urbana, Ill. 61801

T. A. Rogers
U. of Hawaii
Honolulu, Hawaii 96822

D. C. Tosteson
Duke Univ.
Durham, N. C. 27706

A STATEMENT RECOMMENDING THE SPECIAL CATEGORIZATION OF GRADUATE STUDENTS WITH SUBSTANTIAL TEACHING RESPONSIBILITY

(Under the terms of the Selective Service Act, 1967)

Prepared by the Executive Committee of the Federation Board
Federation of American Societies for Experimental Biology

The Federation of American Societies for Experimental Biology wishes to emphasize the immediate need for a decision for deferment of graduate students in fields of national concern under the Selective Service Act, 1967 as essential for the present efficiency and future survival of the universities as well as medical and dental schools. Graduate students, being carefully selected, are the top level students who will be tomorrow's teachers and investigators. Further, graduate students presently serve as teachers and laboratory instructors in universities as well as in medical, dental and health related sciences, many while not holding or working toward degrees in health related fields. The failure to defer graduate students would therefore dry up the supply of the teachers for tomorrow but as an immediate and drastic effect would interfere seriously with the current teaching efforts in the medical, dental and health related fields, as well as in the universities. The contribution of graduate students as a group to the collegiate and professional school instruction must be realized fully so that action to defer them can be taken in time to prevent a catastrophic injury to American education and the supply and quality of scientists.

Loren D. Carlson, Ph. D.
American Physiological Society
University of California at Davis

Stanford Moore, Ph. D.
American Society of Biological Chemists
Rockefeller University

Allan D. Bass, M. D.
American Society for Pharmacology and Experimental Therapeutics
Vanderbilt University School of Medicine

Kenneth M. Brinkhous, M. D.
American Society for Pharmacology and Experimental Therapeutics
University of North Carolina

Henry D. Moon, M. D.
American Society for Experimental Pathology
University of California School of Medicine

Edwin H. Lennette, M. D., Ph. D.
California State Department of Public Health

Arnold E. Schaefer, Ph. D.
American Institute of Nutrition
U. S. Public Health Service

INSULIN AND FUEL HOMEOSTASIS*

G. F. CAHILL, JR., O. E. OWEN, AND P. FELIG

The physiology of fuel homeostasis has challenged researchers for over a half a century. Typical questions are: How does muscle release that amount of amino acid required for gluconeogenesis by liver or for ammoniagenesis by kidney, the former to supply brain with glucose and the latter to preserve cation for fluid volume and acid-base homeostasis? Likewise, how does adipose tissue release that amount of fatty acid required by carcass for its energy needs, and how is it increased during exercise? Man has proven to be an excellent subject to study these problems, and this brief review will present data summarizing some qualitative and quantitative observations on human fuel homeostasis.

The human central nervous system has been shown to be an obligatory utilizer of glucose with a respiratory quotient approximating unity and with little or no net exchange of any other substrate. This amount approximates 140 grams per day (3) and is unchanged except for a progressive small decrease with age in later life or with a gross disturbance of function as with anesthesia. High local levels of metabolism are associated with increased nerve activity in discrete areas during excitation, but the "background" energy needs are such that no gross alteration in overall substrate consumption is detectable. As far as fuel economy is concerned, brain acts as a large "ATP'ase" system, utilizing one-quarter to one-fifth of total basal calories as glucose and producing CO_2, water, and heat.

All other tissues in the body have the potential to utilize glucose as fuel, but, as originally suggested by Benedict's classical study of fasting man (1), fat is quantitatively far more important. The characterization of free fatty acids as the transport form of fat delivery from adipose tissue to the fat-consuming tissues was a major advance (4), and numerous studies since then have shown that the fuel requirements of heart, liver, renal cortex and skeletal muscle can all be satisfied by free fatty acid metabolism. There are certain tissues which derive their energy mainly from glycolysis of glucose to lactate. By three methods of calculation, 1) determination of Cori cycle by radioactive isotopes in intact man (2), 2) using in vitro rates of glycolysis and multiplying thereby the mass of the tissue and 3) directly determining lactate uptake by liver and kidney in vivo, these tissues consume approximately 40 grams of glucose per day, two-thirds to three-quarters of this amount being due to the red cells and the remainder due to renal medulla, peripheral nerve, platelets, leucocytes, to name a few (2).

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* Taken from the introductory remarks given at the session on Insulin I at the 1968 Federation Meetings. From the Elliott P. Joslin Research Laboratories, Dept. of Medicine, Harvard Medical School and the Diabetes Foundation, Inc. Supported in part by USPHS Grants AM-05077 and AM-09584.

This utilization of glucose appears large at first sight, but due to the low yield of ATP produced by anaerobic glycolysis, only about 0.5 per cent of the body's total caloric expenditure is so used.

Determinations of net splanchnic glucose output in man have yielded divergent values, but an approximate mean is 180 grams/day, fitting well with the calculations above (3). Since liver in normal post-absorptive man contains only 75 grams of glucose, gluconeogenesis must supply the needed glucose when none is available via the diet. In contrast to the rodent, man utilizes little of his liver glycogen, accelerating gluconeogenesis, instead, to maintain glucose levels. As shown in Figure 1, glycogenic amino acids provide the major difference between splanchnic glucose output and the glycerol from triglyceride lipolysis in adipose tissue added to the lactate and pyruvate from the glycolytic tissues. The remainder of the glucose is derived from liver glycogen and other possible glucogenic precursors such as lactate derived from a slight decrease in muscle glycogen levels.

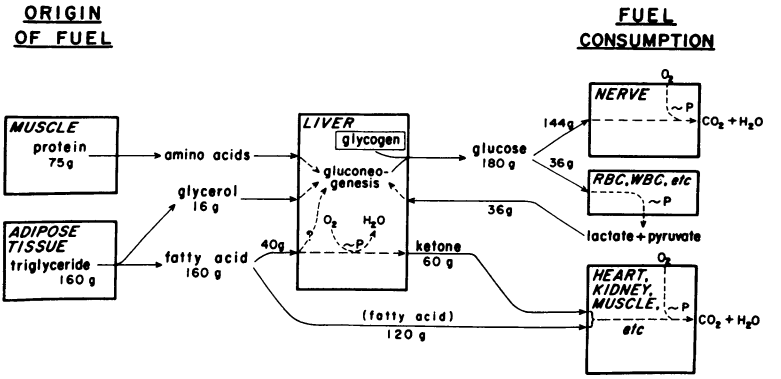

Fig.1. Fasting Man (24 hours, basal : - 1800 Cal.). Daily substrate flow in a normal man after 24 hours of fasting.

Of extreme importance, however, is the economy of the system. The peripheral tissues essentially cease to oxidize glucose to CO_2 with the exception of brain. Likewise, all potential precursors of gluconeogenesis, lactate, pyruvate, glycerol, glucogenic amino acids, are incorporated, within the limit of the methods, in toto into glucose. Liver's own energy needs, which approximate one-quarter to one-fifth of the total of the body, are derived mainly from the partial oxidation of long-chain fatty acids to acetoacetate and β-hydroxybutyrate.

What regulates these metabolic sequences? Although there is some evidence for direct CNS control of free fatty acid mobilization, the bulk of data suggest insulin and the beta cell as the principle control (2). The capacity of insulin in very low concentrations, concentrations which occur in vivo during fasting, to modulate free fatty acid release from adipose tissue is well documented. A similar effect of insulin in in-

hibiting amino acid release from human forearm has just been reported (7). Figure 2 describes a working servomechanism whereby glucose-insulin interrelationships modify the rates of release of free fetty acids and amino acids. This hypothesis does not exclude direct effects of insulin on liver glycogen metabolism or on liver gluconeogenesis, but suggests that during fasting, the primary control is at the step of substrate release from the peripheral depots, and liver gluconeogenesis follows as a passive process. Administration of small amounts of alanine results in a rapid acceleration of gluconeogenesis in fasting man, corroborating the above hypothesis (Felig and Owen, in preparation).

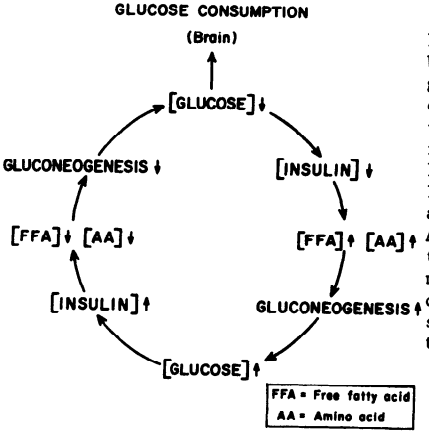

Fig.2. Hypothetical scheme whereby the concentration of blood glucose is detected by the beta cell, decreasing insulin secretion. Since the half-life of insulin is 10 minutes, insulin levels fall rapidly, causing release of free fatty acid and amino acid from the periphery. An increase in their concentration accelerates hepatic gluconeogenesis to elevate the glucose level, which, in turn, stimulates insulin release from the beta cell.

A major problem, however, is that were gluconeogenesis to continue as shown in Figure 1, survival would be limited to several weeks due to the limited nitrogen reserves. As shown in Figure 3, this is alleviated by brain's adaptation to utilization of acetoacetate and β-hydroxybutyrate, decreasing the need for proteolysis to 20 instead of 75 grams per day (6). The biochemical mechanisms of this adaptation by brain, as well as the concomittant decrease in ketoacid utilization by the remainder of the carcass are unknown. These occur without any gross change in the overall concentrations of ketoacids from the fourth or fifth day of fasting on, the levels approximating 6-8 mM β-hydroxybutyrate and 1-1.5 mM acetoacetate.

So far, two metabolic states have been described with quantitative data derived from the literature or collected in recent studies by the authors. Figure 4 presenta data on a hypothetical fasting subject in net negative carbohydrate balance. The two previous states, the "fasted" and "fasted-adapted" states are compatible with and necessary for survival. The theoretical metabolic picture presented in Figure 4 is transient, and if allowed to persist would progressively worsen with more severe ketosis, glycosuria and death. What separates this state from the two previously described is the loss of glucose in the urine in addition to the loss of large quantities of ketoacids. Apparently brain has not had sufficient time or perhaps an unfavorable substrate and hormonal environment to adapt to ketoacid utilization. Peripheral metabolism of the ketoacids, in fact, is probably decreased, possibly due to the higher levels of free

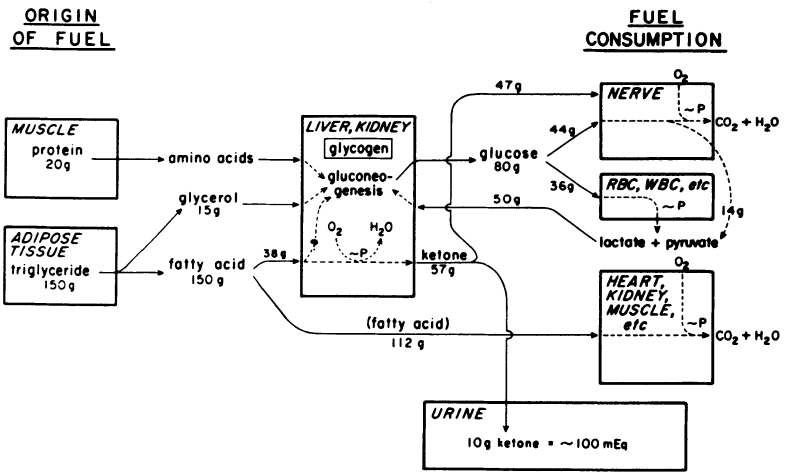

Fig.3. Fasting Man, Adapted (5-6 weeks)(24 hours basal : - 1500 calories) Protein breakdown is now limited to 20 grams/day due to the diminished need of brain for glucose.

fatty acids providing more energy for the carcass. In any case, keto-acid levels in the blood increase markedly and rapidly, in contrast to simple starvation, which is not associated with a net negative carbohydrate balance. This rise in ketoacids is more rapid than the kidney can titrate by ammonia production, resulting in a more severe acidosis and cation deficit.

The net negative carbohydrate balance superimposed on starvation could just as well have been produced in the non-diabetic by inhibition of tubular reabsorption of glucose with phlorizin. Likewise, since the sole source of fuel for the gravid uterus is glucose, pregnancy superimposed upon starvation presents a similar metabolic picture, namely progressive ketoacidosis, but this usually terminates by death of the fetus and its expulsion. In ruminants, lactation enhances the tendency of excessive ketoacidosis thanks to the net negative carbohydrate balance in milk, a fact well-known to the veterinarian.

Figure 5 represents a simplified scheme of four metabolic states. The fed state is characterized by availability of exogenous substrate and is associated with high levels of insulin, lipid synthesis and protein anabolism. The fasted state is associated with a lower insulin level, but still a close insulin-glucose relationship, which, when glucose falls, insulin falls, and peripherally stored substrate is mobilized. What ketoacids are produced are metabolized mainly by muscle. The "super-fasted" state results from a more severe insulin deficiency and is synonymous with diabetes. Peripheral release of stored fuels is unopposed, gluconeogenesis increases unchecked, as does ketogenesis, and eventually death occurs unless the message (insulin) is returned to

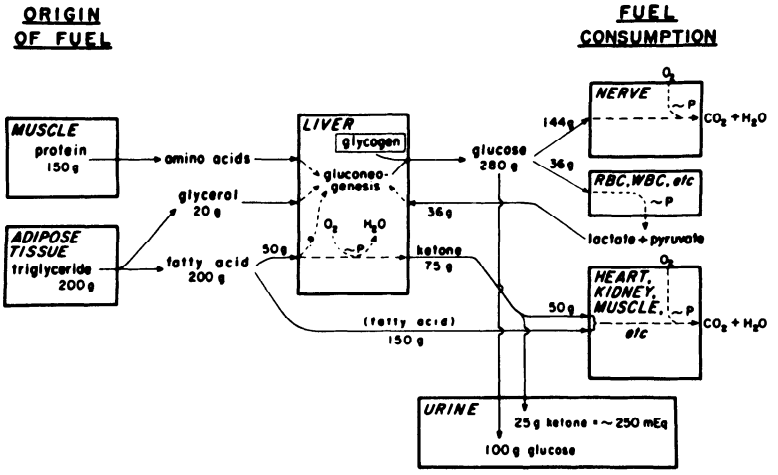

Fig.4. Severe Diabetes (24 hours : - 2400 Cal.) A metabolic state due to insulin deficiency and resulting in net negative carbohydrate balance.

the body that there are adequate quantities of glucose. The "fasted-adapted" state, as described, occurs with low insulin levels and several days of time, in contrast to the "super-fasted" state which occurs within hours and with a more marked insulin deficit.

Adrenal glucocorticoids have also been indicted as playing a major role in mobilization of peripheral fuels. The human data from these and other studies suggest that these are necessary for fuel mobilization, the so-called "permissive" effect as described by Ingle, but they do not serve to modulate the fasting process. Growth hormone has also been mentioned as playing a role, thanks to its capacity to increase free fatty acid levels, particularly after induced hypoglycemia (5), but, its variable levels are almost unpredictable, and its possibly inconsequential sporadic peaking from time to time decreases its importance as a major control. Glucagon is another possible modulator, and it is increased in fasting, but difficulty in its assay and cross-reactivity with other factors have limited its elucidation. It is, however, a potent gluconeogenic stimulus, and, as such, may be more important than previously considered (8). The in vitro data, however, suggest that it may

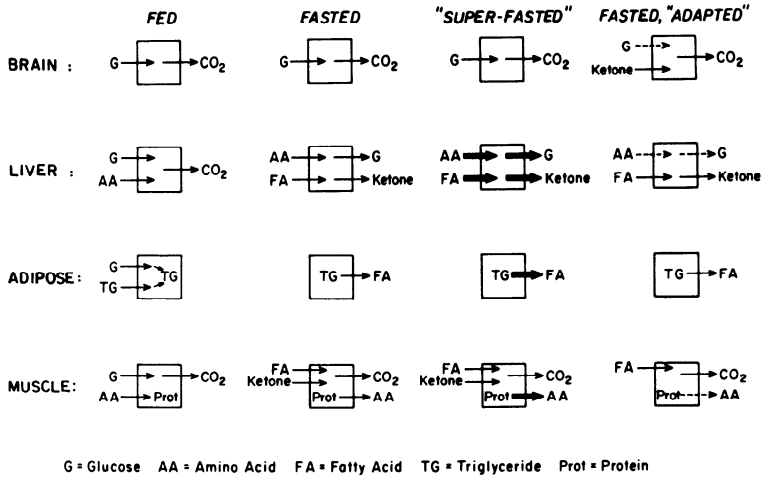

Fig.5. Schematic breakdown of the four principle tissues involved in fuel homeostasis as they respond to four metabolic states.

also, like the adrenal glucocorticoids, be more "permissive" in nature instead of playing an active role.

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GLOMERULO-TUBULAR BALANCE OF SALE AND WATER*

E. E. WINDHAGER**

The term "glomerulo-tubular balance" was first used by Homer W. Smith (18), but in a different sense than that given to it today by a majority of nephrologists working in the field of renal electrolyte metabolism. Webster's dictionary defines "balance" as an equality between the two sides of an account. The adjective "glomerulo-tubular" implies that the two sides of the account involved are the glomerular load and tubular transport function. It follows that "glomerulo-tubular balance" in the strict sense of the word means equality of rates of filtration of a substance and of its reabsorption. This is normally true for glucose, to take just one example, but it is certainly not true for sodium, chloride, or water, at least not under ordinary circumstances.

Recently, however, several laboratories (2, 7, 17) including our own (20), have applied the term "glomerulo-tubular balance" to the normally observed proportionality between the rate of glomerular filtration and of proximal tubular reabsorption. This is not "balance" between fluid delivery and tubular transport. However, this is part of the regulatory mechanisms that help to maintain the various fluid compartments of the body in a "balanced" state. It is in this broader sense that we may justify our current usage of this term.

As part of the regulatory mechanisms involved in homeostasis, glomerulo-tubular balance for sodium and water is absolutely essential, but it is also a very puzzling phenomenon. In contrast to all observations on salt and water transport in isolated tissues such as frog skin or toad bladder, in vivo, proximal tubular reabsorption changes in proportion to alterations in the rate of fluid delivery. The problem of glomerulo-tubular balance has received considerable attention during the past years and there are essentially two questions that have been asked within this context. The first concerns the magnitude of adaptive changes in reabsorption in response to changes in load delivered to various nephron segments. The second question deals with the actual mechanisms responsible for proportional variations in rate of reabsorption and glomerular filtration.

Landwehr and his associates (10) have studied the quantitative response of tubular reabsorption to acute reductions in glomerular filtration rate in the rat. A micropuncture recollection technique was

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*Taken from the introductory remarks given at the session on Renal Tubule I at the 1968 Federation Meetings. This work was supported by grants from the American Heart Association, New York Heart Association, Life Insurance Medical Research Fund, National Science Foundation, and P. H. S. Grant No. 1 RO1 AM 11489-01.

** Career Scientist of the New York Health Research Council, No. 1-405

used and samples of tubular fluid and plasma were analyzed for C^{14}-labeled inulin and for sodium concentration. In addition to the usual procedures needed for micropuncture experiments, the renal artery was dissected for several millimeters close to its origin. A small, adjustable silver clamp, designed by Munnel and Gregg (16), was placed around the renal artery. After collection of control samples, a mean reduction of glomerular filtration rate of 45 per cent was produced by partially closing the renal arterial clamp. Calculation of individual nephron filtration rates showed that GFR in the sampled nephrons was reduced to a similar extent as overall filtration rate.

Figure 1 shows late proximal tubular fluid/plasma (TF/P) inulin concentration ratios for 25 paired collections obtained from the same tubular segment during periods of normal and reduced GFR. Since a majority of the TF/P inulin ratios was increased during low GFR, constancy of fractional fluid reabsorption was not completely achieved. The mean increase was from a ratio of 1.98 during normal GFR to one of 2.77 during reduced rates of filtration. This change, which represents an increase in fractional sodium and water reabsorption of 14 per cent, was statistically significant ($p<0.01$). It should be noted that although the mean reduction in filtration rate was 45 per cent, the mean increase in fractional reabsorption in the proximal tubule was only 14 per cent. Thus, although perfect constancy of fractional reabsorption was not present, partial matching of reabsorption to filtration did occur. Similar results have been obtained in rats by Gottschalk (11) and Berliner (1) and their respective collaborators.

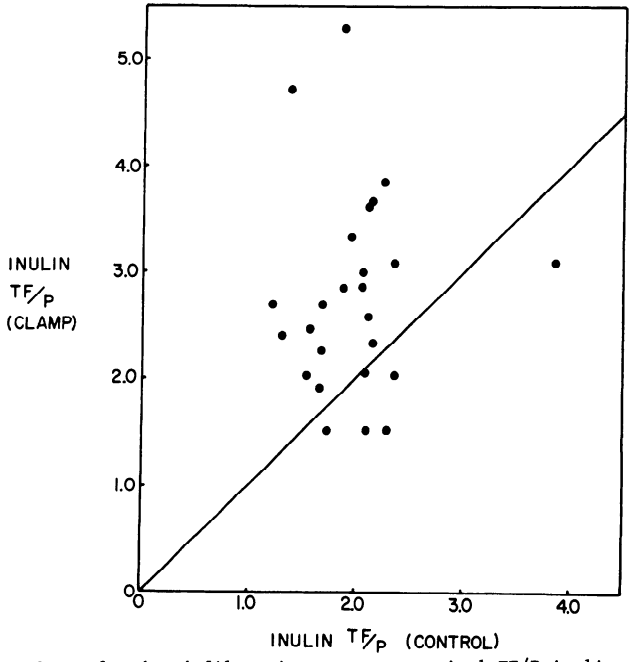

Fig.1. Effect of reduced filtration rate on proximal TF/P inulin ratio (from Landwehr et al. ref.10).

Figure 2 illustrates the response of fractional sodium and fluid reabsorption in Henle's loop to reductions in the load leaving the distal end of the proximal convolution. These results were obtained by comparing late proximal and early distal tubular fluid samples with respect to inulin concentration, sodium concentration and rate of fluid collection during micropuncture. Per cent reabsorption is plotted on the ordinate as a function of tubular flow rate at the end of the proximal tubule. As indicated by the upper regression line in Figure 2, a relatively constant fraction of sodium entering the loop is reabsorbed in a manner which is independent of flow rate. Sodium reabsorption apparently follows a pattern which is similar to that observed in proximal convoluted tubules. In both nephron segments, proximal tubules and loops of Henle, a direct proportionality exists between load delivered and amounts reabsorbed.

On the other hand, fractional fluid reabsorption declines with increasing flow rates in loops of Henle (see lower regression line in Figure 2). Stated in terms of absolute amounts of fluid reabsorption it appears, however, that load and rate of reabsorption are directly proportional. Compared to sodium reabsorption, the factor of proportionality is smaller with respect to fluid transfer. An approximate calculation shows that when the absolute rate of sodium reabsorption increases threefold in response to increased loading, the absolute rate of water reabsorption is only doubled. Thus, although fluid movement in Henle's loop is still quantitatively related to sodium transport, water absorption becomes relatively diminished at high flow rates. It is likely that the site of the relative lag of water versus sodium transfer is along the ascending limb of the loop of Henle.

The apttern of sodium concentration changes in the distal convoluted tubule during partial arterial clamping is shown in Figure 3. Partial occlusion of the renal artery resulted in the majority of observations in an increase in tubular sodium concentration. The mean increase of all distal samples was 21 mEq/l($p < 0.01$). Seventeen sample pairs collected from the first third of the distal tubule are contained in the data shown in Figure 3. During reduced GFR, the sodium concentration of these samples increased by a mean of 19 mEq/l. These experiments, therefore, demonstrate that a reduction in flow rate through Henle's loop leads to increased sodium concentrations in fluid entering the distal tubule.

The fraction of filtered sodium reabsorbed by the time fluid reached the early distal tubule was calculated from the sodium and inulin TF/P ratios of fluid collected from the beginning of the distal convoluted tubule. Although proximal data indicated a mean increase of 14 per cent in proximal fractional sodium reabsorption, early distal data showed a mean increase in fractional sodium reabsorption of only 2.4 per cent. A comparison of these early distal samples with ureteral urine indicated that fractional reabsorption of sodium in the last two thirds of the distal tubule and collecting duct was not significantly changed during reduced GFR. It should be noted that although the sodium concentration of samples collected from the entire distal tubule was elevated during reduced GFR, the sodium concentration of final urine was significantly decreased This indicates that the collecting duct is responsible for the diminished

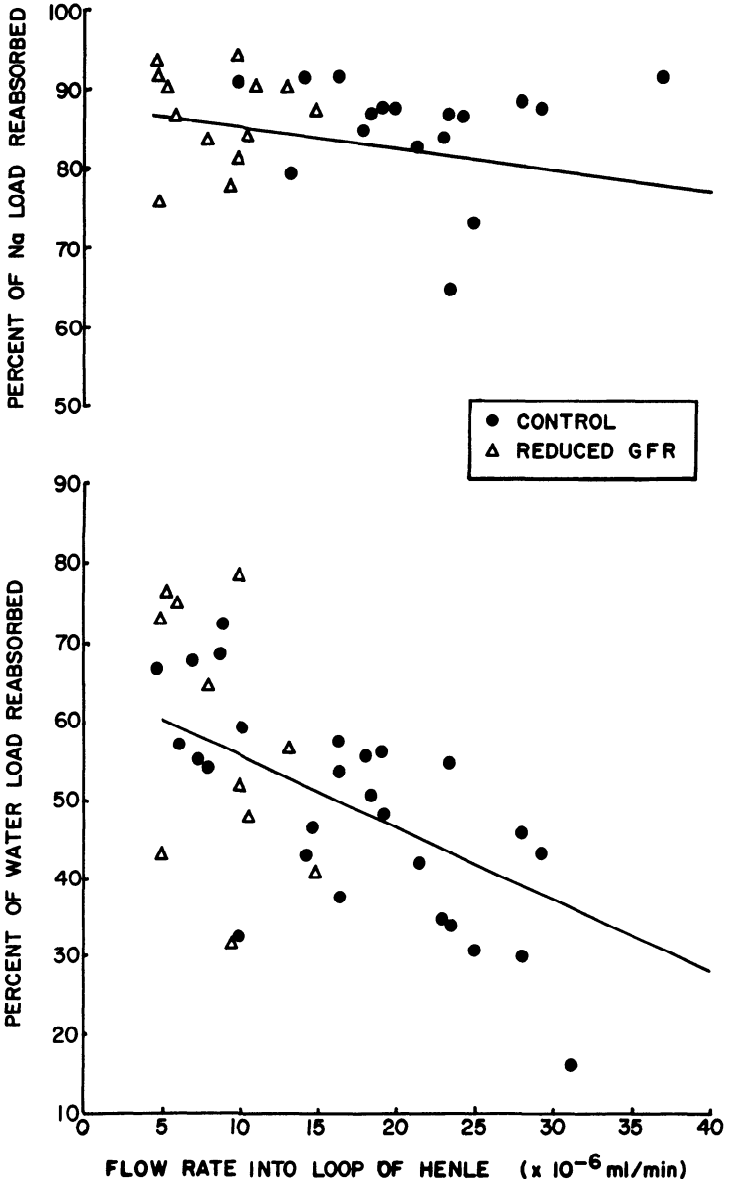

Fig.2. Top - Relationship between fractional reabsorption of the loop sodium load and flow rate entering the loop of Henle. Bottom - Relationship between fractional reabsorption of the loop water load and flow rate entering the loop of Henle (from Landwehr et al., ref.10).

sodium concentration which is found during reductions in GFR.

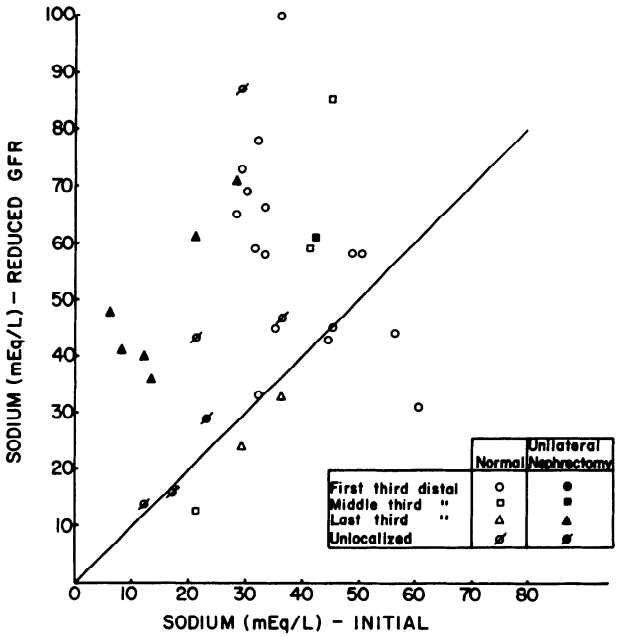

Fig.3. Effect of reduced filtration rate on distal tubular sodium concentration (from Landwehr et al., ref.10).

Turning now to the mechanism responsible for the adaptive changes in reabsorption, there are a number of hypotheses that have been advanced to explain glomerulo-tubule balance. According to one view, changes in the level of a circulating humoral agent occur either in response to alterations in sodium load reaching some nephron segment (12), or in response to changes in the size of the extracellular fluid volume (13, 15, 19). Supposedly, this humoral factor then regulates the rate of tubular sodium reabsorption. The second type of hypothesis tries to explain glomerulo-tubular balance on the basis of changes in the geometry of the tubular lumen (7). Finally, an essential role has been assigned to extraepithelial events by their ability to alter either the sodium concentration or the hydrostatic pressure in the spaces that probably exist between neighboring tubular cells and basement membrane (14). There is some controversy among the proponents of these views, and we are still far removed from having a final answer to our problem. However, it should be stressed that the three hypotheses are not necessarily mutually exclusive. We are inclined to believe that humoral control of proximal sodium reabsorption plays a role at least during expansion of the extracellular fluid space. And it seems possible that tubular luminal geometry is just one of the extraepithelial events

that modify net transport of sodium.

We have been led to this view on the basis of micropuncture studies in rats performed in collaboration with Dr. John E. Lewy and more recently with Dr. Adrian Spitzer. The results of these experiments suggest the possibility that peritubular capillary absorption may in part control epithelial transport. Earley and Friedler have reached a similar conclusion on the basis of clearance experiments (5). As a starting point, a condition of partial renal venous occlusion was chosen as a method of raising peritubular capillary pressure and diminishing renal blood flow. Micropuncture was performed before and during partial renal venous occlusion to assess relative and absolute rates of proximal fluid reabsorption. These were correlated with changes in glomerular filtration rate, renal plasma flow, hydrostatic pressure in tubules and peritubular capillaries, and with tubular dimensions and transit time of tubular fluid.

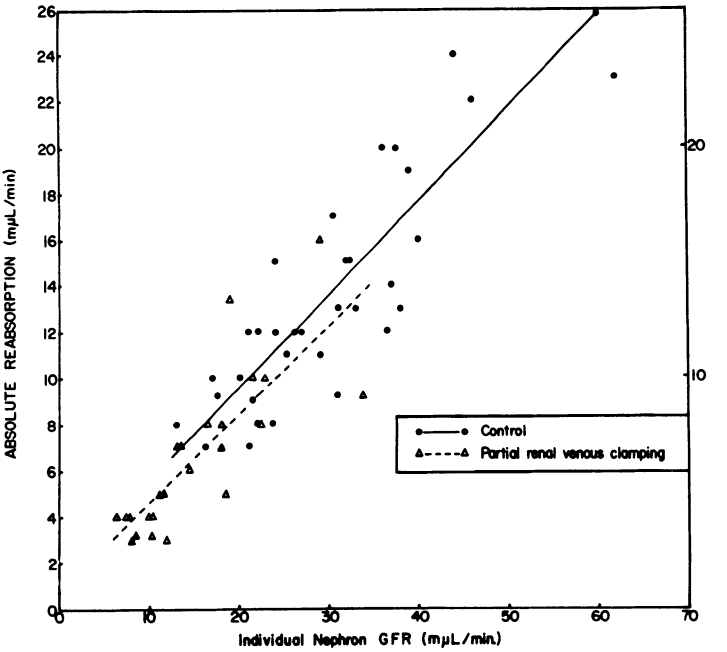

Fig.4. Relationship between individual nephron GFR and absolute rate of fluid reabsorption in the convoluted proximal tubule of the same nephron (from Lewy and Windhager, ref.14).

We were first interested to see whether glomerulo-tubular balance is still maintained under conditions of venous clamping. For this purpose, individual nephron GFR was compared with the absolute rate of reabsorption from the same proximal tubule. At all measured levels of GFR, in controls and in clamped kidneys, absolute rate of reabsorption varied directly with GFR (see Figure 4). In other words, despite

reductions of individual filtration rates to less than 10 mμl/min, glomerulo-tubular balance was sustained.

As the next step in this investigation we compared measurements of luminal cross-sectional area at the puncture site with the corresponding rates of reabsorption in the same nephron. This relationship was studied under control conditions and during partial renal venous occlusion. Figure 5 summarizes the results obtained. In the control series we found, despite a considerable scatter of the data, a statistically significant relationship between luminal cross section and absolute magnitude of fluid reabsorption. In contrast, during clamping, this relationship was lost and the absolute reabsorption remained low in tubules of widely differing diameters. Thus, although some reservation might be expressed concerning the relationship under control conditions because of the large scatter of the data, it seemed an inescapable conclusion that glomerulo-tubular balance is maintained during partial venous occlusion by a mechanism other than changes in tubular luminal cross-sectional area.

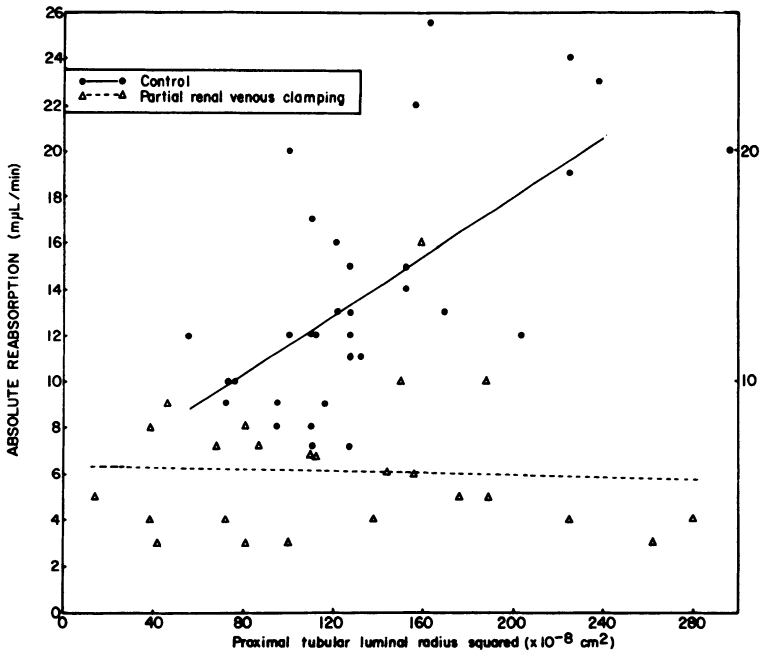

Fig.5. Relationship between the relative cross-sectional area of proximal tubular lumina and the rate of absolute fluid reabsorption in the same convoluted proximal tubules (from Lewy and Windhager, ref. 14).

One possible alternative was a direct action of changes in glomerular load on tubular transport. It was, therefore, decided to assess the effect of renal vein clamping on proximal tubular transport, independent of changes in glomerular filtration. For this purpose, we measured

the intrinsic proximal tubular reabsorptive capacity in split drop experiments, using the method of Gertz (6). Venous clamping significantly prolonged the half times of fluid reabsorption from a mean of 9.8 ± 0.4 (SEM, 14 obs.) to 17.1 ± 1.6 (SEM, 19 obs.) seconds. Thus, the capacity of the proximal tubular epithelium to reabsorb a given amount of fluid is reduced by partial venous occlusion. It is in the nature of split drop experiments, that glomerular load is excluded as a potential factor in determining transport. Furthermore, our free-flow micropuncture data had excluded tubular cross-sectional area as a factor regulating reabsorption during venous clamping. We, therefore, proceeded to test whether removal of reabsorbate might be rate limiting during venous occlusion, by plotting overall renal plasma flow against individual tubule reabsorptive half times. Figure 6 demonstrates that decreases in the clearance of PAH are associated with exponential increases in reabsorptive half times. Hence, during partial occlusion of the renal vein, renal plasma flow can apparently become a rate limiting step in tubular reabsorption.

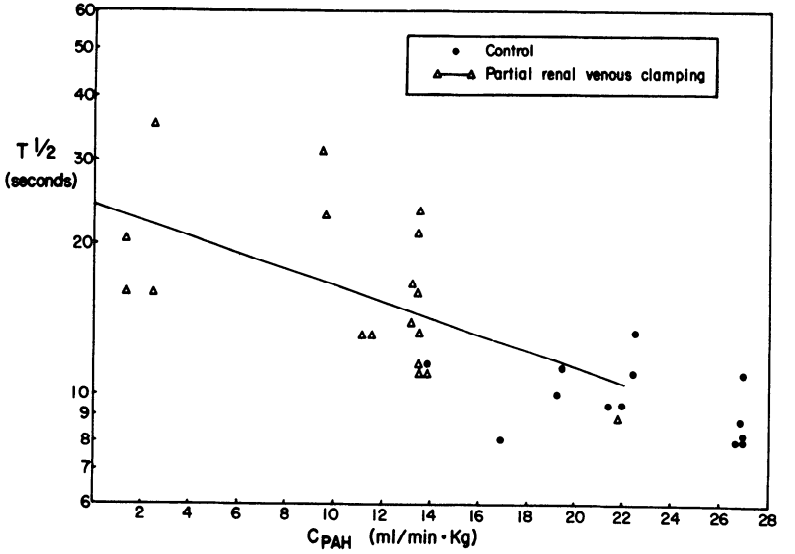

Fig.6. Relationship between reabsorptive half-time observed in split-drop experiments and simultaneously measured clearance of PAH per 2 kidneys per kg body weight (from Lewy and Windhager, ref.14).

This finding makes it tempting to speculate about the mechanism of the reduction in tubular fluid reabsorption observed during partial occlusion of the renal artery. All investigators who have studied this experimental condition agree that during free-flow, the absolute magnitude of proximal tubular reabsorption is reduced. Brenner et al (1) reported that the reabsorptive rate during arterial clamping is governed by some other factor than tubular geometry. One might therefore consider that the reduction in peri-tubular blood flow, most likely a consequence of clamping the renal artery, is causally related to the observed decrease in rate of tubular transport.

Under control conditions, however, it is unlikely that renal plasma flow per se is rate limiting to transport. More pertinent might be changes in the magnitude of the forces responsible for capillary absorption of the epithelial reabsorbate, that is first of all the colloid-osmotic pressure of the peritubular capillary blood. We, therefore, tested whether the tubular reabsorptive capacity is related to variations in filtration fraction, measured as the ratio of inulin/PAH clearance. Figure 7 demonstrates that the half-time of fluid reabsorption in split drop experiments decreases linearly with increasing filtration fractions. These results suggest that a rise in oncotic pressure of peritubular capillary blood facilitates net movement of fluid from tubular to capillary lumen.

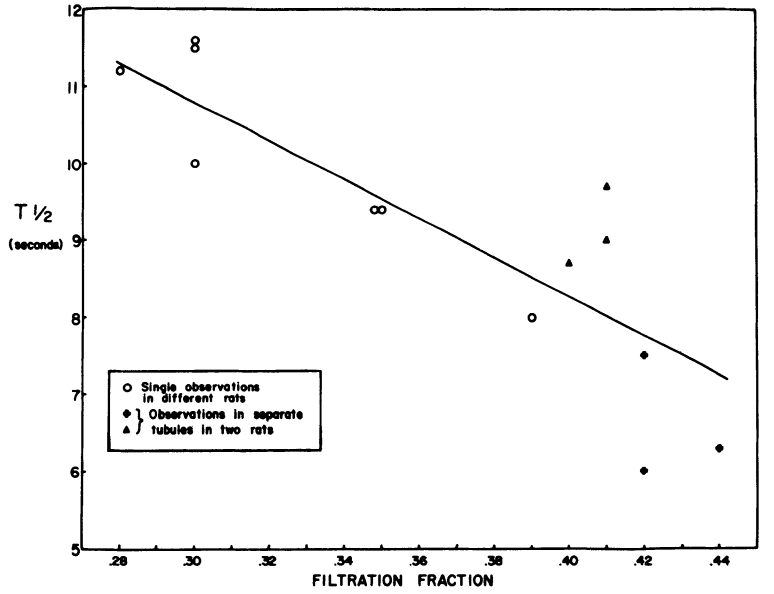

Fig.7. Relationship between filtration fraction and half-time of fluid reabsorption observed in split-drop experiments during control periods (from Lewy and Windhager, ref.14).

In collaboration with Dr. A. Spitzer we have recently attempted to study the effect of the oncotic pressure within peritubular capillaries, by directly changing the colloid concentration of its contents. For this purpose, single efferent arterioles on the surface of the rat kidney cortex in vivo were perfused through a micropipette. Fluid reabsorption in proximal tubules, which at least in part obtained their vascular supply from the perfused capillary bed was then measured during and after cessation of peritubular perfusion. Using a recollection technique, tubular fluid/plasma inulin concentration ratio, rate of fluid collection and transit time of lissamine green to the site of tubular puncture were estimated. The reabsorptive capacity of the proximal tubule was calculated from the inulin concentration ratio and the transit time, as proposed by Gertz (7). Using colloid-free Ringer's as vascular perfusion fluid, we found a mean of 0.026 ± 0.006 sec $^{-1}$ (SEM, 12 obs.), a value

significantly lower ($p < 0.001$) than the average reabsorptive capacity of 0.094 ± 0.009 sec^{-1} (SEM, 9 obs.) obtained by tubular recollection after cessation of peritubular perfusion. In other series of experiments, peritubular capillaries were perfused with Ringer-Dextran solution. The average reabsorptive capacity was 0.060 ± 0.012 sec^{-1} (SEM, 12 obs.), a value significantly higher ($p < 0.02$) than the mean obtained during perfusion with colloid-free Ringer's solution. Although these experiments are still in a preliminary state, the results support the view that capillary absorption can influence the rate of fluid reabsorption by the proximal tubular epithelium.

It should be emphasized that the view of capillary fluid reabsorption partly determining tubular salt and water transport does not mean that the force responsible for tubular reabsorption is the colloid-osmotic pressure of peritubular blood. Previous studies by several investigators (8, 9) have shown that a reversal of the oncotic pressure gradient produced by intraluminal injection of protein solutions did not significantly affect tubular reabsorptive capacity. Hence, the driving force for reabsorption is active transport of sodium, with peritubular factors in part determining the rate of reabsorption by the transporting epithelium.

Any attempt to explain and integrate peritubular factors in the general concept of tubular epithelial transport can at present only be based on speculation. Hypothetically, however, it could be visualized that sodium ions which have entered the cellular transport pool are actively transported into the basal and lateral interspaces of the epithelium, that is the basal labyrinth located between cell membranes proper and basement membrane. Water follows passively across the almost semi-permeable cell membrane, thus elevating the hydrostatic pressure in the basal labyrinth. A small hydrostatic pressure gradient leads to ultrafiltration across the tubular basement membrane. The reabsorbate is finally moved from the interstitium across the capillary wall by the force defined by the net balance of hydrostatic and oncotic pressure gradients across this barrier. Some backflux of solute and water might occur across the cell membranes and possibly in part through intercellular channels. The basal labyrinth thus might act as the middle compartment of the model proposed by Curran and McIntosh (3), with the addition of some back leakage. Any reduction in capillary fluid reabsorption could then lead to volume expansion of the compartments interposed between transporting cell membranes and capillary endothelium. Volume expansion in the basal labyrinth may either widen intercellular channels or increase cell membrane permeability by stretching. If sodium pumping continues normally one of several possible consequences may occur. First, increased backflux of sodium and water may take the route of widened intercellular channels. A second possibility is an increase in the membrane permeability to sodium, leading to augmented sodium backflux from basal labyrinth into the cell interior. Thus, the rate of net movement of sodium and water across the cell membrane would be diminished.

As an alternative we might consider that diffusion of sodium is importantly involved in the movement of this ion from transporting cell membrane to capillary wall. Volume expansion of this unstirred com-

partment must increase the length of the diffusional pathway. If the rate of diffusion is thus reduced, sustained active transport might lead to sodium concentrations higher than normal within the unmixed layer immediately adjacent to the transporting cell boundary. This view seems consistent with the "standing osmotic gradient" hypothesis of Diamond (4). Both back diffusion into the cell and reduced uni-directional transport might result, leading to decreased net movement of sodium and water.

To summarize this rather involved argument: there is reason to believe that the effect of peritubular capillary absorption on epithelial transport is relevant to the phenomenon of glomerulo-tubular balance, since filtered load and peritubular oncotic pressure may be set by changes in the effective resistance of the efferent arterioles. Thus, a relative increase in GFR will be accompanied by increased peritubular oncotic pressure, increased driving force for removal of the epithelial reabsorbate and increased tubular volume. Relative reductions in GFR would result in the opposite effects. Glomerulo-tubular balance might thus be achieved by the simultaneous setting of load - that is GFR - and oncotic or hydrostatic pressure, with concurrent changes in the size of intercellular spaces and epithelial transport.

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A VIEW OF SYSTEMS PHYSIOLOGY

FOREWORD

In 1966 the National Institute of General Medical Sciences asked each of its training committees to prepare a description of the scope and trends of its branch of health science. The report of the Physiology Training Committee titled "Status of Research in Physiology" was subsequently published in The Physiologist, Vol. 10, pp. 60-74, 1967.

During 1967 the training committees proposed a second report, for the guidance of NIGMS, and the following article presents the Physiology Training Committee's latest report, slightly modified for the general physiological audience. This report differs from the first one in that the Committee has now focused attention on one aspect of contemporary physiology, and examined its characteristics in detail. Future reports will deal with other aspects of physiology.

The subject of the present report is Systems Physiology, and we present our views in the hope that we can illustrate clearly what we interpret as the strongest and most powerful conceptual development in modern physiology. In fact, we believe the concepts presented are the central ideas underlying both theory and practice that give the otherwise diffuse science of physiology the cohesiveness and vigor that preserves its independent character in spite of the outgrowth of biochemistry and biophysics from physiology.

Although the report in its original form, and also here, appears in the name of our entire committee, it is only fair to acknowledge the special role played by Professor F. E. Yates in its formulation.

Physiology Training Committee

W. F. H. M. Mommaerts	G. Hoyle
F. N. Briggs	J. W. Moore
D. K. Detweiler	B. M. Schmidt-Nielsen
F. S. Grodins	F. E. Yates

DISAPPEARANCE OF SUBSPECIALTIES IN LIFE SCIENCE

In 1966 the training committees of the National Institute of General Medical Sciences presented views of the scope and achievement of the various branches of life science. Each field claimed for itself many of the major developments of modern biology. The various specialties also clearly revealed overlapping activities - so much so that the "specialties" appear far less specialized than might be expected from the common view that scientists respond to the accumulation of know-

ledge by narrowing the scope of their own interests and abilities. Although the rapid growth of information in the life sciences must be dealt with today by men whose personal intellectual capacities do not exceed those of their predecessors who had less information to cope with, nevertheless the predicted trend toward provincialism has not in fact dominated the recent developments in biology. Instead we find all of the various specialties increasingly dependent upon physics, chemistry, mathematics, the availability of advanced instruments - and upon each other. The separation of specialties is disappearing.

CURRENT TRENDS IN THE VIEWS OF BIOLOGISTS TOWARD THEIR ACTIVITIES

Medawar has suggested that biologists now favor a classification of their activities according to the levels of organization at which they work, rather than according to their specialties. Thus we have molecular biologists, cell biologists, organ system and organism biologists, and population biologists. Men working at each level of organization find communication with others working at the same level quite natural, regardless of what variety of life - plant, animal or bacterial - may be the particular object of study at a given level. In contrast, communication between men working at different levels of organization is not so easily achieved, and may fail so conspicuously as to lead to misunderstanding, suspicion, condescension, or even hostility and a cold lack of interest.

LEVELS OF ORGANIZATION IN BIOLOGY

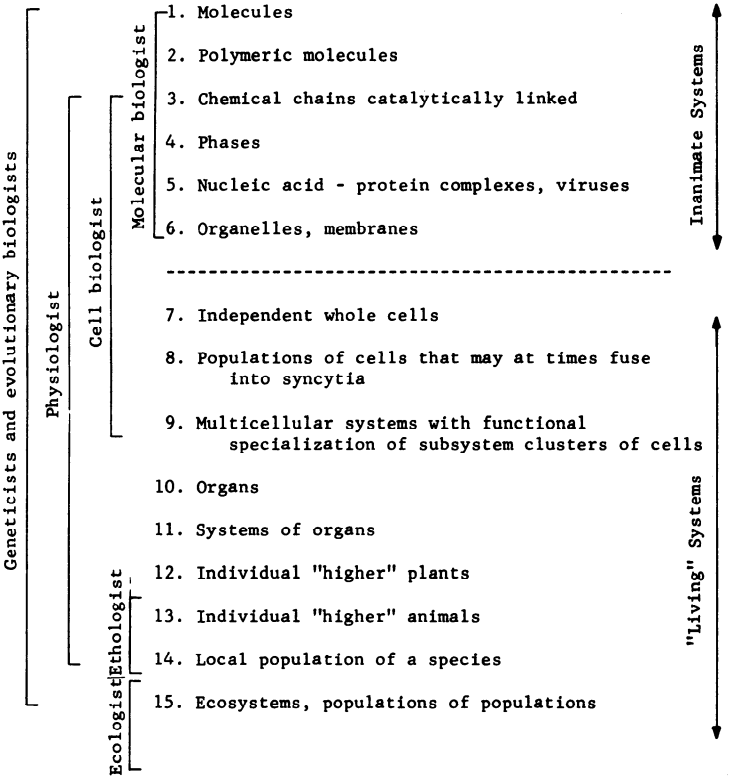
Various levels of supra-atomic organization of matter within biological systems are listed in Table I, in order of increasing complexity of properties. The range of the major activities of different kinds of biologists is indicated. Level 7 is the lowest level usually considered to possess all the attributes sifficient for "life" yet no definition of living systems that sharply distinguishes them from non-living systems has ever been achieved. We can say only that a "living system" is an arrangement of matter that yields an ensemble of properties which, taken as a whole, characterizes the system, by definition, as living. The elusive and tautological nature of this view of a living system cannot yet be escaped.

Unnecessary and useless disputes sometimes arise between proponents of reductionist (analytic) approaches in biology, and those of the holistic viewpoint in biology. Gerard has commented that such contention arises out of a failure to discern the choices to be made about relevant levels of organization in a biological investigation. Investigation at any level can be justified on intellectual grounds, and if the choice of relevance is that of a high level of organization, the investigator is committed to invoke information from other levels only insofar as demanded by the identification and specification of those processes dominantly involved in the system performance at his chosen highest level of interest. Nevertheless, living systems themselves in fact reconcile all the many phenomena at the multiple levels of organization, and they are states of matter that now appear to be much more probable

than once thought.

TABLE I

SUPRA-ATOMIC LEVELS OF ORGANIZATION OF MATTER IN "LIVING" SYSTEMS

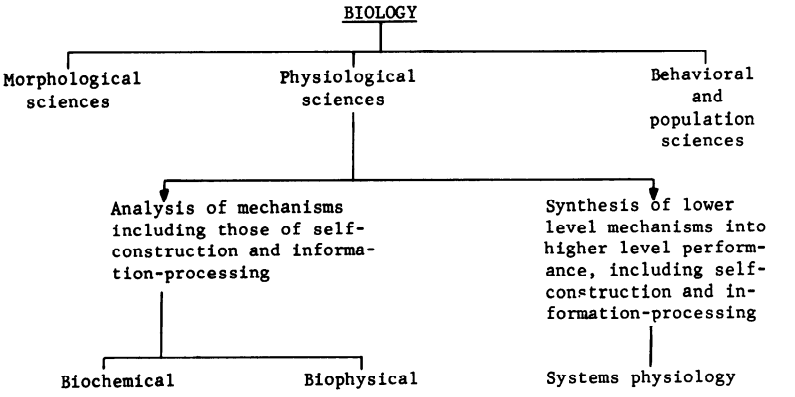


The development of a reconciled understanding among the multiple levels of biology would be a magnificent scientific achievement, but may not be possible. Physicists have not produced a fully reconciled view of the fundamental particulate and wave-like properties of light, so biologists must expect disappointments, and be prepared to move beyond them as physicists have done, by substituting convenient, operational concepts for a more detailed and satisfying understanding. Yet it remains inevitable that biologists will be driven by curiosity and intellectual compulsion to seek a general understanding of living systems that embraces the physical chemical laws of matter at all levels of complexity of its organization found within man. Physiology is committed to the synthesis of analytical knowledge into such a general understanding. In this commitment is to be found the special, eclectic beauty of the science.

THE SCIENCE OF SYSTEMS PHYSIOLOGY

Table II presents a view of the relationships among major subdivisions of biology. The science of physiology generally concerns the understanding of function in complete, living individual organisms of all kinds. It embraces studies of all the levels of organization from molecular to individual man, shown in Table I, and it is equally dependent upon both analysis and synthesis.

TABLE II



Description of Systems Physiology

The part of modern physiology to be emphasized in this article is Systems Physiology. The central concept of this branch of physiology is that an arrangement of biological components, coupled, connected and interacting, has properties beyond the sum of those to be found in the components individually. Therefore, Systems Physiology is the science of the static, quasi-static and dynamic properties of connected, coupled, interacting components. The properties of a system of connected components depend upon: 1) the nature of the components individually, 2) the nature of the individual connections and coupling relations, and 3) the arrangement of components and the paths of communication among them. These system properties by definition lie outside the scope or competence of molecular biology and represent the province of Systems Physiology in which the structural integrity of components is accepted into experimental design and the dissolution of structure is minimized. Systems Physiology emphasizes those attributes that define a system as living.

Systems Physiology poses the question and sets the goals for analytical biology generally. It is characterized by its point of view, by the kinds of questions it asks, and the kinds of answers it seeks, rather than by the level of organization at which a study is made. Thus, Systems Physiology defies classification in the term suggested by Medawar. The power of the systems viewpoint lies precisely in its general appli-

cability for many levels of organization in biology, and in its emphasis on the characterization of detailed mechanisms and their incorporation into dynamic performance at higher levels.

The major objectives of Systems Physiology are first, the determination of those properties and arrangements of components and of signal pathways that give rise to the conspicuous functional attributes of a higher level system, and second, the rationalization and ultimately, mathematical abstraction of these dynamical system attributes in terms of the component properties and pathways of connection and coupling.

An overall system is considered "animate" when it reveals the capacity to sustain itself in a state in which observable processes occur without causing the system itself to follow a path toward the most general mechanical, chemical, thermal and electrical equilibrium for all the processes observed. According to this view, some animate systems of physiological interest are composed of connected inanimate systems, in which instance the animate state, or "life," is itself revealed as a systems property. In other instances the system of physiological interest is composed of connected, animate subsystems, in which case the overall system is a "higher form" of life. "Life" in either case is a system attribute ultimately, and not an attribute of molecular components. In this strict sense, Systems Physiology is "life science."

Strategy

The modern concern about system dynamic properties goes beyond the historical interest in function, though the two are of course related. They differ in that the historical concern was mainly for the observation of function and its qualitative description. Quantitative description sometimes followed, but, if so, the emphasis was strongest upon steady-state quantification. In modern Systems Physiology, the emphasis includes the dynamic properties of system arrangements as revealed by their transient responses, and with this changed emphasis comes a more explicit strategy of research - one common to other branches of natural science.

Admittedly a strategy of research, particularized, depends upon the personality and the inclinations of the scientist conducting the investigation. Yet modern physiology has such a strong conceptual basis in systems theory that an illustration of a generalized strategy is given below. The experienced scientist will see immediately that the strategy described is merely a familiar one of sound science generally. For the student, however, we thought is useful to expose it explicitly, since not all the steps are obvious.

General steps in Systems Physiology, common to other branches of natural science, include the following (but not all steps are necessary or possible in every case):

1. Choice of a system of interest.

2. Choice of the describing variables to be measured.

3. Selection of measurement techniques and estimate of errors of measurement.

4. Estimate of the relevant time domain for system activity and transient responses. Does the system respond over milliseconds, seconds, minutes, days, months, etc?

5. Choice of sampling rates appropriate to the time domain (when discontinuous measurements must be made).

6. Choice of stimuli, input signals or forcing functions to perturb the system.

The above steps comprise the stage of planning. The following five steps comprise the stage of experiment.

7. Observation of the performance of the system without experimental perturbation (non-interacting experiments).

8. Observation of transient and steady-state responses of the system following perturbation.

9. Proof of recoverability. (Can the system recover its initial state after perturbation, or is it permanently altered?)

10. Experimental intervention to discover components and connections within the system, and coupling between it and other systems.

11. Mapping of signal flow pathways and components into an operational diagram showing the connectivity of the system.

12. Determination of the dynamics of isolated components.

At this point in the stage of experiment, it becomes necessary to identify the "unit processes" that underlie the component process dynamics. (This analytical step is essential for the subsequent synthetic stages of systems physiological work, and will be commented upon further in the next section.)

Systems Physiology then proceeds to the stage of modeling.

13. Development of a model that incorporates the unit processes of components, to stimulate selected system performance characteristics.

14. Test of the model (almost always, except in very elementary cases, a computer is necessary). The model must be tested for adequacy in reproducing the data that served as the basis for the model - this is the minimal criterion for a satisfactory model. A more powerful model will serve to make predictions of system performance under circumstances not directly incorporated into the development of the model.

15. Experimental tests of predictions by performance of the analogous experiments on the real system.

16. Modification of the model; further predictions and modifications within the same general structure.

17. Development of a new kind of structure for the model and fresh kinds of predictions and experiments.

The Unit Processes

In the above delineation of the strategy of systems investigation in biology, a system model is revealed as a nest of models of component processes or parts. The question arises as to how much structural or functional detail at the component level of organization or below must be included in the overall system model. The answer to this question is an overriding concern in physiology work and the considerations involved in arriving at the answer are therefore worth making explicit here.

The unit process in physiological work is that lowest level process bestowing particular characteristics upon a given component that are detectable in the dynamics of that component as it participates in the performance of the whole system. In general, these unit processes lie at one, or at most, two levels of organization of matter below that of the relevant system itself. For example, if the system of interest is that which may be considered to determine total body water volume in a mammal over a period of weeks, the relevant component processes will include sodium and water excretion by kidneys, albumin synthesis by hepatocytes, hypothalamic and posterior pituitary neuronal release of antidiuretic hormone, and genesis of the thirst sensation, renin-angiotensin-aldosterone release as determined by renal hemodynamics, and antidiuretic hormone release as determined by thoracic volume (stretch) receptors, etc. These are unit processes in the determination of total fluid volume. In this analysis, and in the subsequent synthesis of a model of this system, the physiologist would not need to specify the structural details of m-RNA production in the renal justaglomerular apparatus, nor the quantum states open to carbon atoms in the Δ^4 double bond in Ring A of each aldosterone molecule. These latter considerations lie at levels of organization too low to have particular bearing on water volume determination - they are not aspects of unit processes of that system performance.

In contrast, if the system of interest to the physiologist is the tention-developing system of skeletal muscle, then the unit process is molecular, and an appropriate model would deal with formation and breaking of particular types of chemical bonds, or with chemical adsorptions as unit processes; but the exchange diffusion of water molecules across muscle cell boundaries, though present, would not be incorporated into the model because the latter process is not now known to have any particular bearing on the contractile system.

As another example of the decomposition of a macroprocess into its

component, lower-level unit processes, the oxygen consumption process of mammalian respiration is shown with its unit processes in Table III. Note that control arrangements are not shown. The means by which respiration is made cyclic reflect controller properties and arrangements, and these, together with the controlled process (oxygen consumption) and those coupled to it (excretion of carbon dioxide, hydrogen ion excretion, etc.) comprise a still higher-level system - the respiratory system in toto. Table III illustrates the pertinent decomposition into relevant unit processes of the oxygen consumption component only, in the total ensemble of processes comprising mammalian respiration.

TABLE III

UNIT PROCESSES OF MAMMALIAN OXYGEN CONSUMPTION

Unit Steps in the Overall Process	Examples of Chemical or Physical Principles Applicable to the Unit Processes
1. Alveolar ventilation	Fluid mechanics of laminar and turbulent gas flows
2. Pulmonary gas exchange	Diffusion: Henry's Law; Law of Mass Action, including allosteric conformational effects on hemoglobin
3. Circulation of oxygenated blood	Fluid mechanics; physical chemistry of hemoglobin
4. Distribution of oxygen throughout extravascular regions	Diffusion
5. Transport of oxygen into cells and mitochondria	Diffusion; Henry's Law; Mass Action
6. Cell respiration	Kinetics of electron transport chains; (semiconductor theory?)

Other physicochemical formulations that would not be relevant as unit processes of oxygen consumption include: the statistical mechanical representation of non-ideal gases; the molecular basis of viscosity coefficients; absolute reaction rate theory. All these considerations, though applicable to the matter involved, do not have particular bearing on the overall process, and so they are not unit processes in the analysis.

These features of Systems Physiology are similar to those of quantum mechanics in physics as described by Weisskopf: "It is one of the blessings of quantum mechanics that we can completely forget about effects of the internal structure of the unit when dealing with phenomena involving energies much lower than the excitation threshold of this unit. We can forget about atomic structure in kinetic gas theory, about nuclear structure in most of atomic theory, and about mesons and hyperons in most of nuclear theory."

It is the purpose of the analytical stages of physiological work to

identify and characterize mechanism - the relevant unit processes - of a system of interest. It is the purpose of the synthetic stage of Systems Physiology to demonstrate how the dynamic system properties at the highest level of interest arise from the unit process characteristics and couplings. Such a demonstration requires the development of a model of the system.

Models in Systems Physiology

Models have served well in physics and chemistry to codify understanding. Systems physiology accepts this practice of physics or chemistry and supposes that the proper aim of a line of investigation in physiology is the synthesis of a dynamic (computer) model that simulates the dynamic characteristics of a system of interest, within the time domain of interest, using (as subsystem or component structure in the model) simulations of the unit processes present in the real biological system. It is not enough merely to simulate a given set of system performance data: a family of formal, empirical models will exist capable of such a simulation. The aim instead is to demonstrate how the dynamic characteristics of a system arise out of the constrained specification based upon the unit processes involved. When that is accomplished, the investigation should lead to an advance in physiological knowledge and understanding.

From the foregoing, it can be seen that model building is inherent in physiological work, and that simulation is the expression of understanding of biological attributes in the physiological domain. This point deserves strong emphasis, for those who have never been engaged in computer simulation of biological system performance may not have discovered for themselves the powerful demands for intellectual precision and clarity that simulation imposes upon a scientist. In his computer models, the physiologist has a physical embodiment of his hypothesis, and shortcomings, contradictions, or failures, as well as the need for new data of previously unsuspected importance. These are made startlingly evident during simulation. Simulation invigorates and pervades physiological endeavor in such a fundamental manner that it is synonymous with high achievement by that endeavor.

Successful simulation codifies facts efficiently, predicts some new aspects of system performance accurately, and represents what is meant by "understanding" of complex systems. Successful simulation leads to the assignment of weighting factors to unit processes, and suggests points of attack on systems that may be exploited by disease or by rational therapy. Successful simulation also defines the stability regimes for biological systems, relates these to the average operating point of the system, and in so doing it reveals modes of oscillation and instability that may appear when systems are overdriven outside their "normal physiological ranges," as may occur in disease.

Techniques of Modeling in Modern Physiological Work

Techniques of modeling currently available for physiological work are summarized in Table IV. The heavy demand placed by physiological

science on simulation has already provoked some development of computational equipment and in the future may be expected to have a more profound effect. Furthermore, the distributed character of physiological systems, their marked and essential nonlinearities, their time-varying parameters and memory for their recent past history may invigorate the development of general systems theory. At the present time a deterministic systems approach is mathematically limited by the intractable properties of nonlinear differential equations. For that reason, the use of computers in physiological modeling is absolutely essential. In fact, Shannon, as well as Minsky, have expressed the view that computer use is superior to the use of classical mathematics for modeling certain functions such as those of neural elements and brains.

TABLE IV

FORMS OF MODELS

I. Nonmetric

- A. Semantic-verbal
- B. Heuristic computer programs (e.g., computer simulation of psychoneurosis)
- C. Topological

II. Metric (quantitative)

- A. Sets of equations
  1. Continuous deterministic
  2. Piecewise continuous deterministic
  3. Stochastic-deterministic (e.g., statistical mechanics)
  4. Finite-state discontinuous (e.g., Boolean)
  5. Stochastic non-deterministic
- B. Physical Analog
  1. Direct (special purpose analog computer)
  2. Indirect (electronic differential analyzer - general purpose analog computer)
- C. Digital Computer Program
  1. Direct simulation by programmed equation sets
  2. Digital - analog simulation programs
- D. Hybrids
  1. Hardware hybrids
  2. Equation set hybrids

The use of the machine shifts the attention of the physiologist from an over-enthusiastic development of mathematical expressions of transfer functions of limited applicability, and instead directs him toward mechanisms as manifested in unit processes. The use of linear, electrical models for the simulation of biological processes has such severe limitations as to constitute a real danger to the tyro. The nonlinearities inherent in real chemical, thermal, fluid mechanical, mechanical and biological systems are not so conspicuous in electrical systems, and the seductive formalisms of linear control theory and feedback theory that have formerly prospered so well in electrical engineering, will not serve for more than crude approximations in physiological work. Thus the demands of physiology may be expected to elevate the art and

science of modeling itself, for, after all, physiological systems are so far the most complex systems known to man. Herein lies one of the most important reasons for vigorous research and training in Systems Physiology. Such endeavor may be expected to stimulate the advancement of relevant physical, chemical, and mathematical sciences.

As Bullock has pointed out, the development of physiological models proceeds from models that represent a way of thinking that codifies what a system accomplishes (formal models), toward the richer and and more truly physiological models that represent a construct of how a system might work, formulated in explicit, unit-process terms (isomorphic models). The mature physiological model leads to considerations of biological systems one level higher and one level lower, at least, from the level of the system of interest. The physiologist expresses in the system model how the particular system works as part of a larger whole, as well as how its lower level unit processes support its macroperformance. In such model building there is as much uncertainty in building up from below, that is, in deriving the performance of macro-observables from the performances of micro-observables, as there is in building downward from a gross description of system characteristics to an understanding of component function. Either way alone leads to families of seemingly equivalent models - an unsatisfactory result that can be avoided only by accepting constraints of structure imposed by simultaneous consideration of system and unit process characteristics.

The purpose of the above discussion of the strategy of Systems Physiology and the requirements of model building in the science has been to define by implication the unique appeal and importance of Systems Physiology. It may be expected to enrich all of systems theory with benefit to applied physics and mathematics. This expectation is based on the assurance that in the still marvelous and mysterious performance of these most complex systems we know, will be found the inspiration for new developments in natural science generally. Up to the present time, neither biology, mathematics nor physics has been mature enough separately to support modern physiology. At the present time advances in biology will be based largely on convergence in an effective way with physics and mathematics, and in that convergence lies the future of modern Systems Physiology, which because of its preoccupation with general systems theory remains quite distinct from the future of analytic services of biophysics and biochemistry.

CONTRIBUTIONS OF SYSTEMS PHYSIOLOGY TO HUMAN HEALTH AND WELFARE

Systems Physiology supports modern medicine in three major ways:

A. Systems physiology provides the basis for rational diagnosis and therapy in medicine.

Every patient presents the physician with a systems problem at the organizational level of the "whole man." To deal with it, the physician must first recognize that there is a systems problem in which overt

symptoms, signs, and responses to therapy represent the multiple interactions of many related components, and second, he must be able to "understand" this synthetic picture in terms of a useful and appropriate level of analysis. Occasionally the latter will extend to the molecular level but more often the relevant unit processes will be much larger.

In these terms we might think of rational diagnosis as a kind of simultaneous solution of both the "inverse" and "converse" systems problems, i.e., of the identification of parameter modifications produced by disease, and their cause. In similar terms, rational treatment would comprise restoration of parameter values to normal by removal of the disturbing input whenever possible or, when this is not possible, by other appropriate countermeasures. Deciding what is "appropriate" can be a tricky business in a complex, multiloop system if the treatment is not to be worse than the disease.

Consider, for example, a patient whose respiratory center is greatly depressed by an anesthetic drug and who is obviously hypoventilating and cyanotic. Assuming we cannot immediately remove or chemically counteract the anesthetic, we might be tempted to treat the cyanosis by having the patient breathe 100% O_2. But this could be tragic. We are dealing here with the multiloop respiratory control system and we must look carefully before we leap. In system terms, the disturbance (i.e. the anesthetic) has reduced the central controller Pco_2-(H+) gain to zero or perhaps even to a negative value and what ventilation remains is entirely dependent upon peripheral hypoxic drive. Removing the latter by providing 100% O_2 could cause an apnea from which spontaneous recovery would not occur. The rational solution is to restore controller gain to normal by providing artificial ventilation until the disturbing input can be removed. This is a relatively simple example of the sort of problem we must always face if we are to avoid trouble in tampering with a complex system.

As another example, when we know what a drug does to system dynamics, we better understand how its action might be therapeutic. The issue of immediate importance with respect to digitalis compounds, for example, concerns the time course and extent of their effects on mechanical performance of the heart as part of the circulatory system. Whether these compounds achieve their effects by increasing myocardial protein synthesis, or by reducing the electrical resistance for ephaptic conduction among cells coupled electrically, etc., is a more remote consideration in judging the efficacy of a compound in medicine. The effects of the compounds on cardiac ejection force and time, on cardiac output, and on myocardial oxygen consumption determine the use of the compound. It is not sufficient merely to elucidate the molecular basis of action of a compound to establish its value in modern therapeutics. Its effects in the systems physiological terms obviously must be known.

The central place of Systems Physiology in the rationalization of diagnostic and therapeutics in medicine today stands out as a compelling reason for the expansion and updating of education in physiology.

B. Systems Physiology sets the specifications for the design of

artificial organs.

Systems physiological investigation has as its natural by-product the acquisition of dynamic specifications of systems and subsystems. If a heart, kidneys or limbs fail or are lost, the functional demands on the surrogate part are found from physiological studies. The engineering talent that is beginning to influence medicine strongly through equipment and prosthetic design is being most effectively focused on medicine through physiological work, as would be expected from the nature of physiological science as defined above. The dynamic characterization of components and their coupling relations are the natural interest of both physiologists and the design and systems engineers, and from their collaboration fruitful new developments in prosthetic construction are occurring.

C. Systems Physiology is a field well fitted to provide intellectual leadership in modern biology.

Systems Physiology is above all a quantitative and largely physical science. It is through this branch of physiology that the predominantly qualitative achievements of biochemistry become understood in the systemic terms of how much?, how fast?, how often?, how stable?, at what frequency?, that are of extreme importance in the understanding of complex systems. Thus Systems Physiology proves to be a unifying biological science. Biology is after all not chemistry of matter, or physics of matter - it is rather the study of the properties of matter that emerge from its organization, because of connectivity relations. Systems Physiology has connectivity and dynamics as its cynosure, and the strongest contributions of Systems Physiology to human welfare will come from its schievements in demonstrating how the performance of systems arise from the characteristics of lower level unit processes.

CURRENT PROBLEMS IN SYSTEMS PHYSIOLOGY

Below are listed arbitrarily several current problems of outstanding interest in Systems Physiology. The list is introduced to illustrate the character of current physiological work.

A. Determination of the computational processes used by brains, and how these arise from neuronal properties, connections, and simpler networks.

B. Information storage and retrieval from brains and how these processes arise from neuronal networks. (At the present time it appears that memory is a distributed and not a lumped system property: that is, a given fact remembered cannot be localized within one molecule within one neuron or glial cell. If information is stored directly in macromolecules - a point still unproved - it nevertheless must reside in macromolecules distributed through multiple neurons. Therefore, the apparent problem is how neurons are selected for storage and how they are scanned for retrieval, but it is not even certain that these are the proper terms for describing the problem. In any case, memory is a multicellular system problem, and not primarily a problem in molecular

biology.)

C. Analysis of the aging process and the decline of system function. Aging disturbs the coupling relations among systems so that systems whose dynamic ranges are becoming constrained with the passage of time, then place increased functional demand on other systems to which they are coupled. The redistribution of demand and coupling relations requires system definition.

D. Exploration of self-constructing system. One of the outstanding problems in Systems Biology is the discovery of the system connections and unit processes that support the process of self-construction and renewal. Differentiation and development and the flow of information during these processes is a major physiological problem.

E. Exploration of behavior. One of the highest system properties of great interest in humans is the behavior of the complete individual. The understanding of behavior as a system property arising out of environmental, genetic, and hormonal influences and mechanisms is the leading problem of physiological psychology and one of the most compelling problems for modern Systems Physiology.

F. Specification of dynamic properties of components. Since Systems Physiology emphasizes how system properties arise from component properties and connections, it is a necessary part of modern physiological work that the dynamic specification of components be carried out in a quantitative fashion more exacting than has been the case in the past. Much of the older characterization of biological components will have to be updated according to modern physiological principles and techniques.

Computers in Systems Physiology

Computer simulation of biological processes represents such an important and necessary stage of investigation by Systems Physiologists that it is worthwhile to emphasize how this use of computational equipment differs from use of other methods and instruments in biological science.

Physiologists have always gladly made use of scientific instruments of a wide variety of types, as these have become available. They have done so without insisting upon the apotheosis of any particular method or device. With respect to computers, however, the physiologist is confronted with a new situation, because to the extent that understanding of the dynamics of complex systems is achievable, it can become transmissible to other scientists in detail only through computer programs. A verbal model will not suffice for quantitative dynamic expression. Verbal models are not dynamic. It is possible when a scientist expresses his opinions about a complex system for him to employ a series of contradictions, even though he believes he has arrived at cognitive harmony. The act of development of a computer model - which is a model that can "live" dynamically in time - exposes contradictions and deficiencies of hypothesis mercilessly, as conversation

cannot be trusted to do for complex problems. Unaided human intuition fails as an explanatory technique for complex systems.

It is not the case that the computer is merely another instrument in a long line of instruments used by scientists. It differs from other instruments we use because it has produced such a quantitative change in our ability to deal with complex systems logically, that a qualitative change in Systems Physiology has resulted. It is true to an extent, that perhaps can only be fully appreciated by those who have attempted computer simulation as a means to express and transmit their working hypotheses, that the computer is utterly unlike other instruments. It is directly useful for thought, rather than being limited to the assistance of observation or measurement (though in other kinds of applications it is an aid there, too.)

These points about the essential contributions of computers as simulators to Systems Physiology underlie the suggestions for the training of future physiologists which are presented later.

FIELDS OF CURRENT RESEARCH THAT EMPHASIZE THE BLEND OF SYNTHESIS AND ANALYSIS IN PHYSIOLOGICAL WORK

An example of how physiological research moves across successive levels of complexity is in the field of vision. Psychophysiologically, of course, this is a most complex matter, yet on the molecular level investigation of the primary receptor process is among the most penetrating research endeavors. The action of light, at least in the case of scotopic vision, is beginning to be understood in considerable detail in terms of the isomerization of a pigment molecule with concomitant changes in a protein molecule (Hecht and Wald). However, so far the receptor process has not yet been elucidated, nor has the step of its translation into a cellular excitatory phenomenon been identified. The bleaching, or conversely, the dark resynthesis of the photosensitive pigment explains a part of the gross psychophysiological event of light or dark adaptation, but only a part: the work of Dowling has shown that the slow and gross adaptations can be so explained, but that rapid adjustments proceed at the next higher level of complexity in the accomodation of one of the next members of the neural visual chain. A yet more complex event, the regulation of the pupillary opening by a servo-mechanism, also contributes to the adaptation. Following the receptor fields of neuronal cells into "deeper" layers of the brain, Hubel and Wiesel have found increasingly interpretative receptor fields and quality distinctions in successive nerve cells. Color vision, too, is being approached by the simultaneous consideration of primary light-absorption processes and subsequent neural interactions.

The processes of muscle contraction and vision represent two of the most important processes to be found in the animal kingdom. In the case of both, physiological studies have required analysis into subcellular details, and a resynthesis of the information discovered there into an explanation ranging over multiple levels of organization. This combination of analysis and synthesis differentiates the physiologist from other biological scientists. Physiology sets the goals and identifies

the major problems in biology. Other advanced branches of biology supply details of mechanisms, but the physiological outlook always returns to the explanation of function in the complete, intact organism.

THE TRAINING OF PHYSIOLOGISTS FOR THE FUTURE

In spite of its great relevance to medicine, physiology is now handicapped in its growth in the United States by being too closely shackled to the narrow demands of medical curricula. Even the current fashionable experiments with medical curricula have largely failed to free physiology from commitments that are too narrow to favor its growth. Physiology is not merely a science of human organ function, as this report has tried to make clear. Physiology favors no particular level of organization. Yet the emphasis in medical physiology on the teaching of mainly qualitative aspects of human organ function has unfortunately, but unintentionally, weakened graduate training in the science. Graduate students of physiology very often are introduced to the science through medical physiology courses. Although medical physiology can be easily and well taught by modern physiologists, the paradoxical fact is that Systems Physiology contributes to medicine in ways not commonly revealed in such medical physiology courses. These courses cannot deal comprehensively with systems theory. It is not necessary that medical students master Systems Physiology - their interests are different from those of the professional physiologist, just as they are different from those of professionals in other sciences basic to medicine. However, the training of future professionals in physiology must present the science in its mature and most powerful form, and that presentation requires the teaching of physiology as the science of systems biology. Furthermore, since physicians must deal with systems and not just components, medical students also require some familiarity with modern Systems Physiology.

The requirements of physiology training programs are the requirements for education in systems science generally. The mathematics, physics, computer science and systems science relevant to such education are themselves now developing and, under these circumstances, it is no wonder that graduate training in physiology currently appears diffuse and confused. This situation contrasts sharply with the situation in biochemistry, in which training in the long-established content of organic and physical chemistry serves to support modern biochemistry. Training in these cognate sciences for biochemists is therefore relatively straightforward. But the cognate sciences for physiology are themselves new and growing.

We conclude that there is currently a crisis in physiology graduate training, and that current programs are not meeting the crisis. To meet the requirements for preparation in Systems Physiology we propose the formation of several centers of excellence in systems science, to be based upon existing physiology departments. Such training centers would conduct research and provide instruction in both the theoretical and practical aspects of the sciences for undergraduate or predoctoral students, for postdoctoral fellows, or for faculty on sabbaticals.

Eligible institutions would be those that chose to apply, and which have elements such as the following: They are to have established programs in physiology with a nucleus of faculty interested in Systems Physiology as described in this report. They are to have established engineering or physics schools or departments near the physiology department, each with some faculty interested in biological systems, or similarly appropriate activities in mathematics or biomathematics. They are to show willingness to make new appointments and to commit space for research to the field of Systems Physiology. They must show willingness to limit the academic assignments of the Systems Physiology faculty to no more than 50 percent time for teaching and administration; the other half of the time is to be allowed for research in systems physiology. Finally, they must show willingness to have the faculty devote much of its teaching effort to special courses for graduate students in the field of Systems Physiology.

If these conditions are met, support should include, besides the usual stipends, tuition, negotiated personnel support and travel, the following major capital item: analog, digital or hybrid simulation equipment to be operated by the systems physiology group. This equipment and all ancillary support for it, including maintenance, supplies, technical help, and air-conditioning, is an absolute requirement for research in Systems Physiology regardless of the capacity of the local computer center. Simulation demands satellite computation, and even very large time-shared installations at computer centers, cannot meet the requirements for the slow, long-running, conversational mode programs essential to simulation. Simulation problems demand development of real time conversational programs of great flexibility, as well as of hardware capable of dealing easily with sets of partial differential equations. Satellite hybrid computers will almost certainly be required. The general-purpose computer center cannot and does not meet the special requirements for the advance of systems physiology, with its great dependence on simulation techniques.

Functions of the Systems Physiology Centers

The Systems Physiology Centers would undertake both experimental analysis and then simulation of selected physiological systems by means of models comprised of simulated unit process mechanisms. The attempt would be made to develop an isomorphic model out of a formal model as a starting point. The science of physiology is now ready for advances of this kind, and there is truth in the opinion that proof of "understanding" or a physiological system requires isomorphic simulation of that system. Anything less than such a model may not reveal the insubstantial nature of most that we call "understanding."

The Systems Physiology Centers would develop both hybrid computational equipment and suitable programs. It must be emphasized that general-purpose computer centers do not usually meet the needs of simulation studies. The kinds of hardware and programs required for simulation are foreign to the specifications used in the design of general-purpose computer centers. Furthermore, existing equipment and programs for simulation are rudimentary, and out of Systems Physiology would come

a strong impetus for the further development of both.

The Systems Physiology Centers would explore and characterize quantitatively lower-level biological processes, emphasizing applications of physics and mathematics in the analysis. By this means, the characteristics of unit processes would be cast in a form suitable for incorporation into higher level models during simulation.

The Systems Physiology Centers would provide leadership for research in the field of the theory of hierarchical systems.

The Systems Physiology Centers would provide leadership for a new focus on physiological research that emphasizes experiments designed for the purpose of revealing the dynamic properties of systems in a quantitative way. Such information is now often an incidental or accidental by-product of investigations designed for other purposes. These Centers, through their education and re-education programs, would invigorate physiology in a general way by strengthening its theoretical core.

We hope that our proposal will lead to funded programs of the type we have described. The future of physiology as a distinct and vigorous science will depend upon fresh activities of this kind.

SUMMARY

Systems Physiology is emphasized as a vigorous division of modern physiology. Its central concept is that biological components when coupled, connected and interacting have properties beyond those of the components in isolation. A strategy of research in Systems Physiology is introduced.

Systems Physiology is a science defined by its point of view rather than by specific techniques. It is the biological science most applicable to multiple levels of organization.

The dependence of systems physiological work upon the formulation of dynamic models is so great that we may expect the demands of physiology to elevate the art and science of modeling itself. Physiological endeavor may be expected to stimulate the advancement of relevant physical, chemical and mathematical sciences to an extent greater than may be expected from any other branch of biology.

The contributions of physiology to human health and welfare are of several kinds. Systems Physiology emphasizes the performance of systems, and consequently provides the rational basis for therapy in medicine. When we know what a drug or a surgical intervention does to system dynamics, we begin to understand how its action might be therapeutic. The central place of physiology in the rationalization of therapeutics in medicine today stands out as a compelling reason for the expansion and updating of the physiology training program. Furthermore, physiology sets the specifications for the design of artificial organs. Physiological investigation has as its natural by-product the

acquisition of dynamic specifications of systems and subsystems. This dynamic characterization of components and their coupling relations are the natural interests also of design and systems engineers, and from collaborations with the physiologists, fruitful new developments in prosthetic design are occurring. Finally, Systems Physiology is especially well fitted to provide intellectual leadership in modern biology because it is through physiology that the predominantly qualitative achievements of biochemistry become understood in the systemic terms that are necessary for understanding.

Current problems in Systems Physiology include determination of the computational processes used by brains, the mechanisms of information storage and retrieval, the analysis of the aging process and the decline of system function, the expiration of self-constructing systems, the explanation of behavior of highly organized systems, and the specification of dynamic properties of components of systems.

In spite of its great relevance to medicine, physiology has heretofore been handicapped in its growth by being too closely shackled to the narrow demands of medical curricula. The training of future professionals in physiology must present the science in its mature and most powerful form, and that presentation requires the teaching of physiology as the science of Systems Biology. The requirements of Systems Physiology training programs therefore overlap with the requirements for education in systems science generally. There is currently a crisis in physiology training, and the current programs are not meeting the crisis.

New programs in Systems Physiology are proposed.

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ASSOCIATION OF CHAIRMEN OF DEPARTMENTS OF PHYSIOLOGY

A new society has been formed, the Association of Chairmen of Departments of Physiology. It became widely felt that there are many professional problems arising which affect primarily those in charge of the actual working units of academic physiology, and that a formal organization among the heads of these units could be dealing with those problems effectively. Some major concerns are the maintenance of physiology as an academic and scientific entity; the strengthening of the criteria of professional preparation among physiologists, and therewith the improvement of the image of physiologists as a highly developed population of scientists competent and qualified to meet any future challenge with which physiology will be presented; the threat of continued fragmentation whereby specialties such as large parts of biophysics and bioengineering remove themselves from physiology instead of contributing to the strengthening they could give; the patterns of funding available to physiology from various sources, which will materially influence the degree to which objectives can be implemented with respect to the creation of educational and scientific opportunities and the generation of manpower; the opportunities for educational contributions, in the context of medical schools both at the preclinical and at the clinical and postdoctoral level, but also in connection with general physiology as a biological science.

The new Association is hoping for a fruitful activity, and a rewarding contact with the American Physiological Society.

The following officers were elected:

President - Dr. Wilfried F. H. M. Mommaerts
President-Elect - Dr. Ernst Knobil
Secretary-Treasurer - Dr. E. B. Brown, Jr.
Interim Secretary-Treasurer - Dr. Alan M. Thompson
Councilors - Dr. Robert Berne, Dr. Ewald E. Selkurt, Dr. Howard E. Morgan
Representative to Council of Academic Societies - Dr. Daniel C. Tosteson