CONTENTS

ACTIONS TAKEN AT SPRING MEETING
April 11-16, 1966

ELECTIONS - Robert W. Berliner was elected to the position of President-Elect. Loren D. Carlson, who had been filling the short unexpired term of Robert E. Forster, was elected to a full four-year term on Council.

C. Ladd Prosser was elected to fill the unexpired term of Robert W. Berliner on Council.

All candidates nominated by Council were elected to membership.

All elections are effective July 1, 1966.

PORTER FELLOWSHIP AWARD - Miss Ann M. Graybiel was appointed Porter Fellow for a two-year period. She will continue her graduate studies in the Biology Department at Tufts University under the supervision of Drs. N. S. Milburn and C. Walcott. Her proposed doctoral thesis is titled "The role of the retinal oil droplets in color vision of a diurnal bird, Coturnix coturnix japonica."

NOMINATING PROCEDURE - At the Business Meeting, membership approved a trial procedure for nominating officers for the Society. Instead of all nominations for President-Elect and Councilman coming from the floor on the first nominating ballot, nominations will be made by mail prior to the meeting. Return post cards will be sent with the February issue of The Physiologist. The Executive Secretary will report the results of these nominating ballots at the initiation of the 1967 Spring Business meeting and the voting will proceed according to the usual pattern. It is hoped this procedure will save time at the Business meeting.

APS BYLAWS - Members approved the new Bylaws with two exceptions:

1. Article III Section 10. Expulsion Procedures.
   This section was deleted from the Bylaws.
2. Article XIII Section 1. Presentation (of Amendments).
   The following was substituted for the wording appearing in the February Physiologist:
   "Amendments to these Bylaws may be proposed in writing by any regular member to Council at any time up to three months in advance of the Spring meeting, or at a business meeting of the Society. Such a proposed amendment must be presented in writing at the following Spring business meeting for action by the Society.

(See the February 1966 issue of The Physiologist for comparison of old and new Bylaws).

RESOLUTION ON ANIMAL BILLS - Membership unanimously approved the following resolution be sent to Senator Magnuson and members of the Senate Commerce Committee:

Whereas:

S3138 deals with interstate commerce in cats and dogs

that might be sold for any purpose or use, and

Whereas:

S3138 does not include "other animals" and therefore would not require cumbersome machinery to regulate traffic in other animals for which no evidence exists that theft or maltreatment is a problem, and

Whereas:

S3138 does not require licensing of laboratories leaving the field of use and care entirely to other legislation,

Therefore be it resolved that

The American Physiological Society urges the Senate Commerce Committee to amend S2322 (Magnuson) to the end that it conforms with the provisions of S3138 (Mondale)

MEMBERSHIP STATUS

April 1, 1966

Active Members	2580
Retired Members	133
Honorary Members	18
Associate Members	189
	2920

SUSTAINING ASSOCIATES

Abbott Laboratories, Inc.
Ayerst Laboratories
Beckman Instruments, Inc.
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.
A. H. Robins Co.
Smith Kline & French Laboratories
E. R. Squibb & Sons
The Upjohn Co.
Warner-Lambert Research Institute
Wyeth Laboratories

DEATHS SINCE FALL MEETING 1965

Alf S. Alving - 5/12/65
W. P. Anslow, Jr. - 3/17/66
Walter R. Bloor - 2/11/66
I. L. Chaikoff - 1/25/66
Joseph Erlanger - 12/5/65
Robert Hodes - 1/27/66
Franklin P. Hollander - 3/25/66
Ralph G. Janes - 8/14/65
E. B. Krumbhaar - 3/16/66
E. K. Marshall - 1/10/66
Enid T. Oppenheimer - 3/18/66
Arthur K. Parpart - 9/17/65
John R. Poppen - 10/9/65
A. N. Richards - 3/24/66

50-YEAR MEMBERS

Samuel Amberg
Aaron Arkin
George A. Baitsell
Olaf Bergeim
Harold C. Bradley
Thorne M. Carpenter
Percy M. Dawson
George Fahr
Mabel P. Fitzgerald
Thomas S. Githens
Charles M. Gruber
Addison Gulick
Frank A. Hartman
Philip B. Hawks
Charles L. Hess
Harold L. Higgins
Paul E. Howe
Dennis E. Jackson
Edward C. Kendall
Israel S. Kleiner
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
Alfred N. Richards
Julius M. Rogoff

George B. Roth
Andrew H. Ryan
Ernest L. Scott
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, 1966.

FULL MEMBERS

ABRAHAMS, Vivian C.: Assoc. Prof., Queen's Univ., Kingston, Canada
APTER, Julia T.: Res. Assoc., Math. Biol., Univ. of Chicago
BADER, Hermann: Asst. Prof. Physiol., Vanderbilt Univ.
BAKER, Robert D.: Assoc. Prof. Physiol., Univ. of Texas Med. Br.
BAR-SELA, Mildred E.: Asst. Prof. Anat., Baylor Univ.
BASKIN, Ronald J.: Asst. Prof. Zool., Univ. of California, Davis
BERLIN, Richard D.: Assoc. Physiol., Harvard Med. Sch.
BLINKS, John R.: Asst. Prof. Pharmacol., Harvard Univ.
BOLLET, Alfred J.: Assoc. Prof. Prev. Med., Univ. of Virginia
BRIEHL, Robin W.: Asst. Prof. Physiol., Albert Einstein Coll. Med.
BRINSTER, Ralph L.: Asst. Prof. Physiol., Univ. of Pennsylvania
CADE, James R.: Assoc. Prof. Med., Univ. of Florida
CAMOUGIS, George: Sr. Neurophysiol., Astra Pharmaceutical Products
CARSTEN, Mary E.: Assoc. Prof. Physiol., UCLA
CRITCHLOW, Burtis V.: Assoc. Prof. Anat., Baylor Univ.
CROPP, Gerd J. A.: Asst. Prof. Pediat., Univ. of Colorado
DANELLIS, Joan V.: Res. Assoc., NASA, Ames Res. Ctr.
DOBSON, Alan: Assoc. Prof. Vet. Physiol., New York State Vet. Coll.
FAJER, Abram B.: Asst. Prof. Physiol., Univ. of Maryland
FELDMAN, Samuel M.: Asst. Prof. Physiol., Albert Einstein Coll. Med.
GALE, Charles C.: Asst. Prof. Physiol.-Biophys., Univ. of Washington
GAZZANIGA, Michael S.: Res. Fellow, California Inst. Technology
GLICK, Gerald: Sr. Investigator, Cardiol. Br., NHI
GLICKSTEIN, Mitchell: Asst. Prof. Physiol., Univ. of Washington
GOLDSTEIN, Robert: Prof. Med., New York Med. Coll.
GORESKY, Carl A.: Asst. Prof. Med., McGill Univ.
HIGGINS, James T., Jr.: Instr., Internal Med., Yale Univ.
HOLLIDAY, Malcolm A.: Cl. Prof. Pediat., Univ. of California, S. F.
JAVITT, Norman B.: Asst. Prof. Med., New York Univ. Med. Ctr.
JOY, Robert J. T.: Med. Corp., U. S. Army
KAKO, Kyochei: Asst. Prof. Physiol., Univ. of Ottawa
LELE, Padamakar P.: Assoc. in Physiol., Harvard Univ.
LEVITIN, Howard: Asst. Prof. Med., Yale Univ.
LISK, Robert D.: Asst. Prof. Biol., Princeton Univ.
LLOYD, Thomas C., Jr.: Asst. Prof. Physiol., Western Reserve Univ.
MALINDZAK, George S., Jr.: Asst. Prof. Physiol., Bowman Gray Univ.
MANNING, John W.: Asst. Prof. Physiol., Emory Univ.
McDONALD, Donald A.: Sr. Res. Assoc., Presbyterian Hosp., Phila.
MILLER, Leon L.: Prof. Rad. Biol., Univ. of Rochester
NACHMAN, Ralph L.: Instr. Med., New York Hosp.
NOVICK, Alvin: Assoc. Prof. Biol., Yale Univ.
OGDEN, Thomas E.: Res. Instr. Physiol., Univ. of Utah

PARLOW, Albert F.: Asst. Prof. Physiol., Emory Univ.
PEARCE, Morton L.: Chief, Cardiol. Sect., Wadsworth Hosp., L.A.
PILKINGTON, Lou Ann: Instr. Physiol., Cornell Univ. Med. Coll.
ROVICK, Allen A.: Asst. Prof., Stritch Sch. of Med.
SACKNER, Marvin A.: Asst. Prof. Physiol., Univ. of Miami
SALTZMAN, Herbert A.: Dir., Hyperbaric Unit, Duke Hosp.
SCHULTZ, Stanley G.: Assoc. in Biophys., Harvard Med. Sch.
STARR, Arnold: Asst. Prof. Med., Stanford Univ. Sch. of Med.
STEWART, Doris M.: Res. Asst. Prof. Zool., Univ. of Washington
SWANN, Henry E., Jr.: Med. Res. Physiol., Rancho Los Amigos Hosp.
TERRES, Geronimo, Jr.: Asst. Prof. Physiol., Stanford Univ.
THOMAS, Lewis J.: Asst. Prof. Anesthesiol., Barnes Hosp., St. Louis
TIERNEY, Donald F.: Asst. Prof. Physiol., Univ. of California, S.F.
VASSALLE, Mario: Asst. Prof. Physiol., State Univ. N.Y., Brooklyn
VICK, Robert L.: Asst. Prof. Physiol., Baylor Univ.
WHITTOW, George C.: Assoc. Prof. Physiol., Rutgers, The State Univ.

ASSOCIATE MEMBERS

BESCH, Emerson L.: Asst. Res. Physiol., Univ. of California, Davis
BROWN, Harold M., Jr.: Res. Assoc., Univ. of Utah Coll. of Med.
CRUMP, Malcolm H.: Asst. Prof. Physiol.-Pharmacol., Iowa State Univ.
DIMMICK, John F.: Asst. Prof. Biol., Wake Forest Coll.
GOLDNER, Andrew M.: Fellow, USPHS Trainee, Geo. Washington Univ.
KABAL, John: Instr. Physiol.-Biophys., Georgetown Univ.
KRANING, Kenneth K. II: Res. Assoc. Occupational Health, Univ. Pittsburgh
LEHMKUHL, L. Don: Sr. Instr. Physiol., Western Reserve Univ.
MORGAN, Horace C., Jr.: Asst. Prof. Physiol.-Pharmacol., Univ. Georgia
PURPLE, Richard L.: Instr. Physiol., Univ. of Minnesota
RANDALL, Howard M.: Instr. Physiol., Louisiana State Univ. Med. Ctr.
REEVES, Elizabeth: Deputy Head, Envir. Stress, Naval Med. Res. Inst.
RICHARD, Rene S.: Trainee, Anat. Sci., UCLA
RIDLEY, Peter T.: Postdoct. Fell., USPHS, Geo. Washington Univ.
SCHMEER, Sister M.R.: Assoc. Prof. Biol., Coll. St. Mary's of Springs
TWARDOCK, Arthur R.: Asst. Prof. Vet. Physiol.-Pharmacol., Univ. of Illinois
WAGGONER, William C.: Staff Physiologist, Colgate-Palmolive Co.

1965 FISCAL REPORTS

SOCIETY OPERATING FUND

INCOME

Regular Membership Dues	$36,229
Associate Membership Dues	905
Sustaining Associates	6,925
Interest on Savings Accounts	3,945
Reimbursement from Federation Spring Meeting	13,589
Reimbursement from Grants, etc. (overhead)	2,959
Sale of Laboratory Experiments, net	383
Physiology for Physicians Subscriptions	14,752
Councilman's Tour, net	149
Miscellaneous Income	29
Total Income	79,865

EXPENSES

Salaries and Benefits	$30,030
Auditing and Legal Fees	220
Hotel and Travel	3,495
Addressing, Mailing & Shipping	3,268
Telephone	427
Printing	8,074
Supplies and Equipment	969
Duplicating	1,386
Rent	1,077
Depreciation on Furniture & Equipment	435
Repairs and Maintenance	293
Honoraria for Authors (Physiol. for Physicians)	1,200
Editorial Expenses (Physiol. for Physicians)	65
Copyright charges (Physiol. and Pharm. for Physicians)	100
Bank charges & foreign exchange	29
APS Business Office Expenses	737
Dues to Federation	14,850
Dues to AIBS	750
Dues to AAAS	20
Dues to National Society for Medical Research	250
IUPS News Letter	500
Revision of Lab. Experiments	200
Bowditch Lecture	500
Miscellaneous Expenses	33
Fed. Business Office Service Charge	6,425
Total Expenses	75,333

Excess of Income over Expenses	4,532
Amount in Savings as of Dec, 31, 1965	$60,000

PUBLICATION OPERATING FUND

INCOME

Subscriptions	$293,376
Sale of Reprints, net	52,726
Other Publication Sales	10,990
Advertizing, net	15,651
Page and Article Charges	72,634
Royalty Income	985
Interest on Savings	3,300
Miscellaneous Income	31
Total Income	$449,693

EXPENSES

Salaries and Benefits	$55,475
Section Editors Expenses	21,269
Redactorial Expense	35,858
Professional and Other Personal Services	4,616
Printing and Engraving	233,840
Supplies and Duplicating	3,426
Communications and Shipping	42,247
Hotel and Travel	2,573
Repairs and Maintenance	198
Promotional Expenses	7,521
Depreciation on Furniture and Equipment	1,021
Rent	7,359
Miscellaneous Expenses	282
Fed. Business Office Service Charge	43,446
	459,131
Less Allocations to Publication Inventories	25,111
Total Expenses	$434,020

Excess of Income over Expenses	$15,673

PUBLICATION CONTINGENCY AND RESERVE FUND

Balance Dec. 31, 1964	$671,568
Gain on Sale of Securities	12,637
Dividends and Interest Paid to APS	(25,098)
Dividends Reinvested	17,752
Balance Dec. 31, 1965	$701,957

PICTURES OF APS PRESIDENTS

The fourth composite picture of APS Presidents is now available. Orders may be placed with the Central Office of APS. This composite (11" x 14") shows the last ten Presidents and is a follow-up of the three previous composites. (See the Physiologist Vol. 2, #4, Nov. 1959). The price for the fourth composite is $4.00.

PRESIDENTS
OF THE
AMERICAN PHYSIOLOGICAL SOCIETY

L. N. KATZ
1957

H. DAVIS
1958

R. F. PITTS
1959

J. H. COMROE, JR.
1960

H. W. DAVENPORT
1961

H. S. MAYERSON
1962

H. RAHN
1963

J. R. PAPPENHEIMER
1964

J. M. BROOKHART
1965

R. E. FORSTER
1966

FUTURE MEETINGS

1966 - Fall Meeting - Baylor Univ., Houston, Texas, Aug. 29-Sept. 2

1967 - Spring Meeting - Chicago, Ill., April 16-21

1967 - Fall Meeting - Howard Univ., Washington, D. C., Aug. 23-27

1968 - Spring Meeting - Atlantic City, N.J., April 15-20

1968 - Fall Meeting - Cancelled due to IUPS Congress

1968 - IUPS Congress - Washington, D. C., Aug. 25-30

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

1969 - Fall Meeting - Oklahoma State Univ., Stillwater and Univ. of Oklahoma Medical Center, Oklahoma City

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

DUES NOTICES

Members will be receiving dues notices for the year July 1966 to July 1967. Dues are payable in advance. Along with the dues notices will be the assessment notices for the 1968 Congress. If at all possible, please submit separate checks. This will facilitate banking procedures. Checks for dues and assessment are to be sent to the APS Central Office. It should be remembered that billings for APS journals subscriptions are separate from dues and run from January to January. Billings for subscriptions are sent out by the APS Business Office.

FALL MEETING 1966

Baylor University College of Medicine
and
The University of Texas Dental Branch
Houston, Texas
August 29 - September 2

The refresher course this year is scheduled for Tuesday, August 30th, in Cullen Auditorium in Baylor University College of Medicine and is under the chairmanship of Dr. Arthur C. Guyton. The topic for discussion is "Mathematical and Computer Analyses of Circulatory and Body Fluid Control" with the following topics and participants:

1. Overall View of the Cardiovascular System from a Control Standpoint - Dr. Fred S. Grodins, Northwestern University Medical School.

2. Transfer Functions for Individual Portions of the System - Dr. Fred S. Grodins, Northwestern University Medical School.

3. Use of the Computer for Quantitative Measurements of Circulatory Function - Dr. Homer R. Warner, University of Utah College of Medicine.

4. Use of the Computer for Testing Mathematical Models of Circulatory Function - Dr. Homer R. Warner, University of Utah College of Medicine.

5. Integration of Cardiovascular and Body Fluid Control Systems - Dr. Arthur C. Guyton, University of Mississippi School of Medicine.

6. Analyses of Cardiac Output, Arterial Pressure, and Body Fluid Volumes in Normal and Representative Abnormal States - Dr. Arthur C. Guyton, University of Mississippi School of Medicine.

On Friday morning, September 2nd, two symposia will be held. One will be under the chairmanship of Dr. James W. Campbell, Associate Professor of Biology, Rice University, on the Physiology and Biochemistry of Molluscs, and will be held in Room 111 at Baylor. The second symposium will be under the chairmanship of Dr. Charles A. Berry, Chief of Manned Spacecraft Center Medical Programs at NASA and will be held at NASA. Transportation will be provided free of charge. The subject will be "Man's Physiological Response to the Space Flight Environment."

The Bowditch Lecture for 1966 will be given at 4:15 p.m. on Wednesday, August 31st, in Cullen Auditorium at Baylor by Dr. David H. Hubel, Dept. of Neurophysiology, Harvard Medical School. The subject will be "Visual Cortex and Perception."

Other activities open to members of the Society, wives, and registrants will be a "Texas-style barbecue" on Thursday evening and the Annual Banquet on Wednesday evening at the San Jacinto Inn, at which

our Past President, Dr. John M. Brookhart will address the members of the Society.

In addition, boat rides on the Houston Ship Channel will be scheduled for Wednesday and a trip on Thursday to NASA, primarily for wives and children, although anyone interested may go. If there is sufficient demand, a morning sight-seeing tour of Houston and a luncheon for the women will be arranged for Friday, September 2nd.

Limited housing will be available at Jones College of Rice University. In addition, special room rates have been negotiated with the Shamrock Hotel for this meeting. Both of these are adjacent to The Texas Medical Center. The Houston Convention and Visitor's Council will set up an information desk in the lobby of the Shamrock to answer any questions about Houston. There will, of course, be an information desk set up in the Registration area at Baylor.

Registration begins Monday, August 29th, at 1:00 PM and will continue through Thursday, September 1st in the Rayzor Student Lounge at Baylor.

Scientific sessions will be held in lecture rooms in Baylor and The University of Texas Dental Branch.

MILTON O. LEE PORTRAIT

The APS Council commissioned Miss Irene Higgins of Charlottesville, Virginia to paint a portrait of Dr. Lee as a lasting reminder of his many services to the Society, particularly his management of the Society's publications.

The portrait was unveiled at a small party in the Society's new quarters on February 26, 1966. Several of Dr. Lee's former associates on the Board of Publication Trustees were in attendance along with members of Council. Dr. Philip Bard gave a short talk on Dr. Lee's past accomplishments for the Society and President Brookhart unveiled the portrait.

The portrait now hangs in the new quarters and members and their friends are cordially invited to drop in and see it whenever they may be in Washington.

APS REFRESHER COURSE

MATHEMATICAL AND COMPUTER ANALYSES OF CIRCULATORY AND BODY FLUID CONTROL

Baylor University, August 30, 1966
Chairman: Arthur C. Guyton

1. Overall View of the Cardiovascular System from a Control Standpoint - Fred S. Grodins

2. Transfer Functions for Individual Portions of the System - Fred S. Grodins

3. Use of the Computer for Quantitative Measurements of Circulatory Function - Homer R. Warner

4. Use of the Computer for Testing Mathematical Models of Circulatory Function - Homer R. Warner

5. Integration of Cardiovascular and Body Control Systems - Arthur C. Guyton

6. Analyses of Cardiac Output, Arterial Pulse, and Body Fluid Volumes in Normal and Representative Abnormal States - Arthur C. Guyton

ELEVENTH BOWDITCH LECTURE

Dr. David H. Hubel, Professor of Neurophysiology at Harvard Medical School has been chosen to give the eleventh Bowditch Lecture at the Society's Fall Meeting at Houston, Texas, August 31st in Cullen Auditorium at Baylor University College of Medicine. The title of his lecture will be "Visual Cortex and Perception."

COUNCILMAN'S TOUR

LOREN D. CARLSON

Some Remarks about Physiology

On the premise that the future of physiology might be determined by a consideration of the character of the training programs, I visited several departments in different academic settings. These formal stops on the councilman's tour were augmented by a number of opportunities to "site visit" institutions with physiology training grants. I am indebted to many for their cordial reception and time.

Physiology has been a fecund science, fruitful in offspring; prolific; and rich, although slow, in invention. The ephebic offspring are healthy and thriving and family reunions are more likely then resorption.

Officers and councilmen have previously expressed anxieties about the role of physiology. Pappenheimer (Physiologist, 8:341-347, 1965) used the term integrative physiology to distinguish the parent and to show cause for application of the fruits of the labors of the molecular biologist, the biophysicist and the biochemist. He roughly and rudely interpreted Forster (Physiologist, 7: 347-349, 1964) as suggesting that our colleagues of related fields think of physiology as a sort of functional gross anatomy, parts of which are exhumed annually for first year medical students but moribund in terms of contemporary research. Moribund freely translated means not likely to excite Congress to provide NIH or NSF with funds for research or training in this area. Rahn (Physiologist, 7: 334-342, 1964) emphasized the need for synthesizers, catalysts and evaluators. The parent, Physiology, is committed to the role characterized by the words integrate and synthesize. We do not exhume every year - we reevaluate and reinterpret in light of new information from whatever the source. The keen insight of some have focussed so well on needs for information as to stir the origins of whole new fields and to attract men with training in other fields.

By certain criteria, physiology has been eminently successful. Its concepts are now solidly entrenched as the basis of the applied biological sciences. Its success has led to its disintegration or fragmentation if you choose those words.

I believe that a group of physiologists will continue to collect data - and reasonably so as it is necessary to describe the performance of various systems. Descriptions of pulmonary function in young and old, lean and fat, fit and unfit - and on and on - seem pedestrian and uninspiring without the end view of supporting a concept or illustrating an analogue. Techniques will be refined and concepts expressed with greater clarity. There are many areas of interest where the provision of accurate descriptive information will serve as a key to synthesis and the force to open new fields.

I believe that parts of physiology will continue to merge into clinical and applied areas (human, animal or plant). Here a reunion with

biochemistry and molecular biology will take place.

I believe major contributions in physiology will come from cell and systems analysis with emphasis on a conceptual base and the emergence of a theoretical biology. What has and will continue to distinguish physiology is not the object of its study but the viewpoint.

While departmental programs of instruction vary, all are characterized by the addition of more mathematical backgrounds and by the cosmopolitan (academically) nature of the staff. The problem of producing an appropriate end product in training is so challenging and so complicated that there should be a range of solutions as wide and diverse as our imaginations allow.

APPEAL FOR APS JOURNALS

The Society has moved into its new quarters and now has an adequate library and conference room. We are trying to stock the library with all of the APS publications along with other reference books. There are several issues of the journals that we have been unable to obtain as yet.

This is an appeal to members who might have copies of the following issues that they would be willing to donate to the Society.

Physiological Reviews:
Vol. 24 - 1944
Vol. 25 - 1945
Vol. 26 - 1946
Vol. 27 - 1947

American Journal of Physiology:
Vols. 1 thru 66
Vols. 96, 97, 98 & 99

SUPPLY AND DEMAND

As a follow-up of the short note published in Vol. 3, #4, page 19, of the November 1960 issue of THE PHYSIOLOGIST the following gives some indication of the trends in the supply of and demand for physiologists since 1960. As stated in the first note the data are taken from the records of the Federation Placement Service. It is freely admitted that this may not be a true picture of the overall market for trained physiologists but it is believed to be a large enough sample to indicate trends.

The figure indicates that in 1963 the number of trained physiologists began to increase after a steady decline of several years. This could have been due to many factors such as the institution of various training programs supported by Federal agencies and, we like to feel, the increased emphasis on physiological careers and the recruitment program of the APS Education Committee. It is hoped that the beginning trend of increased numbers of trained physiologists, indicated in the last few years, will continue. With the advent of new medical schools and the expanding government needs for physiologists the need for more trained physiologists is evident.

The tables give some indication of the training of available physiologists and the types of positions available.

Candidates for Positions as Physiologists

Training	1961	1962	1963	1964	1965
Holding Ph.D. in physiology or zoology	29	22	40	43	49
Advanced graduate student candidates for Ph.D.	12	14	15	26	26
Holding M.D. with strong experience in physiology	3	4	0	6	6
Totals	44	40	55	75	81

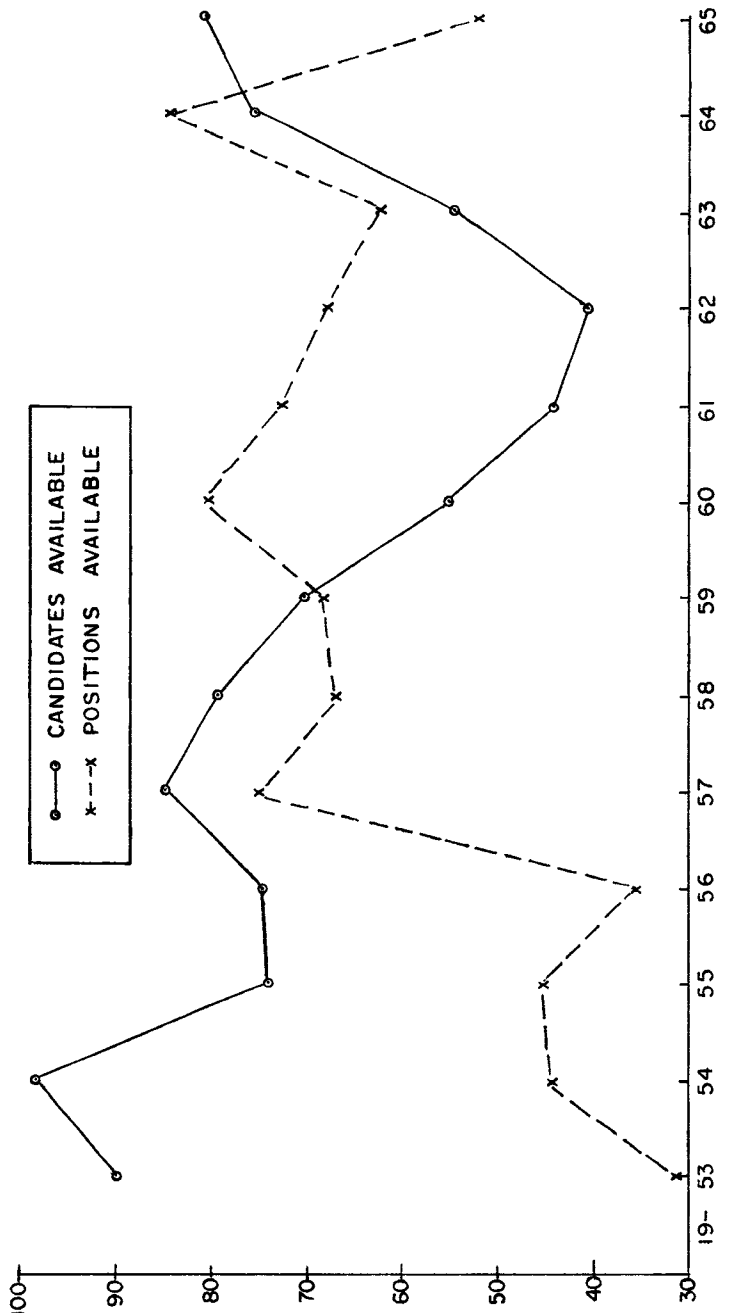
The major interests of the candidates were: - endocrinology and reproduction; neurophysiology; cardiovascular physiology; cellular physiology; and environmental physiology - in order of frequency.

Positions Available for Physiologists

Positions	1961	1962	1963	1964	1965
Academic Positions.					
Medical Schools, preclinical teaching & research	26	23	22	18	13
Medical Schools, clinical research	20	18	14	16	6
Undergraduate Schools, teaching & research	10	4	9	19	19
Government & Industry, research	17	23	18	21	14
Totals	73	68	63	84	52

There is indication of an increasing need for physiologists as teachers and research workers in non-medical school academic institutions.

Most physiologists believe that physiology should continue as a specific discipline and science. Due to the wide diversity of applications of physiological knowledge there is a growing trend to absorb physiology or parts of it into clinical departments in medical schools and into various non-physiological labeled courses in undergraduate and graduate schools. In one sense this is a good trend in that physiological thinking is permeating many medical and biological areas. In another sense, physiology may lose its identity as a science if specific courses and departments lose their physiology labels. Should we continue to train physiologists per se or should we train people in specific specialties based upon parts of physiological knowledge and label them something other than physiologists? In any event a larger number of "physiologically" trained scientists will be needed in the next several years.


CANDIDATES AVAILABLE
POSITIONS AVAILABLE
100
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FEDERATION PROCEEDINGS TRANSLATION SUPPLEMENT - SOME PROBLEMS PAST, PRESENT AND FUTURE

ROBERT W. DOTY

For more than 100 years a reading knowledge of German, French and English was sufficient to gain direct access to almost all the physiological literature. The appearance of major work in other languages was sufficiently rare that loss of such information could either be accepted or retrieved by occasional translation, as with the work of Pavlov or Ramon y Cajal. Within the past decade, however, this situation has changed drastically. A loosening of tradition and control within the Soviet Union together with a vigorous support of scientific endeavor there has begun to be produced great numbers of articles in Russian which definitely belong in the mainstream of physiological thought. Since very few West European or American physiologists read Russian, a considerable amount of significant information will remain inaccessible unless it is retrieved through an adequate translation program.

The full import of the potentialities can be emphasized by economic considerations. A grant of $100,000 per year given to a group of physiologists generates perhaps 100 pages of hopefully significant information. If published in a carefully edited and regularly appearing journal it becomes useful to the world at large and this constitutes by far the major return of the $100,000 investment. It is quite possible, however, that $100,000 invested in the translation and distribution of Russian articles could yield ten times as much equally significant information, i.e. 1,000 pages. While it would obviously be ridiculous to suggest that the National Institutes of Health could retire solely into the translation field, it is equally foolhardy to ignore such an economic bargain in scientific information.

During the 1950's this developing situation was met in two ways: 1) by increased numbers of translations deposited on microfilm in various libraries and 2) by cover to cover translation of several Russian journals. The microfilm endeavors provided many librarians with a great deal of work in cataloging and listing the translations, but few ever came to the attention let alone into the hands of a working physiologist. The cover to cover translation revealed that much Russian physiology was still concerned with outmoded concepts and methodologies and even the best articles suffered heavily from translations devoid of feeling for scientific English.

Recognizing these shortcomings, the National Library of Medicine contracted with FASEB to produce the Translation Supplement to the Federation Proceedings. The advantages envisioned were: 1) the elimination of articles having limited use or interest for the Federation audience, 2) editorial correction to achieve current and appropriate scientific terminology, 3) wide distribution to those directly concerned with using the translated material. The first few issues showed signs of haste in that a few articles of questionable value were published simply because no others were yet translated and editorial control of

style and terminology was still incomplete. Within the past two years, however, these early problems have been resolved and a large number of significant, well-translated articles have been published.

Many serious problems remain, however. One insoluble problem is that in certain fields there is simply no significant amount of Russian work and Federation members with interests limited to those fields will thus inevitably find the Translation Supplement of no value to them. Another problem is that editorial control in Russian journals seems to be even less stringent than in our own. Thus many basically sound articles lose much of their value because of an author's failure to delineate his methods with adequate precision or because he neglects discussion of alternative explanations of his data, etc. Many of the best articles appear in Biokimia, Biofizika and the Dokladii (Proceedings of the Academy of Sciences of the USSR) which are still translated in their entirety. Although, because of their cost, these translated journals go almost exclusively to libraries rather than to individuals, the Translation Supplement to avoid duplication of effort has usually excluded these articles.

There are a number of pressures of cost and equitable representation. In the early stages as the editor for physiology I endeavored to represent all interests of the American Physiological Society and selected articles for translation in endocrinology, gastroenterology, renal, respiratory and cardiovascular physiology as well as in my own area of neurophysiology. It was soon obvious, however, that I was not competent to evaluate most non-neurological articles; that since there were six societies participating in the endeavor there was simply not enough space even for the neurological articles I was certain had merit; and finally there being in the Soviet Union a great emphasis upon the neural sciences, the majority of the better articles were in this field. Thus it has developed that the Translation Supplement serves almost exclusively the interests of the neurophysiological segment of our Society.

This latter fact raises difficulties of its own. Besides the obvious one of the Supplement serving only a minority of the Society it is equally significant that the Supplement fails to reach directly the great majority of individuals who potentially at least, would be interested in the neurological portion of its contents. These include neuroanatomists, psychologists, clinical neurologists, electroencephalographers, zoologists and foreign neurophysiologists, few of whom are members of the Societies of the Federation.

The National Library of Medicine, sensing the possibility that similar considerations apply throughout the Federation, i.e. that only a minority of the membership is benefited by the Translation Supplement and a potentially large outside audience remains inaccessible, felt that the Federation membership should display its interest by making a substantial contribution to the financial support of the Supplement. Obviously it would not be a very popular move to require the entire membership to subsidize the interests of a few. Nor is it reasonable to expect much enthusiasm for individual subscriptions to the present Supplement in which six societies amass a conglomeration of material far in excess

of any individuals interests. Naturally then, the Federation Board rejected the National Library of Medicine's proposal, and with this impasse the Translation Supplement may cease with the November-December 1966 issue. This would be unfortunate since it then becomes just another shot in the scatter of translation efforts already cluttering the libraries and the now efficient organization for achieving high quality translations would be dispersed.

Efforts are presently being made to find other support for the Translation Supplement. Regardless of the success or failure of these efforts, it seems that some reorganization might be in order. I personally feel that there are many more good articles in the neural sciences in Russian, as well as some in Japanese, Spanish and Italian, than the Translation Supplement will be able to accomodate. I would therefore propose that some organization, such as the International Brain Research Organization or an American affiliate thereof, be charged with producing a continuing journal of translated articles in the neural sciences which, with heavy subsidization, could be available to all for a very modest subscription fee. The Federation Proceedings Translation Supplement relieved of the demand for publishing the extensive neural sciences material, would then be freed to explore more adequately the potentialities in other areas of physiology. Such exploration, however, will require the participation of individuals having editorial competence in these areas.

As one of your editors for the Translation Supplement, I would greatly appreciate advice and suggestions concerning these problems, and I am sure the officers of the Society join me in this desire to obtain guidance from the membership.

PHYSIOLOGICAL REGULATION: THE STEADY STATE*

JOSEPH ENGELBERG

The Constancy of the Internal Environment

In the course of its life the mammalian organism is exposed to a variety of external conditions, of which the extremes of environmental temperature form one example. It is to Claude Bernard (1813-1878), the great physiologist, that we owe the clear recognition of the fact that though the external environment is subject to continuous change and perturbation, the internal environment of the organism, that is the immediate environment of the cells, remains in a state of relative constancy. For example, a liver cell in a mammal resides in an environment in which the temperature is always close to 38°C.

The constancy we speak of is relative rather than absolute. For every physiological parameter there will be, at the very minimum, small random and cyclical fluctuations.

What is remarkable about this constancy, moreover, is that it is not confined to a given individual at a given time but that it extends over whole populations and over immense periods of evolutionary development.

1) Constancy within the population. Table I, lists the range and median of so-called normal values for a number of physiological parameters in man. The fact that such a table can be assembled and that it has clinical usefulness implies that the values of these parameters are roughly the same for healthy individuals in the human population.

2) Constancy during evolution. In Table II we see evidence for the remarkable constancy in the composition of body fluids in the course of evolution. If we disregard the possibility of convergent evolution, then the data in Table II imply that ion concentrations in the blood have remained relatively constant over perhaps 60,000,000 years or more.

Claude Bernard not only recognized the constancy of the internal environment; he also had a clear vision as to how it was achieved, namely, by the ceaseless adjustment of physiological conditions. It is our aim here to obtain some insight into what these adjustments are and how they are obtained.

Some Thoughts about Stability

As L. L. Boyarsky pointed out to me a number of years ago, the concepts, "constancy of the internal environment", "homeostasis", "physiological regulation", "negative feedback", "control", etc. may be treated as aspects of a more general concept, namely, stability. The degree of stability of a system is a measure of the extent to which

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the state of the system remains invariant in the face of disturbing influences. In a stable system, when the system is displaced from its undisturbed state, a response is generated which tends to return the system to the undisturbed state. Temperature is said to be regulated in mammals because large fluctuations in environmental temperature lead only to small fluctuations in internal temperature. In this respect regulation provides a dynamic insulation of a system from its environment - the internal state of the system becomes independent of the environment to the extent of the effectiveness of the regulatory mechanisms.

TABLE I

Physiological "Constants"

	Median	Range	Variation
Serum albumin (gm/100ml)	4.6	4.0-5.2	± 13%
Calcium, serum (mg/100ml)	10	9-11	10
Carbon dioxide tension, serum, (mmHg)	39	38-40	3
Chlorides, serum, as Cl (mg/100ml)	366	355-376	3
Glucose, fasting, blood (mg/100ml)	90	70-110	22
Sodium, serum (mEq./L)	140	137-143	2
Potassium, serum (mEq./L)	4.5	4-5	11
Erythrocytes, blood (millions per cu. mm)	4.9	4.2-5.5	14
Blood pressure, average, arterial, systemic (mmHg)	125	110-140	13

(From: R. L. Cecil and R. F. Loeb, A Textbook of Medicine, Saunders, 1960)

TABLE II

Average plasma ion levels in two mammals (mM/L blood)

	$\frac{Na+}{145}$	$\frac{K+}{6}$
Rat		
Man	145	5

In preparing for the discussion of physiological regulation it is helpful to examine three mechanical systems which manifest some of the characteristics of physiological regulatory systems.

1) The potential well. Consider a marble at the bottom of a well (Fig. 1). Suppose the well is shaken; the energy thus supplied to the system causes the marble to move up the well to point 1. We will imagine the sides of the well to be coated by some viscous film. Thus, the marble then slowly glides down the sides of the well, possibly oscillates about the lowest point, and then comes to rest at the bottom. We see that as long as the disturbance to the system is sufficiently small so that the marble does not ascend the well beyond point 2, that a restoring force comes into play bringing the marble back to its undisturbed state at the bottom of the well. The stability of the system resides in the fact that when the marble is displaced, there arises a motive force which points in the general direction of the bottom of the well. Once a large disturbance, however, takes the marble beyond the top of the well (point 2) the force points away from the bottom of the well and the system does not return to its undisturbed state. We may think of the potential well in a metaphoric way as representing a biological system. Disease stress represents a displacement induced by some disturbance. When the displacement exceeds the depth of the well the system moves progressively away from its undisturbed state, to death. Within this metaphor aging is represented by the progressive decrease in the depth of the well.

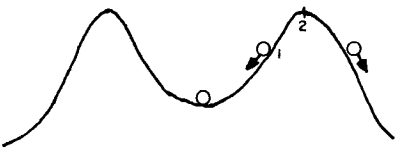

Fig. 1. Marble in well.

2) The fluid tank. Consider the tank of Figure 2 into which fluid is flowing at a constant rate of F ml/sec. Initially the tank is empty. As the fluid level in the tank rises, fluid begins to flow out through the exit pipe. The rate of outflow will be roughly proportional (under the assumption of laminar flow) to the height of fluid in the tank. Thus, as the tank fills the rate of outflow increases. Ultimately, the fluid in the tank reaches a level h corresponding to which the rate of outflow precisely equals the rate of inflow. The height, h, then remains constant. The fluid level, h, is to some extent a regulated variable. If a bucket of fluid is emptied into the tank the fluid level rises temporarily : h is increased. The increase in level increases the outflow though the inflow is unaffected. As a result the fluid level drops and the fluid level returns towards its original value. The effect of the disturbance (the bucket of fluid) is erased as the system returns to its undisturbed state.

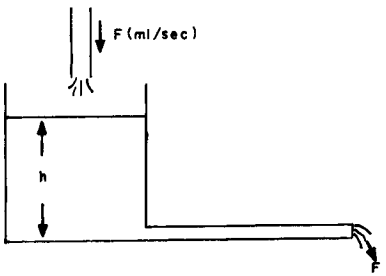

Fig. 2. Fluid tank.

3) The tank with level control. The fluid tank system of Figure 2 stabilizes the fluid level with respect to transient disturbances obtained when finite volumes of fluid are added or withdrawn from the tank; it does not stabilize the fluid level with regard to other disturbances. If,

for example, the inflow F is increased the fluid level increases proportionately. Similarly, changes in the diameter or length of the outflow pipe also result in changes in fluid level. Even these disturbances can be compensated for, however, by modifying the system. In Figure 3, S, is a sylphon (a metal accordion) which lengthens as the fluid pressure at the base of the tank increases. As S lengthens the linkage L moves the valve V so as to reduce the flow F of fluid through the inlet tube. Consider a disturbance, D, consisting of an additional small, steady flow of fluid into the tank. This disturbance causes the fluid level in the tank to rise above the undisturbed level h. As a result he pressure at the base of the tank increases, the sylphon lengthens and valve closure increases, reducing the flow into the tank and reducing the water level. The effect of this regulatory system, then, is to reduce the effect of a disturbance on the water level. The regulatory system of Fig. 3 is said to be a "feedback" system.

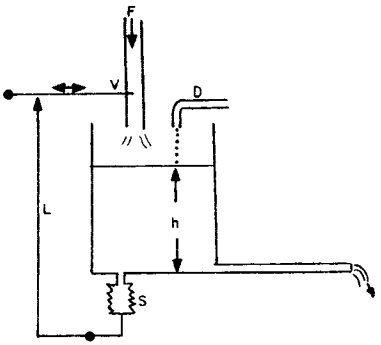

Fig.3. Tank with level control.

A number of useful observations and generalizations may be derived from the rather simple mechanical regulatory systems which we have just discussed.

a) Set point. Physiologists tend to assign two separate but related meanings to the words "set point". With regard to a man-made regulatory system the set point is 1) the level at which a regulated quantity is held or 2) the particular mechanism in the system by means of which this level can be changed. If the thermostat in a house is set at 72°F then according to these definitions "set point" refers to 72°F as well as to the knob on the thermostat which must be turned to set the temperature. For the system of Fig. 3 the set point is the fluid level h, or alternatively any part of the system which can be adjusted so as to cause regulation to take place at a new fluid level. Since such an adjustment can be made either by changing the sylphon or by changing the linkage between the sylphon and the valve or by changing the valve, it is evident with regard to the second definition of "set point" that there does not exist a unique set point in a regulatory system. Rather, in man-made systems the set point is a particular, convenient point at which a person can change the level of the regulated variable.

b) Error. The set point of a mechanical regulatory system is preset by a human agency; it expresses the wish of some person to hold a given quantity at some level. When this quantity departs from the desired level the degree of departure is said to represent the "error" of the system. The system of Fig. 3 exhibits such an error. In the steady-state (that is, when none of the quantities of the system, including the intensity of the disturbance, D, vary with time) the fluid level in the tank is slightly higher in the presence of the disturbance D than

it would be in the absence of the disturbance. The reason for this "error" is relatively easy to see. For the sylphon to increase the closure of the valve, the sylphon must lengthen beyond the position it would have were the fluid at level h. This lengthening can only arise from an increase in pressure at the bottom of the tank. This increment in pressure is required as long as the disturbance remains. Thus, the fluid level must remain higher in the presence of the disturbance and the regulatory mechanism reduces (moderates) but does not eliminate the increase in fluid level which results from the disturbance. Following Siemens (1866) we may call systems which reduce the effects of a steady disturbance, but which do not eliminate these effects, "moderators". Physiological regulatory systems appear to be moderators. Let it be noted, however, that there are man-made regulatory systems which incorporate components called "integrators" which can, in principle, reduce the effects of a steady disturbance to zero. Siemens called this class of regulators "governors".

c) Feedback systems as examples of stable systems. Stability and regulation are not synonymous with feedback. That is, feedback systems form only a sub-set of the set of all stable systems. From the point of view of clarity of thought it is preferable, for example, not to force the systems of Figs. 1 and 2 into the system of feedback nomenclature and feedback mathematics.

d) Negative and positive feedback. In Fig. 3 S, L and V are so connected that an increase in pressure (reflecting as it does an increase in h) leads to a greater closure of the valve V and thus to a decrease in the flowrate into the tank. This arrangement is called negative feedback since an increase in pressure leads to a decrease in inflow. The components could, of course also be connected so that an increase in pressure leads to a further opening of the valve and, thus, to an increase in inflow. This latter arrangement is called positive feedback, since an increase in pressure calls forth a response from the system which augments the pressure even more. Clearly, positive feedback does not lead to stability or regulation, but rather to the opposite - a sort of explosive change in one direction.

e) The dichotomy of regulatory system components. The components in a regulatory system can be divided into two classes: 1) Those which do not change the level of the controlled variable when they are altered. 2) Those that do. In Fig. 2 the tank itself (its dimensions and shape) may be altered without appreciably affecting h. Changes in the inflow or outflow systems, however, change h. In Fig. 3 the inflow and outflow pipes and the tank fall in class (1) S, L and V in class (2). Any element in class (2) can, in principle, be adjusted to change the region of operation of the regulated variable.

The Organism as a Society of Cells

A multicellular organism is a society of cells. The cellular units manifest, as do the units of any complex society, division of labor, specialization, mutual interaction according to a set of rules, and centralized control. The fundamental feature of a society is the strong

interaction among its units. A population of units which are isolated from one another and which do not interact in any way do not constitute a society. Thus, for an interaction to occur between units it is necessary that some signal pass between them. The signal itself may be a piece of matter, for example, a molecule; or a piece of energy, for example, an electromagnetic quantum; or a wave-like disturbance which propagates through matter, for example, the nerve impulse.

In the mammal the interactions between groups of cells which are separated by appreciable distances are propagated by two systems, 1) the circulation and 2) the nervous system. (1) The circulation, Fig. 4, is a river which goes round and round. The various tissues are located along the banks of the river. Tissue A can send a signal to tissue B by dropping a message (molecule) into the circulation; the message is later picked up by tissue B. As an example of this we may take the posterior pituitary gland (the sender) and the kidney (the receiver). The gland secretes the substance ADH (antidiuretic hormone) into the bloodstream. At the kidney ADH increases tubular reabsorption of water and thereby decreases urinary output. Thus by virtue of the transit of ADH the pituitary and kidney cells interact. We may note two things about the circulatory communication system. a) The system only works when blood is circulating. Thus, when the heart stops this communication system is inactivated, a large number of interactions between different tissues are severed, and the "society of cells" degenerates into an uncoordinated mass of individual cells. This is why stoppage of the heart has profound effects on the organism. b) Each message is not funneled directly from sender to receiver. Rather a large number of copies of the message are dropped into the circulation. These copies go to all tissues; however, only the appropriate target tissues respond to the message.

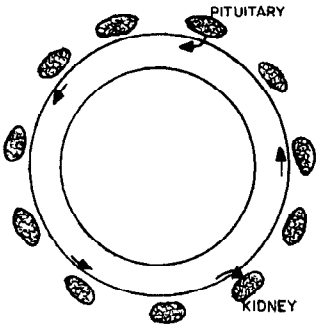

Fig. 4. The Circulation.

2) The nervous system. Here the message consists of a series of disturbances (action potential) which are propagated along nerve cell axons. In principle, by appropriate switching operations, signals can be precisely sent from sender to receiver. In this sense, but only in this sense, is the peripheral nervous system analogous to a conventional telephone system.

Because a "society" can be largely defined by the set of interactions among units, sociology and mammalian physiology focus more upon interactions than upon units. Although the words, "message", "signal", "information", "sender" and "receiver" are anthropomorphic terms, they form a convenient and pictorial nomenclature for the discussion of interactions between non-human units, e.g., cells. Thus, information theory, a discipline dealing with the transmission of message along communication channels, becomes applicable and useful in describing certain basic features of system interactions in general. We will not

digress here to discuss the principles of information theory since these have been clearly presented in other places. There is, however, one important and fundamental point which should be made about those interactions in which the transmitted signal is in the form of a molecule; namely, if the interaction is to be maintained then there must exist a mechanism in the system for destroying or disposing of the messenger molecules; for, if the messengers were not removed, then they would accumulate and the receiver tissue would continue to respond to the molecules irrespective of the state of the sender tissue - the interaction would be broken. As an example we may take the adrenal cortical hormones which are secreted by the adrenal cortex. These hormones are destroyed by the liver; they are also excreted by the kidneys.

Physiological Stability

Let us relate these rather abstract notions to the stability observed in biological systems.

Systems without Feedback

Blood epinephrine level. The hormone epinephrine (M.W. 183) is secreted into the blood primarily by the adrenal medulla. Under basal conditions its concentration in human blood is about 0.1 μg/liter (about 10^{-10} moles/liter). If epinephrine is injected into the blood for clinical purposes the plasma epinephrine concentration may rise to 20 μg/liter. Following such an injection, however, the plasma epinephrine concentration gradually falls with time and returns to its previous level. The fall results from the inactivation of epinephrine by enzyme systems in the body. One would expect the rate of this inactivation to be proportional to the plasma epinephrine concentration; hence, when the blood epinephrine concentration rises the rate of epinephrine inactivation rises. A steady-state blood epinephrine level results when the epinephrine concentration has dropped to the point where rate of inactivation equals rate of secretion into the blood. Analogy: The epinephrine system bears some similarities to the system of a marble confined in a well. (Fig. 1). The disturbance which jars the marble is analogous to the sudden introduction of exogenous epinephrine. The fluid tank system of Fig. 2 is an even closer analogy. The fluid inflow corresponds to the epinephrine secretion into the blood. The fluid level in the tank corresponds to the blood epinephrine concentration. The fluid outflow corresponds to the rate with which epinephrine is degraded. The amount of fluid in the tank corresponds to the amount of epinephrine in the circulation. Yates and Urquhart (1962) have made use of the fluid tank analogy in their analysis of the regulation of adrenocortical hormones.

Systems with Feedback

a) Humoral feed-back systems: Regulation of blood calcium. The normal calcium concentration in the blood is about 10 mg%. Departures from this concentration lead to serious physiological consequences. At levels of about 5 mg% and below convulsions resulting from tetanic muscle contraction occur. An increase in the calcium level to 20mg% or above leads to considerable increases in the blood non-protein nitrogen, urea

nitrogen, phosphates and osmotic pressure. The blood becomes highly viscous.

According to current concepts, the regulation of blood calcium involves the interaction between the parathyroid glands and the calcium stores in bone. Parathyroid hormone induces the liberation into the blood of calcium ion from the bones. When the blood calcium level falls there is an increased secretion of the hormone from the parathyroid glands. Similarly, an increase in blood calcium leads to a decreased secretion of hormone.

In Figure 5 we have a schematic representation of this regulatory system. The representation is of a type we will use for other systems as well. A few remarks about it, therefore, may be in order. In a systems diagram of this sort the boxes represent organs or tissues; the lines connecting the boxes represent pathways of interaction, namely, the circulation or the nervous system. The "signal" which carries the information from one organ to a second organ is written next to the interaction line. The signal, for example, which travels from the parathyroid gland to bone is parathyroid hormone. A plus sign (+) over a system signifies a stimulatory interaction; that is, at the bone an increase in blood parathyroid hormone concentration (input) leads to an increase in calcium output from the bone. A minus sign (-) signifies an inhibitory interaction; that is, at the parathyroid glands an increase in blood calcium (input) leads to a decrease in parathyroid hormone output by the glands.

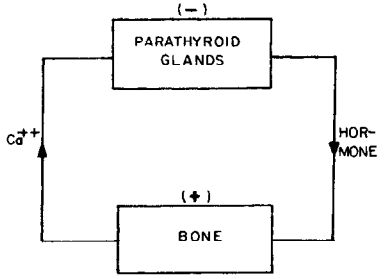

Fig. 5. Regulation of blood calcium.

b) Neural feed-back systems: Postural Reflexes. According to current concepts the length of a given mammalian muscle is regulated as follows. Associated with the muscle is the muscle "spindle". This is a sensory structure which sends afferent nerve impulses to the spinal cord - the greater the length of the spindle the greater the rate of firing. Mechanically speaking the spindle is connected in parallel with the muscle bundle; hence, the greater the length of the muscle the greater the length of the spindle and the greater the number of nerve impulses per unit time which travel from the spindle to the central nervous system. The output of the spindle is fed back to the muscle (Fig. 6), the greater the rate of firing of the spindle the smaller the length of the muscle. The interaction between the spindle and the muscle tends to keep the length of the muscle constant; for if the muscle shortens, the spindle excitation decreases, the rate with which impulses are incident on the muscle decreases, and the muscle relaxes. Similarly, if the length of the muscle increases, a sequence of events is initiated which tends to reduce muscle length.

c) Neurohumoral feedback systems. In the two previous examples the feedback loops passed either along the circulation or along the

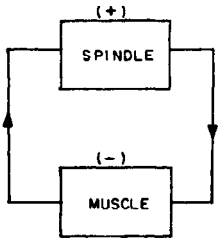

Fig. 6. Regulation of muscle length.

nervous system, but there was no admixture of the two. In many physiological regulatory systems based on feedback, however, the interactions along the feedback loop travel partially in the circulation and partially in the nervous system (see, for example Problem 2). Consider, for example, the hypothalamus-anterior pituitary gland and adrenal cortex system (Fig. 7) which is involved in the regulation of blood adrenocortical hormone levels. The adrenal cortex secretes these hormones, the greater the concentration of ACTH in the blood, the greater the rate of hormone secretion by the adrenal cortex. The anterior pituitary gland releases ACTH molecules, the greater the blood adrenocortical hormone concentration the lower the rate of ACTH release. The interaction between the adrenal cortex and the hypothalamus-anterior pituitary gland system leads to the regulation of blood adrenocortical hormone and ACTH levels for reasons similar to those given in the previous examples.

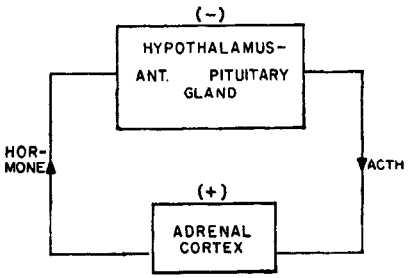

Fig. 7. Regulation of adrenocortical hormone.

Some Mathematical Aspects of Physiological Stability

The previous examples of physiological regulation have certain elements in common. Since science is concerned as much with clarity of thought as it is with the pursuit of truth, it is worthwhile to generalize these examples. In principle, there is no sharp line of demarcation between man-made machines and biological systems. Hence, we shall find that these generalizations apply to engineering systems as well; indeed, many of the technical words which we will use were coined in the engineering sciences.

Input - Output Systems

Clinical death is usually not a consequence of the destruction of the living units of the human body, namely, the cells but rather of a disturbance among the relationships between these units. The fact that it is these relationships which are fundamental to the study of a mammalian physiology makes it desirable that we establish some sort of general and formal logical framework within which these relationships can be explored in a systematic way. Two obstacles are encountered. The first is that sometimes very little is known about the details of the internal workings of a given tissue. The second is that sometimes very much, more than we can easily handle, is known about a given tissue. These

obstacles can be circumvented by the following simple procedure. We agree not to look at the "inside" of a given system but only at what goes into the system (the input) and what comes out of the system (the output). To counteract the tendency to peek inside we imagine the system to be enclosed in a box. There are pipes or wires passing through the walls of the box and by the terms of our agreement we will only look at what passes through these pipes and wires. We will call a system of this kind an "input-output system" (Fig. 8). It is clear that any system or subsystem can be conceptualized this way when it becomes convenient to do so. Lest the reader think that out approach is too trivial, let it be noted that there are entire disciplines in science in which the workers agree to primarily study input-output relationships. Psychology is such a field.

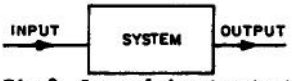

Fig.8. General input-output system.

The Transfer Function

Since we agree to say nothing about the interior of a system there is only one thing left to describe, namely, the relationship between input and output. By relationship we may mean a mathematical equation or a set of rules or an input-output dictionary by means of which the output corresponding to a given input can be predicted. This relationship (Fig. 9) we will call the transfer function of the system(1).

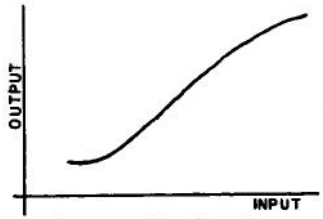

Fig.9. Transfer function.

Let us illustrate these ideas with a simple example by treating a weighing scale as an input-output system. The numerical magnitude of the weight put on the pan is the input, i, and the number to which the indicator points is the output, o. Since no scale is perfectly calibrated the transfer function of this system might be o=0.95 i, that is, a 1 lb. weight brings the indicator to the position 0.95. This is not a complete transfer function, however. It only tells us what the output is after the balance has stopped jiggling, that is, after the transients have died down. A complete transfer function would predict the complete output, jiggling and all. Such a relation would have to be expressed in the form of a differential equation (together with a set of initial conditions). We will confine ourselves, however, primarily to the discussion of steady-state transfer functions of physiological systems. We will confine ourselves to the question: when an input to a system is changed what is the output when one has waited long enough to allow the transient disturbances to die down?

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(1) We will confine ourselves to deterministic input-output systems, that is, systems for which to every input there corresponds a definite and unique output. There are, of course, probabilistic systems, such as roulette wheels, for which to a given input there does not correspond a unique, predictable output. Here only the probability for each possible output can be stated.

Stability of ACTH and Cortisol Blood Levels

It seems best to continue this discussion in terms of a specific biological example. The methods and results can be easily generalized by the student. Let us return to the consideration of the anterior pituitary-adrenal cortex system. Since the quantitative details of this system are not known at present, we will express ACTH and cortisol concentrations in arbitrary units and we will sketch transfer functions (input-output relationships) without investing the shapes of the resulting curves with any particular significance.

In Fig. 10a we have sketched a steady-state transfer function for the adrenal cortex. The graph slopes upward to the right and represents a stimulatory relationship - the greater the ACTH concentration in the

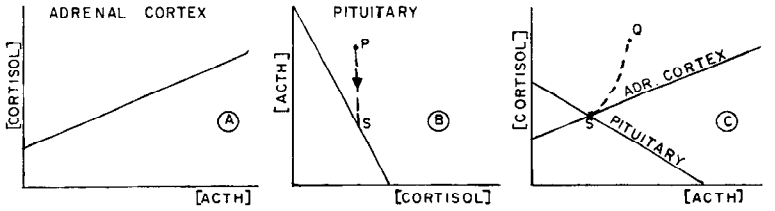

Fig. 10. Transfer functions of pituitary-adrenal cortex system.

blood the greater the steady-state cortisol concentration. By steady-state we mean that if by some means the ACTH concentration in the blood were to be held at a fixed level and one waited for transient disturbances to die down, then the resulting final, steady-state cortisol concentration in the blood would be that shown in the graph of Fig. 10a. Note that in a graph of a transfer function of a system the input variable appears on the abcissa, the output variable on the ordinate.

A similar transfer function for the anterior pituitary gland (more precisely, the anterior pituitary-hypothalamus system) is shown in Fig. 10b. The graph slopes downward to the right and represents an inhibitory relationship between input and output - the greater the blood cortisol concentration the smaller the blood ACTH concentration.

The student should note the following: one may temporarily and arbitrarily establish any cortisol and ACTH concentrations in the blood by injecting these substances. Thus, point P in Fig. 10b is a possible point for the system at a given moment. However, at P the system will not be in a steady-state. At point P, the rate with which ACTH is degraded exceeds the rate with which ACTH is put into the circulation by the pituitary gland. Thus, the ACTH concentration falls until point S (Fig. 10b) on the transfer function is reached, whereupon it remains fixed with time. Thus, the transfer function lines in Fig. 10a and 10b represent only those points for which the rate with which a gland puts hormone into the blood exactly equals the rate with which the hormone is elsewhere degraded or excreted.

Now let us draw both transfer functions on the same set of coordinate axes (Fig. 10c). (This requires rotating Fig. 10b by 90° and reflecting its cortisol axis). From this graph one can deduce at what levels the anterior pituitary-adrenal cortex feedback system maintains steady-state ACTH and cortisol concentrations in the blood. Remembering that each line represents the only points at which each system can be maintained in the steady-state we conclude that it is the point of intersection, S, of the two transfer curves which represents the steady-state ACTH and cortisol concentrations in the blood. If due to some transient disturbance the ACTH and cortisol levels in the blood are displaced from point S (point Q, Fig. 10c), the concentrations will again drift towards S until this point is reached.

Changes in the transfer function. We have so far treated the pituitary-adrenal cortex system as if the output of the adrenal cortex depended only on the blood ACTH level, and as if the output of ACTH by the anterior pituitary gland depended only on the blood cortisol level. This is a first approximation. We must recognize, however, that the anterior pituitary gland is subject to influences from other organs (e.g. the cerebral cortex). These influences can change the transfer function of the anterior pituitary gland. The solid line (Pit.) in Fig. 11 is the same transfer function of the pituitary gland as that shown in Fig. 10b and 10c.

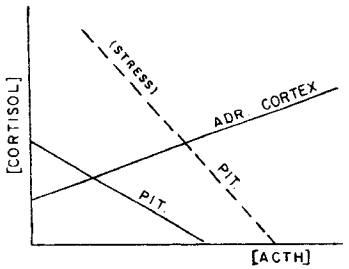

Fig. 11. Effect of stress.

Let us suppose that as a result of some stress (e.g. infection), the transfer function changes to the one shown as a dotted line in Fig. 11. This figure shows the effect the change in transfer function has on the point of stability of the pituitary-adrenal cortex system: the blood ACTH and cortisol levels rise, but stability and regulation about the new point of stability exist as before.

The stability conferred by negative feedback.

We have noted that whenever there exists a hormone, that there must also exist somewhere in the organism a system for destroying the hormone. Thus, even if there were no interaction between the pituitary gland and the adrenal cortex, the output of the adrenal cortex would be stabilized by analogy to the fluid tank model of Fig. 2 and the previously discussed adrenal medulla system. We can demonstrate, however, that the interaction between the two glands provides an additional element of stabilization.

Let us suppose that due to some toxicity, or poor nutrition, half of the cells of the adrenal cortex become non-functional. The steady-state cortisol level in the blood corresponding to a given blood ACTH level will then be roughly halved (dotted line, Fig. 12). In the absence of feed-back this would lead to blood cortisol levels which would be one-half of the normal values. In the presence of feed-back, however, that is, when an interaction between the adrenal cortex and the anterior

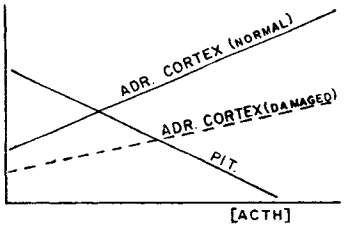

Fig. 12. Stabilization due to feedback.

pituitary gland exists, the cortisol level falls to a lesser extent (Fig. 12). Feed-back stabilizes the blood cortisol level.

Discussion

The role of analogies in biological thought. Claude Shannon provides an interesting perspective on the influence of technology on biological thought. He points out that in the seventeenth century, at a time when water-clocks, fountains and mechanical devices were developed in profusion, Descartes viewed living things as automata of this kind and assumed that nerves transmitted signals by tiny mechanical motions. In the nineteenth century the steam engine caught the imagination of the intellectual community and resulted, among other things, in the laying of the foundation of the science of thermodynamics. There was a tendency (persisting to the present day in elementary text books of biology) to view biological organisms as "engines which burn food and do work". Similarly the advances in the understanding of electric and magnetic phenomena made by Faraday and his contemporaries led some biologists to view the mitotic spindle of the dividing cell as a manifestation of an intracellular electro-magnetic field with the spindle fibers falling along the lines of force of this field. More pertinent to our subject and closer to our day are the areas in the engineering sciences of information theory, computers and automatic control devices. These areas developed rapidly during World War II. After the war the terminology and viewpoint of these sciences began to permeate physiology, and to a lesser degree, other biological sciences. A wave of hope swept through parts of the biological community that an intellectual machinery for grasping the complexity of biological phenomena was at hand; that the biologist needed merely to master these sciences and then to apply them systematically to his own problems.

It is strange how enthusiasm of this kind periodically make their appearance in biology, particularly when we consider the nature of those biological theories and generalization which have withstood the tests of time. We need only consider some of the originators of these theories and generalizations: Harvey, Schwann, Schleiden, Mendel, Darwin, Bernard, Weismann, Pavlov, Sherrington. One is struck by the fact that these individuals were biologists in the deepest sense and that the theories which we identify with them arose naturally from within the biological realm. Only remotely, if at all, can one detect in these theories elements which might be considered to be analogs of physical or technological ideas. On the other hand, the evanescence of analogistic explanations of biological phenomena, leads one to surmise,

to borrow an expression of Mazia, that "history has not been kind" to biological explanations in the form of physical analogies. While such analogies occasionally have a transient didactic value (c.f. Fig. 2), they clearly cannot be dignified by the title, "theory", nor should one expect them to unlock the gates to biological discovery.

In a sense, reflections of this kind can be a source of liberation for the student of physiology. Rather than have in the back of his mind a soft voice of conscience which continues to tell him that he should study more math, that he should take engineering courses in control theory and information theory, he can console himself with the following thoughts. The physiologist is a pioneer; and pioneers travel light. Pioneers and craftsmen rely on simple and basic tools; complicated, specialized tools are the counterpart of the comfort loving town dweller or the amateur craftsman. To be a physiologist is to leap into the midst of a complicated problem with no more armament than one's wits. If the physiologist, and in a larger sense the biologist, will lead, those who consolidate his advance will follow. The final stage of a biological problem is best left to the specialist be he chemist, physicist or mathematician. Let us drop preconceived notions and cease to force physiology onto the procrustean bed of cybernetic theory upon which it is shortened, stretched, cramped, distorted and obscured. Let physiologists be free to use physical theories as they are needed, rather than to stumble under the weight of these theories when they are not.

Engineering Analogs. Man-made regulatory systems are sometimes conceptualized as shown in Fig. 13. The feed-back loop contains a sensor, a comparator, and an effector. The sensor detects the magnitude of the quantity which is to be regulated. The signal emanating from the sensor is compared to the "set-point" or "command" in the comparator. The comparator then sends out a signal which causes the effector to make compensatory changes. These changes tend to return the regulated variable to its desired value. Let it be noted that the sensor, comparator, effector formalism is not of sufficient generality to serve as a fundamental approach to physiological regulation. It is not effective in describing either the regulatory system of Fig. 3 or the thermostat system which regulates the temperature in a home (see problem 5). In most hormonal systems there exists a symmetry between two interacting glandular tissues: two variables are regulated simultaneously. In the pituitary-thyroid gland system TSH and thyroxine blood levels are simultaneously stabilized. It would be somewhat artificial to ascribe a unique sensor function in the feed-back loop to either the thyroid gland or the pituitary gland. The two glands participate symmetrically in the regulation.

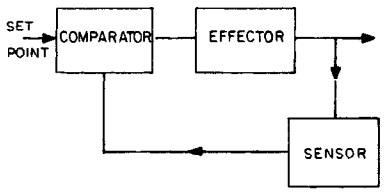

Fig.13. Engineering control system.

The Set Point. The set point concept is an anthropomorphic concept. It derives from the fact that in man-made regulatory mechanisms there

generally is one component which has been designed so that an adjustment of this component determines the desired level of the controlled variable. What gives the set point its significance in man-made systems is that it actually is a point of regulation willed, set and aimed for by a human agency. Even in a man-made system, however, the point in the system at which the value of the controlled variable is set is not really unique. As we have pointed out in connection with the regulatory system of Fig. 3 the controlled variable in a regulatory system can be changed by an adjustment of the characteristics of any one of a number of components in the system.

If the set point is an anthropomorphic concept, and if it is not unique, how are we to identify it in a system which is the product of evolution? Take the pituitary (TSH)-thyroid gland (thyroxine) system. Which component, the pituitary gland or the thyroid gland determines the TSH-thyroxine level in the blood? The answer is of course: both. A change in the transfer function of either component, or even a change in the system which degrades these hormones changes the blood TSH-thyroxine levels. On the other hand suppose we think of the words "set point" as referring to the level of the controlled variable itself. How can one identify this set point in a physiological system (a moderator), a system which manifests a steady-state error in the presence of a steady disturbance? For any complex system what is called the "level of the controlled variable in the absence of disturbance" depends on what conditions are considered normal for the system and what conditions are considered disturbances. Since biological systems are generally in a state of flux and change, a reference state of zero disturbance would have to be arbitrarily and artificially assigned. One would not expect a set point based on such an arbitrary assignment to be endowed with great theoretical significance. The utility of the set-point concept in the context of physiology is, therefore, questionable. The same might be said of words like "amplification" and "error" which when applied to biological situations often serve to obscure them rather than to clarify them.

Block diagrams. In the present paper we have represented physiological regulatory systems by diagrams in which only two subsystems of a given regulatory system are shown (e.g., Fig. 5). The diagrams could have been made much more elaborate in two ways: 1) by showing explicitly subsystems of the subsystems, 2) by showing other systems which interact with the regulatory system. It is with physiological regulation as it is with any other scientific problem: It is easy to make the problem complete and complicated but it is difficult to reduce it to meaningful simplicity. Thus, when, for example, the complexity of a schematic block diagram approaches the complexity of the system which it represents, the block diagram representation tends to lose its utility as a conceptual device. At such levels of complexity ideas at a much higher level of abstraction must come into play - a simple extension of the ideas which we have discussed so far would probably not be useful.

There is one complication, however, which should be taken into account. For the sake of simplicity we have treated physiological control systems so far largely as if the transfer function of each component in the feedback loop were independent of other systems in the organism.

This is evidently a simplification. When a mammal, for example, is exposed to cold, the transfer function of the thyroid gland changes (see Problem 1). Let us see how we can take this into account. We have, so far, drawn input-output systems as if these had but one input and output (Fig. 8). There is no reason, however, why such systems should not have several inputs and several outputs. Let us consider here the case of a system having only two inputs, A and B, and one output (Fig. 14a). The output is a function of the magnitudes of both inputs so that the transfer function of the system can be graphically represented by a family of curves (Fig. 14b). In Fig. 14b the output is plotted along the ordinate. Along the abcissa the magnitude of input A is plotted. Each curve represents the variation of output with variation of input A while input B is held constant. Along the curve b_1-b_1, for example, the magnitude of the B input is held constant at magnitude b_1. Thus from Fig. 14b one can find the magnitude of the output corresponding to any given pair of input values A and B. In the case of the heart (see Problem 2), for example, input A might correspond to the vagus nerve, input B to the sympathetic innervation.

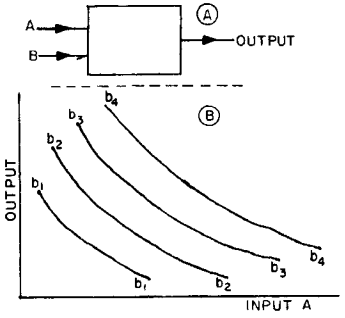

Fig.14. System with two inputs.

Observe from Fig. 14a that formally speaking a system with two inputs and one output looks like what a control engineer calls a "comparator" (Fig. 13). Thus, a physiological system with two inputs and one output might be called a comparator, and one could even say that the system "compares the two input values". There may, however, be no conceptual advantage to this; in this sense even a candy dispensing machine is a comparator -the coin and the plunger are the two inputs, the candy bar is the output.

Static versus dynamic characteristics. Our discussion has been directed primarily at static, i.e. steady-state, characteristics of physiological regulatory systems. That is, we have looked at these systems after enough time had elapsed for transients to die out and for the steady-state to be reached. The transient state of a regulatory system is, however, also of interest. We would wish to know, for example, how long it takes, following a disturbance, for a system to reach the steady-state. Then there are physiological regulatory systems which do not even come near to the steady-state where, indeed, the situation of interest is the transient itself. The student should devote some thought to the dynamic characteristics of physiological regulatory systems. However, we will not pursue this matter here.

ACKNOWLEDGMENT

I am indebted to L. L. Boyarsky and F. W. Zechman for helpful comments and suggestions on the manuscript. The support of this work by a Lederle Medical Faculty Award is gratefully acknowledged.

PROBLEMS

1. Regulation of blood thyroxine level. Let $[TSH]$ and $[T]$, respectively, be the concentration of thyroid stimulating hormone and thyroxine in the blood. The output of the anterior pituitary gland is given by

$$[TSH] = -3/2\,[T] + 6 \quad \text{with the organism in air at } 25^{\circ}C$$

$$[TSH] = -3/4\,[T] + 12 \quad \text{with the organism in water at } 15^{\circ}C$$

The output of the thyroid gland is given by

$$[T] = 4/3\,[TSH]$$

($[TSH]$ and $[T]$ are expressed in hormone "units".)

a) Determine (algebraically) the steady-state concentrations (in units) of TSH and thyroxine in the blood when the organism is at $25^{\circ}C$.

b) Repeat (a) solving for the concentrations graphically (plot the two equations).

c) Repeat (b) for the organism in water at $15^{\circ}C$.

d) Invent (do not consult the literature; your theory is as good as anyone else's) a cellular mechanism on the molecular level which could give rise to the shift in the pituitary input-output function with temperature.

e) The thyroid gland is treated with radioactive iodine. After the treatment only one fourth of the cells secrete thyroxine. Plot the new input-output curve for the thyroid gland on the same graph as 1b. At $25^{\circ}C$ does the thyroxine level in the blood remain the same, decrease or increase? Why?

2. Regulation of blood pressure. The number of nerve impulses per second, f_s, emanating from the carotid sinus is a function of the blood pressure within the sinus. The carotid sinus is said to be a pressure receptor. As pressure increases, f_s increases; as pressure decreases, f_s decreases. The impulses from the carotid sinus travel along a nerve trunk to the medullary vasomotor center in the brain stem. Nerve impulses emanate from this center and travel to the heart. When blood pressure increases the heart rate decreases, and the amount of blood pumped by the heart per unit time is decreased. In your analysis (parts a-c) treat the carotid sinus and the vasomotor center as a single, combined system.

a) Draw a block diagram indicating what material (e.g., blood) or disturbance (e.g., nerve impulses) flows along each path.

b) On separate graphs sketch transfer functions for (1) the heart,

(2) the carotid sinus-vasomotor center system.

c) Sketch both transfer functions on same graph and show point of stability.

d) With the help of a crude anatomical sketch of this system show how the system tends to maintain a constant blood pressure in the aorta when the blood flow to the stomach suddenly increases due to the ingestion of hot fluid.

e) Dr. Irvine Page of the Cleveland Clinic in his recent talk on hypertension at the University of Kentucky Medical Center stated that when some patients with high blood pressure were maintained for a long time on drugs which reduce blood pressure, then taken off the drugs, the average blood pressure was reduced to a level far lower than before the treatment, i.e., the patients were no longer hypertensive. How would you interpret this result?

f) "Opening the feed-back loop". In terms of your analysis what would be the effect of cutting the nerve fibers between the carotid sinus and the vasomotor center on:

1) Heart rate?

2) Blood pressure?

3) Control of Blood Pressure?

3. The Physiology of death. Reflect as to the criteria on which a physician bases the diagnosis of "death". He is like an engineer who notices a fatal flaw in a structure and knows that the structure will collapse before it collapses. It is as with a chain which fails under stress at its weakest link. What is the weakest link in the human organism?

a) What substance is limiting in the human organism? That is, if an organism is deprived of an input of all the substances it needs from the environment, the lack of which substance (x) is felt first?

b) After approximately what period of time of deprivation of substance (x) does one observe irreversible damage of some organ?

c) What is the limiting organ? That is, which organ (y) is the first to be irreversibly damaged by the absence of (x)?

d) Would you be willing to say that in most (or all) cases of death, clinical death, means irreversible damage to organ (y) due to a lack of substance (x)?

4. Regulation of muscle length

a) For the muscle-spindle system of Fig. 6 sketch appropriate transfer functions and indicate the point of stability for the steady-

state.

b) The actual system is a bit more complicated. There are intrafusal muscle fibers along the length of the spindle which receive their excitation independent from that of the main body of the muscle. The contraction of the intrafusal fibers causes the spindle to shorten relative to the muscle.

Assume the transfer functions which you sketched in part (a) to be those which apply when the intrafusal fibers are not stimulated to contract. Sketch (using dotted lines) on the transfer function diagrams of part (a) the transfer functions which might apply when the intrafusal fibers are being continuously stimulated to contract. Show the two points of stability corresponding to stimulation and non-stimulation of the intrafusal fibers.

c) Suppose the muscle in question is the diaphragm and that the intrafusal fibers are excited via a neural pathway from the respiratory center in the medulla. Indicate how the variation in excitation along this pathway can give rise to periodic contraction and relaxation of the diaphragm.

5. Attempt to assign the labels "comparator", "effector" and "detector" to subsystems in the following regulatory systems:

a) As you drive along a highway you attempt to keep the left fender of the car two feet to the right of the white line.

b) The thermostat-furnace system which regulates the temperature in your home. In principle, is the thermostat a moderator or a governor?

c) The regulatory system of Fig. 3.

6. In man-made regulatory systems there usually exists some control point at which, usually by the turning of a knob, man sets the value at which the controlled variable is to be held. According to evolutionary concepts no outside intelligence intervened to "set" physiological variables at given levels.

Consider in this light the pituitary gland-thyroid gland relationships. From Problem 1 we see that by the interaction between these two glands the blood levels of both TSH and thyroxine are stabilized; from this point of view the relationship of the two glands appears symmetrical. On the other hand it is customary to think of the pituitary gland as a master organ which sets the level of thyroxine output of the thyroid gland.

a) Might TSH have any measurable physiological effects other than its role in the regulation of the blood thyroxine level? Reference: A. Grollman, Clinical Endocrinology, J. B. Lippincott, Philadelphia, 1964, p. 31-32.

b) In your estimate which arose first in evolution, the thyroid gland or the TSH secreting pituitary gland cell? Give reasons for your decision.

c) When it is said that the central nervous system "sets" the output of the pituitary gland, and the pituitary gland "sets" the output of the thyroid gland, what "sets" the central nervous system?

d) Let there be three physiological systems A, B and C which interact to regulate a certain physiological variable. Can you define the words "comparator", "effector" and "sensor" so that you could uniquely assign them to the three systems?

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MEMBRANE TRANSPORT OF Na AND K:
A Synopsis of Contemporary Concepts and Experiments*

D. C. TOSTESON

Membrane transport of Na and K is of interest to many kinds of physiologists because of the wide range of cellular functions subserved by these ions. For example, scientists concerned with the physiology of nerve and muscle (cardiac and smooth, as well as striated) are interested in the subject because of the roles of Na and K in excitation and conduction in these cells. Neurophysiologists who concentrate on the central nervous system may pay particular attention to the involvement of these ions in synaptic transmission and the production of generator potentials in sensory endings. Renal and gastrointestinal physiologists share an interest in secretory processes which are dependent on Na and K transport. Physiologists interested in growth and development are concerned with the role of Na and K in regulation of cell volume and of protein synthesis. Endocrinologists study the effect of hormones such as vasopressin and aldosterone on ion movements. Since all of these and many more aspects of physiology are intimately related to the transport of Na and K across cell membranes, it is entirely appropriate that physiologists attempt to understand more clearly the mechanisms of these processes. During this brief introduction to the session, I shall try to indicate to you some of the directions of current research on this problem. A comprehensive review of the field is both impossible and undesirable in this setting. Several fairly recent treatments of the subject are available in the literature (3, 16).

Different types of membrane transport of Na and K can be classified according to the energetics of the processes. Dissipative transport processes are driven by differences in electrochemical potential of the transported ions in the phases bathing the two sides of the membrane, e.g., cytoplasm and extra cellular fluid. Such passive transport processes involve the dissipation of free energy differences in the bulk phases. On the other hand, conservative transport processes are driven by forces generated within the membrane and, therefore, may result in the maintenance or accumulation of free energy differences between the phases. When accumulation of free energy in the bulk phases occurs, the process is often called active transport. The energy for this process apparently derives from chemical reactions occurring within the membrane. The following discussion will consider, first, recent studies of dissipative transport of Na and K and, secondly, certain aspects of active transport of these ions. It should be noted that the operational distinction between dissipative and conservative transport processes is frequently more obscure than the conceptual distinction made above. Furthermore, this classification does not necessarily imply that these two types of transport are spatially distinct in biological systems.

Dissipative Transport of Na and K. The most striking characteristic

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*Taken from the introductory remarks given at the session on Membrane Transport of Na and K at the 1966 Federation Meetings.

of dissipative transport of Na and K across cell membranes is the specificity of the process for one ion as compared with the other. The precise physico-chemical basis for the selectivity of cell membranes for K or Na is not known. One of the major barriers to fruitful investigation of this problem is that the selectivity apparently depends on trace properties of the membranes. To a first approximation, biological membranes are good insulators which allow appreciable penetration by ions only because they are so extremely thin (80-100 Å). Therefore, more adequate characterization of the chemical composition of membranes (e.g., 9,17), while essential to progress in understanding membrane structure and function, is unlikely to provide an easy answer to the problem of selective permeability to Na and K. For this reason, specific compounds which modify selectivity for Na or K may be the most useful approach toward a description of the physico chemical properties of membranes which are responsible for this process. Such a compound is tetrodotoxin, a poison produced by the Japanese puffer fish. In extremely low concentrations (10^{-7}-10^{-8}M), this substance prevents the increase in Na permeability which is associated with the action potential in skeletal muscle (11) and squid axons (15). Detailed analysis of its effect by voltage clamp technique reveals that it reduces the maximum sodium conductance which the membrane can develop temporarily after a sudden change in the membrane potential in the positive direction (e.g., from -80mV to 0mV) but does not modify the rate of change of Na conductance after such a step change in membrane voltage (15). Tetrodotoxin reduces the transient early current after a sudden change in membrane voltage even when such current is carried by K rather than Na (a situation which can be produced by altering the K and Na concentrations on the outside and inside of the membrane). This observation shows that tetrodotoxin does not undergo some specific interaction with Na, but rather prevents the development of the transport pathways which are briefly available after depolarization. These pathways markedly prefer Na, but will accept K in the absence of the favored ion. Since tetrodotoxin has been isolated in crystalline form and its structure characterized, the value of the compound as a tool in the further analysis of the changes in Na permeability which are associated with the action potential is obvious.

It is important to bear in mind that the resistance which biological membranes offer to the dissipative transport of Na and K is not a static but a dynamic property. Thus, the relative permeability of the human red cell membrane to these ions is markedly affected by various metabolic alterations. For example, exposure of the cells to iodoacetic acid and adenosine in the presence of low concentrations of Ca greatly increases the permeability of the membrane to K without affecting appreciably its permeability to Na (12). Definition of the chemical basis of this and related effects could contribute much to understanding the regulation of cell content of these ions.

A major difficulty in applying knowledge of dissipative transport processes which occur in model systems to biological membranes relates to differences in the geometry of the two situations. Until recently, almost all model studies were carried out on artificial membranes which are very much thicker than cell membranes. The development and study

of lipid bilayer membranes during the past few years has substantially improved this situation (10). These films have a thickness (50-100 Å) which is comparable to that of biological membranes. Such films have been prepared from pure lipids (e.g., lecithin or phosphatidyl ethanolamine dissolved in decane) as well as complex mixtures of lipids extracted from biological material (e.g., brain or more recently, in our laboratory, red cell membranes). The relative permeability of these films to Na and K has been measured in only a few cases of films made of pure lipids (1). Although selectivities which exceed those observed in aqueous solution have been seen in these lipid systems, nothing comparable to the selectivity of biological membranes has yet been noted. Nevertheless, it is entirely possible that further work with films of more complex composition may provide important clues about the physico-chemical basis of the capacity of cell membranes to select between Na and K.

Conservative Transport of Na and K: Active Transport. I would like to turn now to a brief discussion of recent work on the active transport of K and Na. The definition of active transport both conceptually and operationally is complicated and often ambiguous. Theoretical formulations which consider active transport within the frame of reference of the thermodynamics of irreversible processes have been put forward by Hoshiko (5) and Katchalsky (6) and others. These contributions substantially clarify the conceptual side of the matter. It has long been recognized that the only completely satisfactory operational definition of active transport is the net movement of a component across a membrane against or in the absence of driving force for the transport component in the phases bathing the two sides of the membrane. This operation can be performed relatively easily with epithelial cell layers such as the toad bladder and the frog skin but only with difficulty if at all with single plasma membranes separating cytoplasm and extra cellular fluid. In the latter situation, the difficulty arises from the problem of controlling independently the electrochemical potential of a component within the cytoplasm. As a result of this difficulty, other less reliable criteria have often been used to define active K and Na transport experimentally. For example, in human red blood cells the portion of Na extrusion which requires external K and is inhibited by cardiac glycosides has often been taken as a measure of the Na.

There is good evidence to indicate that this pump derives energy from the hydrolysis of ATP. Hoffman and Kregenow (4) have recently provided evidence that this operational definition of the pump is an over-simplification. Thus, the addition of ethacrynic acid to a human red cell suspension which already contains a maximally inhibiting concentration of ouabain produces a further reduction in Na outflux. This component of Na outflux which is inhibited by ethacrynic acid but not by ouabain is apparently active since it can be shown to be associated with a net extrusion of Na from the cells under appropriate conditions. The process is dependent on external Na but not external K and continues to operate when the ATP concentration in the cells is too low to support the conventional cardiac glycoside inhibited "pump" and thus may derive energy from some other source than ATP. These observations emphasize the complexity of Na active transport and its sensitivity to different

classes of inhibitors. Work along this important line may be viewed as providing an ever more complete empirical description of the K-Na transport process. It is with such a description that any model for these processes must be validated.

The active transport of amino acids and sugars has been shown to be intimately associated with Na transport in a number of tissues. An example is provided by the observation of Kostyo (7) that glycine uptake by rat diaphragm muscle cells is dependent on the presence of Na in the external medium. It is important to note that this dependence of amino acid transport on Na is not observed for all amino acids since the uptake of leucine is unaffected by the external concentration of Na. The recent work of Vidaver on glycine transport in pigeon erythrocytes suggests that the direct energy source for accumulation of the amino acids in this system is the electrochemical potential difference for Na between cytoplasm and extra-cellular fluid. Elucidation of the mechanism of the interaction between Na and K and transport of sugars and amino acids is clearly an important problem for the future.

Measurements of Na transport across amphibian epithelia such as frog skin and toad bladder has provided much important information during the past two decades of research on membrane transport of Na and K. For example, work on these systems has helped to clarify the way in which hormones such as vasopressin modify the process. During the past few years work in the laboratories of Crabbe, Edelman, Leaf and others has developed promising leads towards improved understanding of the mechanism of action of aldosterone. One of the most interesting such leads is contained in the experiments of Edelman et al. (2) which suggest that aldosterone stimulates Na transport in the toad bladder by inducing the synthesis of a protein. Thus, aldosterone fails to stimulate Na transport in bladders which have been preincubated in actinomycin D prior to addition of the hormone. Since actinomycin D is known to inhibit DNA dependent RNA synthesis, this experiment suggests that an RNA related process such as protein synthesis is involved in the action of aldosterone. However, it is not possible to rule out that actinomycin is producing its effect in some other way in this experiment. Despite considerable additional circumstantial evidence that protein synthesis is involved in aldosterone action, there has not yet been a direct demonstration of increased net synthesis of a specific protein under the influence of the hormone. Equally unknown and hotly debated is the way in which such a protein might act to alter Na transport.

One of the most active lines of research on the mechanism of active K-Na transport involves membrane bound, Na + K stimulated ATPase activity (S-ATPase) first prepared by Skou (14) and subsequently studied by Post, Dunham and Glynn and many others. This enzymatic activity is extremely widely distributed in different types of cells. In a few systems, e.g., mammalian red cells, the sensitivity of enzyme to various activators (e.g., Na and K) and inhibitors (e.g., cardiac glycosides, ethacrynic acid) closely parallels the dependence of active K-Na transport to these factors. Since, in these same systems, ATP has been shown to be a necessary, sufficient but not necessarily direct source of

energy for the Na-K pump, it has seemed reasonable for scientists interested in the mechanism of the pump to examine the membrane bound S-ATPase activity in some detail. Before describing briefly the present state of this examination, I would like to underline the operational difference between the K-Na pump on the one hand and the membrane S-ATPase on the other. Rigorously, estimation of pump activity involves the measurement of the net movement of Na or K ions across a cell membrane from a region of lower to a region of higher electrochemical potential. In general, such measurements can be performed only in intact or relatively intact cells. Estimation of S-ATPase activity involves the measurement of the rate of hydrolysis of ATP in the presence of a membrane preparation which usually has been broken up to such an extent that it no longer provides an appreciable barrier to the diffusion of ions. Thus, systems suitable for assay of the pump are generally not suitable for assay of S-ATPase and vice versa. For this reason, great caution must be exercised in applying the results of studies of one system to the other. Even when membrane S-ATPase is isolated, purified and characterized (an essential, difficult, but in my judgement, definitely possible task) the role of this system in the movement of K and Na across cell membranes will not be solved. Indeed, in an important sense, it will only be then that the question of the relation between the two processes can be asked in a precise way.

With this word of orientation, not to be construed as nihilism or even pessimism, I will summarize my understanding of the present state of knowledge about S-ATPase. For purposes of simplicity, I will make the admittedly unjustified assumption that the enzymatic activity isolated from different sources has essentially similar properties. The enzyme has never been completely purified and its molecular weight is unknown. The inhibition of S-ATPase by phospholipases and exposure to detergents and organic solvents suggests that it is a lipoprotein which requires the presence of lipid for optimal activity. To my knowledge, no successful restoration of activity of this enzyme by addition of lipids to lipid-poor inactive enzymatic protein has yet been accomplished. Inhibitor studies suggest that at least two amino acids, i.e., cysteine and serine, are somehow involved in S-ATPase activity. It is not clear whether these amino acids are actually located at the active catalytic site or whether they are present elsewhere in the protein and modify enzyme activity by means of a so-called allo steric effect. Mg activates the S-ATPase by interacting directly with the protein. The mechanism by which Na and K modify activity is not entirely clear. Their major effect is to increase the V_{max} rather than to alter the apparent K_m for ATP.

This problem has been examined in several laboratories by measuring the incorporation of P^{32} derived from γ labeled ATP into enzyme material. An example of this approach has been described by Post et al. (13) who found that the accumulation of P^{32} in the enzyme protein was markedly stimulated by Na but not by K or other mono valent ions. Observations of this type have given rise to the idea that Na is necessary for the formation and K for the hydrolysis of a phosphorylated intermediate in the S-ATPase. Much circumstantial evidence supports this view. However, certain results cast some doubt on this interpretation. Skou (14) has emphasized that maximum labeling of the enzyme occurs under condi-

tions when the catalytic activity of the preparation is much less than maximal. Thus, in Na alone labeling is very rapid but hydrolysis is quite slow while in Na + K labeling is almost nil while hydrolysis is very rapid. He has pointed out that this result is compatible not only with the model described above but also with the idea that the simultaneous presence of Na + K open a pathway for hydrolysis which is simply not available when Na alone is present. According to this interpretation, the labeled intermediate has nothing to do with the normal activity of S-ATPase but is seen only in the abnormal circumstance of exposure to Na alone. He further suggests that the conversion from the Na-only reaction sequence (in which labeled intermediate is produced) to the Na + K reaction sequence (in which labeled intermediate is not produced) may be related to a conformational change in the enzyme caused by the ions. In support of this suggestion he offers evidence that the protection by ATP of S-ATPase from inactivation by n-ethyl maleimide (NEM) is affected by K and Na. He interprets these effects of the alkali metals and ATP as due to changes in conformation of the protein which alters the availability of cysteine and other reactive amino acids to NEM. To my mind, a definitive decision between the two interpretations of the labeling data is not possible at this time. It is clearly an important problem. Whether or not the labeled intermediate is on the main line of the S-ATPase catalyzed reaction, the sensitivity of the compound to hydrolysis in the presence of hydroxyl amine (shown by Hokin and others) strongly suggests that it is an acyl phosphate of some kind.

To summarize, I could almost say with the New Jersey physician-poet William Carlos Williams, "we know nothing pure and simple beyond our own complexities." What do we really know about membrane transport of K and Na? First, biological membranes display a degree and variability of selectivity for these ions which is unparalleled in non-living systems. Secondly, cell membranes can utilize energy from chemical reactions to do work on the ions in active transport. Both of these properties are influenced and therefore to some extent controlled in subtle, complex and specific ways by the concentrations of Na and K themselves as well as other ions, by drugs such as cardiac glycosides and diuretics, and by hormones such as vasopressin and aldosterone. In at least some cases, the energy for the K-Na pump(s) derives from ATP and may involve the activity of S-ATPase.

I will conclude with a few remarks about what I consider to be the most important areas of investigation of membrane transport of Na and K in the immediate future. To my mind, it is crucial to determine the size of the membrane regions which are involved in the selective dissipative and conservative transport of these ions. At the present time, we have no idea whether the "unit" membrane area which changes its permeability to Na during the action potential or which carries out active K-Na transport is 100 $Å^2$ or 10^6 $Å^2$ or even the entire area of the cell. Although the actual site of ion penetration must by definition be small, the array of macro molecules which determine the selectivity and provide energy for the site may be enormous. Until an adequate determination of size is available, an adequate strategy for isolation and characterization of the transport region of the membrane is highly unlikely.

A second unsolved problem is to define the chemical basis for selectivity both in the pump and the leak for Na and K. Indeed, in this respect, it is important to clarify the relation between these processes. For example, is a model which assumes that only unidirectional movement can occur in the pump with bidirectional movement in the leak really useful? Or is it more realistic to assume that transport can occur in both directions in the pump itself. Both theoretical and empirical considerations strongly suggest that pump and leak must be closely concerted in order to control cell composition of K and Na. This integration of the hypothetical types of membrane transport processes might be more feasible if both dissipative and conservative transport occurred at the same membrane site.

A third important area for future work involves the growth and differentiation of membranes with respect to transport of Na and K. Work with bacteria and mammalian red cells clearly indicates that these processes are controlled genetically. Recent work in our laboratory with young LK sheep red cells shows that genetically controlled changes in the membrane transport of K and Na occur in maturing but non-dividing erythrocytes (8). These changes do not appear to be all-or-none but rather graded. How does DNA in the stem cell direct these changes in membrane function? Is the change in K-Na transport due to events which are intrinsic to the differentiating red cell or rather to the effect of a hormone produced elsewhere in the animal? Are the permeability changes due to alterations in the lipid or protein content of the membrane?

The Jesuit paleontologist Pierre Teilhard de Chardin once said that the criteria for truth are coherence and fecundity. Though the subject of membrane transport of K and Na may be somewhat lacking in coherence at present, I hope that it is clear that the field contains many seeds which seem destined to grow fruitfully.

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THE RENAL METABOLISM OF AMMONIA*

ROBERT F. PITTS

Nash and Benedict (3) were the first to demonstrate that the ammonia excreted in the urine is formed within the kidney from precursors delivered to it in arterial blood. They observed that the arterial concentration of preformed ammonia is so low that even if all of it were extracted by the kidneys, the amount would be insufficient to account for that excreted in the urine. Furthermore, ammonia is not extracted from arterial blood; rather, it is added to renal venous blood. Thus the renal venous concentration of ammonia exceeds the arterial concentration. Of the total ammonia produced by the acidotic kidney, roughly one-quarter is added to venous blood, three-quarters is excreted in the urine.

Some twenty years later, Van Slyke and his colleagues (14) suggested that glutamine is the major precursor of ammonia produced by the intact functioning kidneys of acidotic dogs. They maintained that the amide nitrogen alone of the glutamine extracted from arterial blood could account for all of the ammonia excreted in the urine and for two-thirds or more of that added to renal venous blood. In those instances in which the amide nitrogen of the extracted glutamine was insufficient to account for all of the ammonia produced by the kidney, the remainder was presumed to be derived from unspecified amino acids.

The thesis I wish to present is similar to that of Van Slyke's in some respects, namely that glutamine is the non-excreted, nitrogen-containing compound which is extracted from blood by the kidney in greatest amount. It is, therefore, the probable major source of the ammonia formed by the kidney. I also agree that more of the amide nitrogen of glutamine than of any other precursor nitrogen ultimately appears as renal ammonia. However, my thesis differs from that of Van Slyke's in other respects. The amino nitrogen of glutamine is a significant source of urinary ammonia, and accounts for roughly half as much of the ammonia as does the amide nitrogen. Amino acids, such as alanine, glycine and glutamic acid, and no doubt others as well, contribute their nitrogens to renal ammonia formation to a smaller extent.

However, certain inferences have been drawn from the predominant role which the amide nitrogen of glutamine plays in the formation of renal ammonia. These include the inference that the major pathway of metabolism of glutamine involves its hydrolytic splitting by glutaminase 1 to form glutamate and ammonia. From this has followed the deduction that the control of ammonic production is in some way related to the activity of glutaminase 1 in renal tubular cells. Finally, the presumed direct route from the amide nitrogen of glutamine to urinary ammonia has favored the view that tubular cells are rigidly compartmented, even with

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*Taken from the introductory remarks given at the session on Kidney Ammonia and Urea at the 1966 Federation Meetings.

respect to ammonia, a highly diffusible substance.

I shall develop the thesis that the first step in the metabolism of glutamine involves the transamination of keto acids to form α-keto-glutaramate and a series of amino acids. Subsequently the α-keto-glutaramate is hydrolyzed by an ω-amidase to liberate the amide-nitrogen as ammonia and to form α-ketoglutarate. The control of ammonia production by the kidney must involve, in some degree, the control of activity of glutamine transaminase. Rather than exhibiting rigid compartmentation, the ammonia derived from the several amino and amide nitrogens of tubular cells is thoroughly mixed, and from this pool is drawn the ammonia added to blood and urine.

I shall start with the premise that the uncharged free base ammonia which is formed in tubular cells, diffuses across the luminal cell membrane into acid urine where it buffers hydrogen ions to form non-diffusible ammonium ions (see Fig. 1). The secretion of ammonia is passive and the mechanism may be described as one of non-ionic diffusion, for it is the non-ionic component of the buffer pair which diffuses. One may also describe it as a mechanism of diffusion-trapping, for the diffusible free base, ammonia, enters acid urine and is trapped as non-diffusible ammonium ion. It is also evident from this diagram that ammonia diffuses in lesser amounts into peritubular blood and is carried out of the kidney in the venous blood stream.

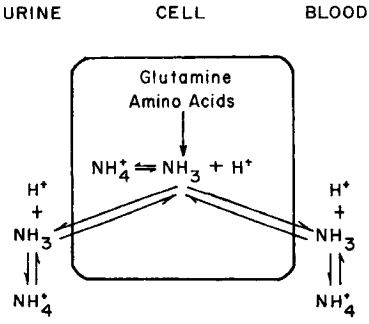

Fig. 1. Passive secretion of the free base, ammonia, by non-ionic diffusion. The major fraction is trapped in acid urine as relatively non-diffusible ammonium ion.

Indeed it is probable, as Denis and Preuss (1) have stated, that the free base is in diffusion equilibrium throughout the cortex of the kidney. The total ammonia concentration, that is, the concentration of free base plus ammonium ion, is therefore directly related to the hydrogen ion concentration of each of the several renal cortical phases: blood, interstitial fluid, cells and tubular urine. The paper to be presented in this session by Dr. Reid (10) supports this view in principle. Other evidence favoring a passive secretory mechanism of non-ionic diffusion has been reviewed by Milne, Scribner and Crawford (2), by Orloff and Berliner (4), and most recently by Pitts (6).

Some five years ago Shalhoub, Glabman, Webber and Canessa-Fisher (11) in our laboratory measured the concentrations of 23 free amino acids in samples of arterial and renal venous plasma collected simultaneously from acidotic dogs. Results obtained in 20 animals are summarized in Figure 2.

On the left, arterial concentrations, expressed in micromoles per

ml of plasma are shown by the upper black bar of each pair. The renal venous concentrations are shown by the lower clear bar. On the right are shown arterio-venous concentration differences: black, if the amino acid is removed from the plasma perfusing the kidney; clear, if the kidney manufactures the amino acid and adds it to renal venous plasma. Essentially similar findings in man were reported by Owen and Robinson (5) at about the same time.

The five amino acids at the top of this graph are the most interesting. It is evident that glutamine is extracted in far greater amount than is any other amino acid, a fact which confirms the finding of Van Slyke and his associates (14).

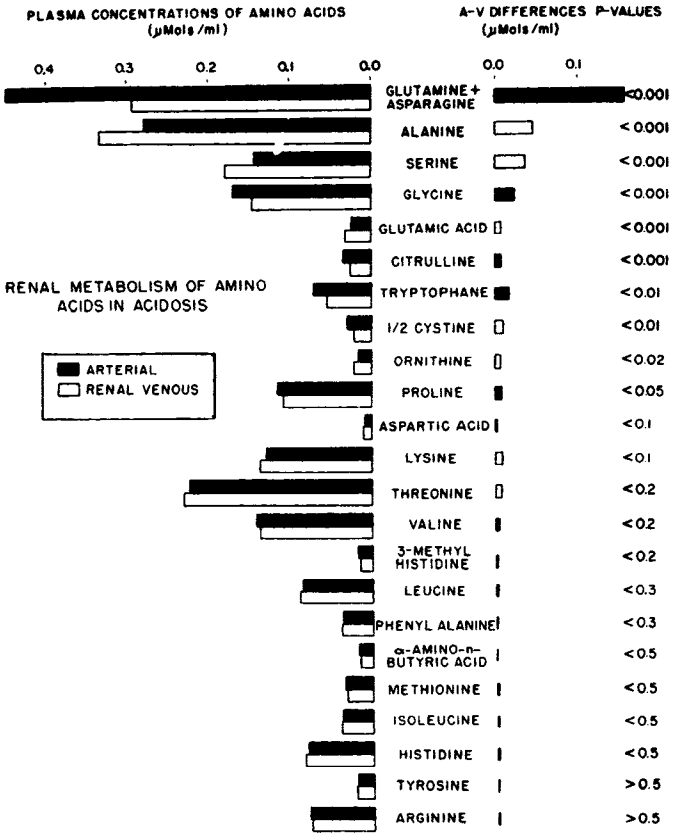

Fig. 2. Arterial and renal venous plasma concentrations and arterio-venous differences in concentrations of 23 naturally occuring amino acids. (From Shalhoub, R. et al. (11).

Glycine is also extracted in a much smaller but still significant amount. In contrast, alanine and serine are produced by the kidney and added to renal venous plasma, and the amounts produced suggest that some of the nitrogen of the extracted glutamine must have been diverted from ammonia production to the production of alanine and serine.

Glutamic acid is also added to renal venous plasma, but it is the smallness of the quantity added which is of special interest. If only the amide nitrogen of glutamine was utilized for the production of ammonia, then for each micromole of glutamine extracted from arterial plasma, one micromole of glutamic acid should have been added to renal venous plasma, for essentially none is excreted in the urine. Actually only 7/100ths of a micromole is added to renal venous plasma. Therefore 93/100ths of a micromole of glutamic acid disappears. This amino nitrogen of glutamine does in fact appear in part in the urinary ammonia and in part in the alanine and serine added to renal venous plasma, a fact which will be subsequently shown by Dr. Stone (13).

If one measures simultaneously renal plasma flow, arterial and renal venous concentrations of all amino acids, arterial and renal venous concentrations of ammonia and rate of excretion of ammonia, one may draw up a balance sheet such as the one shown in Table 1.

RENAL BALANCE OF AMINO, AMIDE AND AMMONIA NITROGEN IN THE DOG IN CHRONIC ACIDOSIS*

Data	μM Nitrogen/min
Total amide and amino nitrogen extracted from plasma	86.0
Amino nitrogen added to plasma	31.1
Net amide and amino nitrogen extracted from plasma	54.9
Ammonia nitrogen added to renal venous plasma	14.4
Ammonia nitrogen excreted in urine	43.1
Total ammonia nitrogen produced in kidney	57.5

NOTE:

$$\frac{\text{Net nitrogen extracted}}{\text{Ammonia produced}} = \frac{54.9}{57.5} \times 100 = 95 \text{ per cent}$$

* Mean of nine experimental studies in eight dogs

Data from Pitts, R.F., J.C.M. de Haas, and J. Klein (9).

The total amide and amino nitrogen extracted by the kidney averaged 86 micromoles per min. This was largely glutamine and glycine. The total amino nitrogen added to renal venous plasma amounted to 31.1 micromoles per min. This was largely alanine and serine. The net nitrogen extraction, therefore, was 54.9 micromoles per min. The sum

of the ammonia added to renal venous blood and excreted in the urine averaged 57.5 micromoles per min.

We could, therefore, account for 95 percent of the ammonia produced by the kidney in terms of the net extraction of amino and amide nitrogen. I consider this remarkably close to 100 per cent, for errors are easily compounded in work of this type.

However, if you think for a moment, I believe you will agree that from such data one can not assign an absolute percentage contribution of any one amino acid, such as glutamine, to ammonia formation. For instance, what is the source of the nitrogen utilized for the production of alanine and serine? The 30 micromoles of nitrogen utilized for these synthetic purposes is more than one-third of the total amide and amino nitrogen extracted by the kidney. It is evident, if one is to learn more concerning the renal metabolism of ammonia, that isotopic nitrogen must be employed, at least to identify source and metabolic pathway.

Figure 3 illustrates the principles of our more recent approach (7, 8, 13) to the study of the origin of urinary ammonia in the intact functioning kidney. The ureters of an acidotic dog are separately catheterized and an infusion of N^{15} labeled amino acid is given at a constant low rate into one renal artery. One of the compounds studied was glutamine, having 95 percent of its amide nitrogens of the heavy isotopic variety. Amide N^{15} glutamine is represented here by the capital G. The normally occuring N^{14} glutamine is represented by the small g.

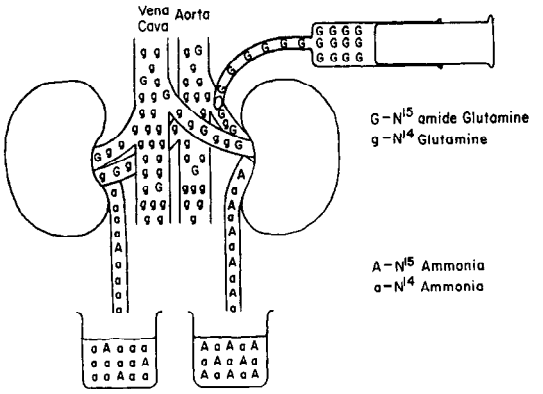

Fig.3. Diagram illustrating the use of N^{15} labeled amino acids in studies on the origin of urinary ammonia. For details, see text.

The urine on the infused side contains N^{15} ammonia, represented by the capital A and derived from the amide nitrogen of the labeled glutamine. Of course the urinary ammonia is largely the normal N^{14} variety derived from circulating non-labeled glutamine. The urine on the opposite side also contains N^{15} ammonia, but in much lower concentration, because all of the labeled glutamine infused into one renal artery is not extracted in one circulation through the infused kidney.

Some gets into the general circulation and is extracted by both kidneys. Therefore if one subtracts the atoms % excess N^{15} in the ammonia excreted by the control kidney from that excreted by the infused kidney, the difference is the specific activity of the ammonia determined solely by the infusion of labeled glutamine into one renal artery. The fact that an animal has two kidneys permits this simple correction for recirculation of label in any form.

The product of the renal plasma flow and the arterial concentration of glutamine gives the perfused renal load of glutamine. Addition of the amount infused into the renal artery gives the total glutamine load. The rate of infusion of N^{15} divided by the total glutamine load gives the specific activity of the plasma due to the intraarterial infusion. This specific activity, like that of the urine, is corrected for recirculation of N^{15} in any form.

Dividing the corrected specific activity of the urine ammonia by the corrected specific activity of the plasma glutamine and multiplying by 100 gives the percent of the urinary ammonia derived from the amide nitrogen of glutamine.

A series of 30 experiments with five labeled compounds are summarized in Table 2, including amide N^{15} glutamine, amino N^{15} glutamine, and amino N^{15} alanine, glycine and glutamic acid.

PRECURSORS OF AMMONIA IN ACIDOTIC DOGS

Number of Experiments	Nitrogen Source Studied	Mean Plasma Conc. μmoles/ml	Urinary Nitrogen From Source Studied		
			Percent		Mean Quantity
			Mean %	Range %	μmoles/min
9	Amide-N of Glutamine	0.455	43.3	35.3-51.4	18.9
6	Amino-N of Glutamine	0.422	18.3	10.1-25.5	8.73
8	Amino-N of Alanine	0.293	5.71	3.03-8.41	2.11
5	Amino-N of Glycine	0.197	3.76	2.92-5.55	1.22
2	Amino-N of Glutamate	0.025	1.88	1.43-2.34	0.98
		Sum	73.0	52.8-92.9	32.0
		Total	100.0		43.9

Data from Pitts, R.F. et al. (7,8,13).

It is evident that the major fraction of the urinary ammonia is derived from the amide nitrogen of plasma glutamine, varying in different experiments from 35 to 51 percent. We have, therefore, confirmed the basic concept of Van Slyke and associates that the amide nitrogen of glutamine is the major precursor of urinary ammonia. However, we have never observed the derivation of as much as two-thirds of the urinary ammonia from the amide nitrogen of this compound, much less all.

The amino nitrogen of glutamine accounts for 10 to 26% of urinary ammonia, roughly half that accounted for by the amide nitrogen. It, therefore, is a major precursor of ammonia, although quantitatively

less significant than is the amide nitrogen. Van Slyke and associates did not specifically mention the amino nitrogen of glutamine. Presumably they included its contribution to ammonia formation in the moiety derived from unspecified amino acids. We have found this moiety to be much larger than did they.

Alanine, glycine and glutamic acid account for lesser proportions of urinary ammonia. Alanine accounts for 3 to 7%, glycine for 3 to 6% and glutamic acid for 1 to 2%.

If we add the maximum contributions of these 5 precursor nitrogens, we can account for 93% of urinary ammonia. If we add the minimum contributions, we can account for only 53%. Using the mean contributions we can account for about three quarters of ammonia production. Failure to account for 100% of urinary ammonia is to be expected for we have studied the contributions of only 5 of the many possible amino acid precursors. A number of other precursors no doubt contribute, each in a small degree, to ammonia production.

One of the factors which accounts for differences in the percentage of ammonia derived from any one amino acid is the plasma concentration of that amino acid. Each of the five compounds studied contributes an increasing proportion of the renal ammonia when its plasma concentration is increased by the intravenous infusion of the unlabeled congener. I shall illustrate this point with only one example, namely glycine (7).

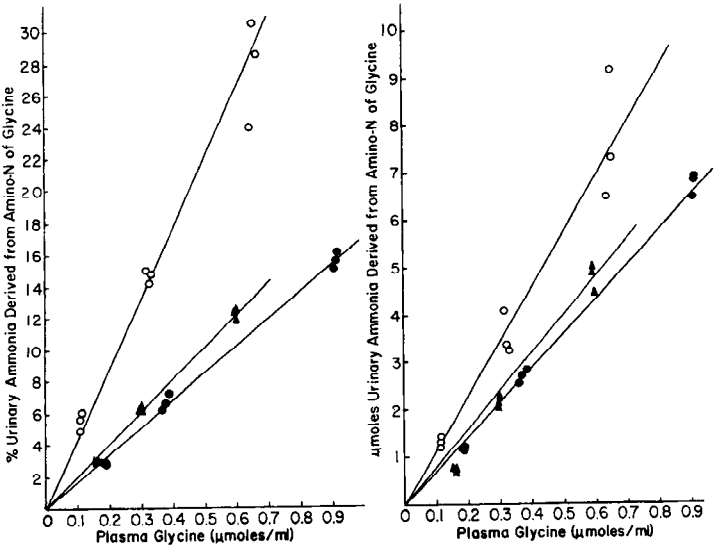

Fig. 4. Relations between plasma concentration of glycine and the percent (left) and absolute amount (right) of urinary ammonia derived from glycine. (From Pitts, R.F. and L.A. Pilkington) (7).

On the left of Figure 4 is shown the relationship between the plasma concentration of glycine and the per cent of the urinary ammonia derived from glycine nitrogen. The 9 points clustered in the lower left hand corner represent findings in 3 experiments at normal plasma concentrations, namely at concentrations of 0.1 to 0.2 μmoles of glycine per ml of plasma. Unlabeled glycine was then infused intravenously at a rate of 100 and subsequently at a rate of 300 μmoles per min to double and then to quadruple plasma concentration. In one experiment as much as 30 per cent of the urinary ammonia was derived from glycine at the highest plasma concentration.

On the right of Figure 4 are shown the actual quantities of ammonia formed from plasma glycine in these same experiments. At high plasma concentration, as much as 9 μmoles per min of ammonia were derived from plasma glycine.

It is apparent, if a dietary excess of one amino acid causes an increase in its plasma concentration, that this amino acid is preferentially used by the kidneys for ammonia production. Some of the variability in per cent contribution of a given amino acid to ammonia formation, therefore, results from normal variations in plasma level. However, it is equally evident that animals differ in the degree to which they utilize a given amino acid. Thus in these three dogs, at any given plasma concentration of glycine, there existed a two fold range in the per cent contribution of this amino acid to ammonia production.

Somewhat similar experiments to be reported by Dr. Stone (13), posed the following dilemma:at normal plasma concentrations, from 3 to 7 percent of the urinary ammonia is derived from plasma alanine. The kidney, therefore, extracts alanine from plasma and metabolizes it to ammonia and pyruvate. However, at these same normal plasma concentrations, the kidney synthesizes alanine and adds it in net amounts to renal venous blood. The amount synthesized is by no means negligible, amounting to 7 to 15 μmoles per min.

These and other experiments suggest that alanine is both synthesized and metabolized by reactions involving transamination. We, therefore, infused into one renal artery of an acidotic dog a mixture of N^{15} amino labeled glutamine and pyruvate labeled with C^{14} in the carboxyl carbon. At the end of the experiment both kidneys were rapidly removed and homogenized in picric acid. By a series of chromatographic procedures, a few representative amino acids were isolated in pure form both from arterial and renal venous plasma and from kidney tissue. In brief, C^{14} appeared almost exclusively in the alanine formed in the kidney tissue and added to renal venous blood. The N^{15} of the amino labeled glutamine of plasma was incorporated into the alanine and to a lesser extent into the serine formed by the kidney. The N^{15} labeling of the alanine was more than twice that of the ammonia and of the glutamate of kidney tissue. Thus the alanine must have been derived at least in part from a more highly labeled precursor than either ammonia or glutamate. Presumably the alanine was formed from glutamine by transamination with pyruvate.

Our view that transamination of glutamine is more significant than

deamidation as a first step in the metabolism of glutamine derives from the following considerations of data obtained in an experiment in which N^{15} amino labeled glutamine was infused into one renal artery. If deamidation were the initial event, top equation of Figure 5, the glutamate of renal tissue should be more highly labeled than other products including urinary ammonia. Actually, the glutamate contained only 1.59 atoms % excess N^{15} in comparison with 11.1 atoms % excess N^{15} in the amino position of the plasma glutamine delivered to the infused kidney. Both figures are corrected for recirculation of label. Only 14% of renal glutamate was derived from the amino nitrogen of plasma glutamine.

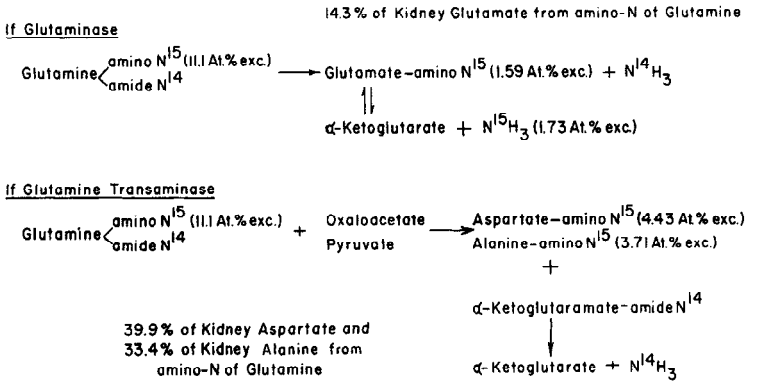

Fig. 5. Evidence for a major role of glutamine transaminase in renal metabolism of glutamine. See text for details.

However, if the initial event were transamination of glutamine, bottom equation of Figure 5, amino acids other than glutamate might be more highly labeled. Actually both aspartate and alanine are more highly labeled than glutamate and ammonia. These data demonstrate that at least some of the nitrogens of aspartate and alanine could not have come from either ammonia or glutamate. They must have been derived more directly from the amino nitrogen of labeled glutamine, presumably by transamination.

Our views concerning the reactions involved in renal ammonia production are summarized in the diagram of a tubular cell in Figure 6. To the right is shown the glutaminase pathway which we believe to be a minor one. More to the left is shown the glutamine transaminase pathway which we believe to be a major one. This latter pathway accounts for a significant fraction of the alanine produced in the kidney and added to renal venous blood and for an even larger fraction of the aspartate stores of the kidney. Aspartate serves as a supplementary reservoir of amino nitrogen and is convertable to ammonia through transamination to glutamate and through glutamate dehydrogenation. Other amino acids probably contribute to ammonia production through transamination to glutamate. Glycine could be metabolized by transamination as a typical amino acid or could proceed to glyoxylate as shown at the far left.

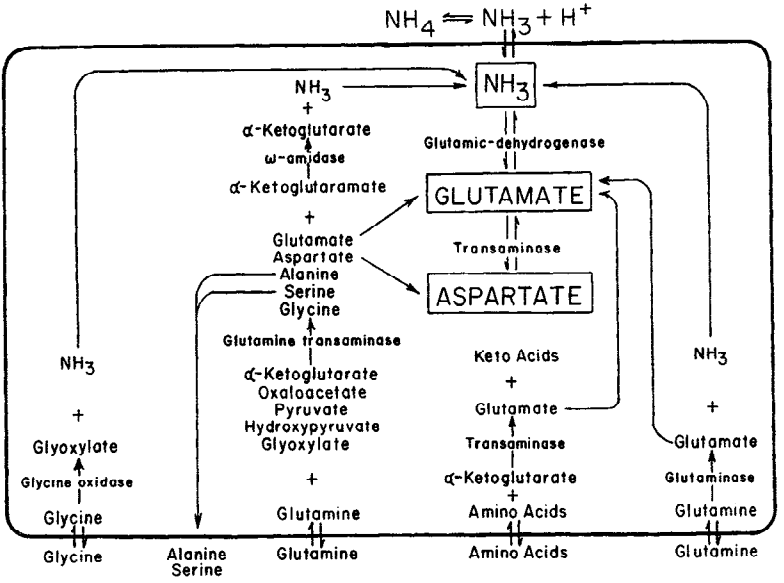

Fig. 6. Diagramatic illustration of metabólic pathways of ammonia formation in renal tubular cells. Luminal border of cell at top of diagram. See text for details.

I should like to emphasize the central position of glutamate in this scheme. Glutamate and aspartate are present in kidney tissue in far higher concentrations than in plasma. Furthermore, there is more glutamate and aspartate in kidney tissue than other free amino acids. Glutamate is no doubt formed in a number of ways: by deamidation of glutamine and also by transamination of amino acids, including glutamine. If it is also formed from ammonia and α-ketoglutarate, as appears probable, the glutamate dehydrogenase reaction could buffer the concentration of free base, ammonia, in tubular cells. Excess ammonia or amino nitrogen would be stored as glutamate and aspartate. On demand, ammonia could be supplied from the primary glutamate reserve backed up by the secondary aspartate reserve.

If these views are correct, one should take a fresh look at possible control mechanisms. I shall present two schemes. I have no evidence for either; neither or both may be correct. It would be nice to have a controlling enzymatic step, sensitive to the pH of the cell at the locus of the enzyme. According to Stern, Ochoa and Lynen (12), the condensing enzyme, now called citrate synthase, which couples acetyl Co A to oxaloacetate to form citrate is exquisitely sensitive to hydrogen ion concentration (see Figure 7). Its activity is markedly reduced when pH is lowered. Reduced formation of citrate in acidosis would lead to a pile up of oxaloacetate and pyruvate. The Krebs cycle would slow and accumulation of oxaloacetate would cease were the cycle not continuously primed with α-ketoglutarate derived from glutamine. The excess

oxaloacetate and pyruvate could then speed up the transamination of glutamine and the production of ammonia would increase. This thesis has one virtue; it should be readily testable in renal homogenates, renal slices and in the intact functioning kidney of the dog. At the moment, this control mechanism is an example of arm chair renal physiology.

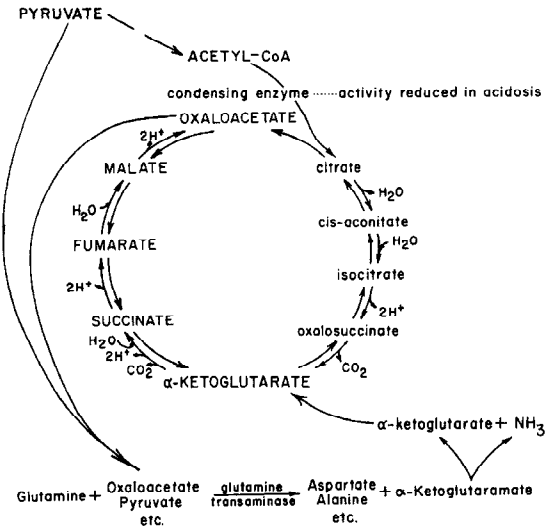

Fig.7. Tricarboxylic acid cycle and glutamine metabolism. See text for details.

Another possibility is to focus on the reversible amination and deamination of α-ketoglutarate and glutamate (see Figure 8). The thermodynamic equilibrium for the glutamate dehydrogenase reaction strongly favors the reductive synthesis of glutamate. However, oxidative deamination of glutamate would be favored by removal of α-ketoglutarate, by secretion of ammonia into acid urine, and by a decrease in the ratio of DPNH to DPN.

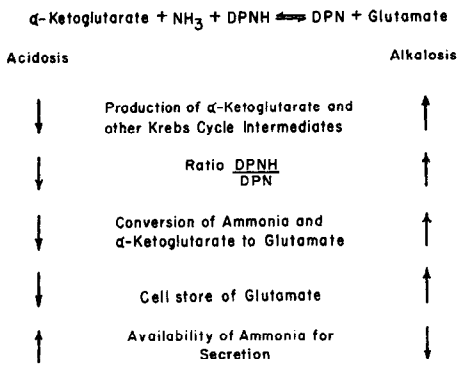

Fig.8. Possible role of glutamate dehydrogenase in control of ammonia production. See text for details.

In alkalosis, the production of α-ketoglutarate and other cycle acids is increased, as is the ratio of DPNH to DPN. Both factors favor conversion of α-ketoglutarate to glutamate and a reduction in the ammonia content of renal tissue. Less ammonia is available for secretion. In acidosis, opposite changes occur in α-ketoglutarate production and in the ratio of DPNH to DPN. Synthesis of glutamate is reduced and ammonia from glutamate stores becomes increasingly available for secretion into urine. Although untested, this is a testable hypothesis. Some might prefer to call it detestable and conjure up another.

I interject a word of caution: I doubt that control of renal ammonia production is exerted at a single enzymatic step. Any function as complex and as important as renal production of ammonia is probably controlled at a series of steps.

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GASTROENTEROLOGY PUBLICATION

The National Institute of Arthritis and Metabolic Diseases began publication in January 1966 of a current-awareness journal for gastroenterologists. "Gastroenterology Abstracts and Citations" will appear monthly and it will alert the reader to all the developments in the current scientific literature on gastroenterology from throughout the world regardless of language and country of publication. Each issue will contain approximately 350 abstracts of the most significant gastroenterological literature and approximately 750 citations covering the remaining gastroenterological literature, as well as other literature closely related to gastroenterology. Each issue will contain a subject and author index, and cumulated subject and author indexes will appear at the end of the year.

The Institute's aim in initiating this new current-awareness publication is to foster greater and more prompt communication and dissemination of current research efforts in gastroenterology. It will also, hopefully, provide additional stimulation for the important research being carried out in the field of gastroenterology.

"Gastroenterology Abstracts and Citations" will be distributed free, on request, to all National Institute of Health grantees working in the field of gastroenterology as well as to medical school libraries, medical school departments of medicine, and government agencies with programs in gastroenterology. This publication will also be available, on request, to all other professional persons with interests in gastroenterology. Physiologists interested in the field of digestion and working on research pertaining to gastroenterology may request publication on an individual basis by addressing a brief letter to the Scientific Communications Officer, National Institute of Arthritis and Metabolic Diseases, National Institutes of Health, Building 31, Room 9A-03, Bethesda, Maryland 20014.

DIFFUSION OF GASES IN THE LUNGS*

R. E. FORSTER

The diffusion of gases between alveolar air and pulmonary capillary blood is still considered a passive physico-chemical process; no active secretion as suggested by Haldane (20) has been uncovered. My remarks on this topic will of necessity be incomplete, but are intended to be pertinent to the papers that follow in this session.

The pulmonary diffusing capacity of the lung,

$$D_L = \frac{\text{rate of gas transfer in ml/min}}{\text{Mean pressure difference between alveolar gas and blood in mm Hg}}$$

This quotient has meaning as an index of the efficiency with which the lung exchanges gas with the blood. It is a poor term and certainly does not represent the total exchange potential as implied by the word "capacity". Other names have been suggested for this ratio (10) but "diffusing capacity" appears firmly established in a growing literature.

Whatever its name, D_L as defined appears to be useful although the emphasis upon it changes with time. It was first calculated by Bohr (1) mainly to study the mechanism of gas exchange in the alveoli. He obtained values for D_{LO_2} and D_{LCO}, the latter from data of Haldane's, which were not great enough to explain the O_2 uptake during exercise, and therefore assumed, with Haldane, that secretion must take place. Krogh responded by measuring D_L at rest and during exercise with carbon monoxide, demonstrating for the first time that D_L increased with exertion and by an amount sufficient to account for the O_2 exchange (25).

Lilienthal, Riley, Proemmel, and Franke (28) initiated a new wave of activity in which D_L was measured with various methods, both with O_2 and CO, and the proponents of the different techniques argued among themselves as to the accuracy of their measurements. More recently we have entered a phase in which the differences between the methods are being used to provide new information about gas exchange in the lung, and more attention is being devoted to the mechanism of control of D_L. Surprisingly enough, the measurement of D_L has turned out to be of pragmatic interest to the clinician, even though the explanation of its alterations in disease states is not entirely understood. In addition, measurements of D_L are being made more widely throughout the animal kingdom and are being used to attack problems of gas exchange where it is sometimes more convenient to measure D_L than the primary variables such as P_{O_2} and P_{CO_2}. This morning's session deals with several of these areas of interest and future activity.

D_L has been shown to be dependent upon a number of factors, a

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*Taken from the introductory remarks given at the session on Pulmonary Diffusion at the 1966 Federation Meetings.

partial list of which is given in Table 1.

TABLE 1

Partial List of Factors Upon Which Measured Pulmonary Diffusing Capacity is Dependent

1. Body size
2. Age
3. Alveolar volume
4. Minute ventilation
5. Body temperature
6. Time of day
7. Alveolar P_{O_2}
8. Alveolar P_{CO_2}
9. Blood COHb
10. Exercise
11. Pulmonary blood flow
12. Pulmonary vascular pressure
13. Body position
14. Non-uniform distribution

O_2 consumption increases with body size in a given species which requires that D_L increase approximately in proportion if the mean P_{O_2} difference between alveolar gas and capillary blood is to remain approximately the same. This last is generally true because normal alveolar P_{O_2} and arterial P_{O_2} are independent of size.

There appears to be a slight decrease in D_L with age, at least when measured with the breath holding and steady state techniques (4, 13). However, Mittman, Edelman, and Shock (31) find no significant decrease in D_{LCO} with age when measured by the equilibration technique, although they confirm the decrease in D_{LCO} with age using the steady state and tidal sample methods. The reason for the decrease in D_L is not known with surety. The total number of pulmonary capillaries may decrease with advancing age, and uneven distribution in the lung may increase with age, both of which would reduce measured D_L.

D_L was originally considered by the Kroghs to be proportional to the alveolar volume, although over a limited range (25). About 12 years ago, Briscoe, Bates and I (15) found a variation of less than 10% in average D_L over the entire range of alveolar volume with the single breath and steady state end tidal methods, and in view of the much larger variation that would have been expected if D_L had been proportional to alveolar volume, considered this change negligible. Cadigan and associates (6) went on to measure D_L single breath over the extremes of lung volume and obtained much larger variations as did other investigators. It is now becoming clear that uneven distribution of diffusing capacity throughout the lung is of critical importance in the relation of D_L to alveolar volume. Several of the papers to follow bear on this point. Gurtner and Fowler (19) have investigated the dependence of D_L, as measured by three different techniques, upon the volume of the lung. Michaelson et al. (30) present findings suggesting that nonuniformity is the major factor in this relationship.

An increase in minute ventilation produces an increase in steady state D_L but does not change single breath, rebreathing, or equilibration D_L (14). The changes in the steady state estimates probably result from an improvement in the distribution of alveolar ventilation in respect to D_L or in part from a secondary increase in mean lung volume.

One would expect that D_L would rise with an increase in body temperature and fall with cold. Otis and Jude (34) found that D_L steady state fell with hypothermia in dogs, but Cander and Hanowell found that D_L did not increase with fever in man (7).

Cinkotai and Thomson (8) have reported that breath holding D_L falls during the day, which fact must be taken into account when interpreting changes over time periods in the order of hours. Nairn and her associates also found a fall in D_{LCO} during the day (33). The cause of this phenomenon is obscure, but it is not a result of obvious factors such as body position or activity.

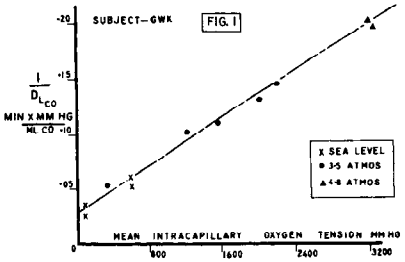
A rise in alveolar P_{O_2} will lower D_{LCO}, presumably because the O_2 competes with CO for the reduced intracellular hemoglobin, slowing up the rate at which the formation of COHb can take place at a given plasma P_{CO}. The interesting point is that the rate at which the red cell can take up CO is slow enough to limit partially its overall exchange, or D_L would not be affected. The relationship between the diffusing capacity of the lung, D_L, the diffusing capacity of the membrane, D_M and the diffusing capacity of the red cells in the capillary bed at any time, θV_c, is expressed as follows (14).

$$1/D_L = 1/D_M + 1/\theta V_c \qquad (1)$$

θ is the rate at which the red cells can take up CO in ml/(min x mm Hg x ml blood) and V_c is the average volume of blood in the pulmonary capillary bed. In practice if one measures D_L at different alveolar P_{O_2} above 200 mm Hg and plots $1/D_L$ against $1/\theta$, this last obtained from in vitro measurements on blood in a rapid reaction apparatus, a graphical solution of equation 1 can be obtained as indicated in Figure 1. The slope of the line is $1/V_c$ and the intercept $1/D_M$. It turns out that $1/\theta$ is proportional to P_{O_2} at least when P_{O_2} becomes much greater than 100 mm Hg. In Figure 2, $1/D_L$ obtained on a normal man in a hyperbaric pressure chamber is plotted against alveolar P_{O_2}. The resulting straight line is a remarkable extra-polation from the previously known data, which stopped at less than 700 mm Hg. These results infer, although they do not prove, both that Equation 1 applies and that $1/\theta$ is proportional to P_{O_2}, over this entire range.

This is a good point to remark that the use of equation 1 was restricted in the original studies (40) to alveolar P_{O_2} greater than 200 mm Hg because it is necessary in its derivation to assume that plasma P_{O_2} is constant along the capillary, which is only true when alveolar P_{O_2} is high enough to saturate the inflowing blood before it has traversed a significant fraction of the vessel. This assumption becomes increasingly dubious as alveolar P_{O_2} falls below about 200 mm Hg. In fact our observations at alveolar P_{O_2} less than 100 mm Hg did not fall on the same straight line as the points at higher P_{O_2}. Since a great fraction of the total resistance to diffusion lies within the red cells at an alveolar P_{O_2} in the region of 650 mm Hg, rather than in the membrane, one could assume that D_L at this P_{O_2} equals θV_c and not bother to draw a graph as in Figures 1 and 2. If there are data at only two different P_{O_2} and the lower P_{O_2} is much less than 200 mm Hg, it may even be more

accurate to calculate V_c in this manner.



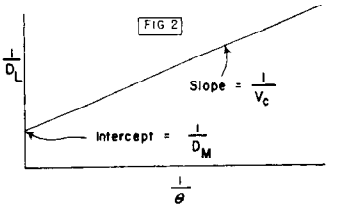


Fig. 1. Theoretical plot of $1/D_L$ against $1/\theta$ demonstrating the method of solving for D_M and V_c. Fig. 2. Graph of $1/D_L$ against mean estimated intra-capillary O_2 tension at sea level, and at 3.5 and 4.8 atmosphere pressure (adapted from 33).

Increasing alveolar P_{CO_2} increases D_L, at least by the breath holding method, and very rapidly. A single inspiration of 10% CO_2 increases D_L about 5% within 10 seconds (36). This could be mechanical, resulting from a constriction of the post capillary vessels with attendant dilation upstream as has been found in the isolated perfused cat lung (21). However, this is a very rapid response for a mechanical phenomenon, and we suspect that the immediate increase in D_L following the rise in alveolar P_{CO_2} results from a chemical effect upon the rate of the reaction of CO with intracellular reduced hemoglobin, in other words an increase in θ. We investigated this superficially when we were first determining θ and found no marked change (17). However, we might have missed a small effect. Theoretically, an increased acidity of the blood would increase the concentration of reduced hemoglobin at any P_{O_2} and increase θ.

COHb in the mixed venous blood will produce a P_{CO} in the alveolar capillary blood in chemical equilibrium with it. This gas tension must be subtracted from the alveolar P_{CO} to obtain the correct driving gradient with which to calculate D_L. Under many circumstances this (COHb) is negligible, but in smokers, or after CO has been absorbed in previous D_L measurements, it may become significant, particularly when alveolar P_{O_2} is high.

The factors in the next group are associated with hemodynamic changes in the lung. The first of these factors is exercise. Although many investigators have verified the Kroghs finding that D_L increases with exercise, using either O_2 or CO, and several different techniques, (14), the mechanism or mechanisms, is still in doubt. Intuitively the pulmonary capillary blood flow should be an important variable in causing the increase in D_L with exercise. Krogh (25) suggested that diffusion gradients built up in the pulmonary capillary plasma, and their reduction by the increased blood velocity in the capillaries was the cause of the increase in D_L with exercise. Modern microphotographs (14) indicate that the red cells are actually squeezed against the capillary wall and that there is no important layer of plasma, stirred or unstirred,

between the red cell and alveolar gas. The diffusion path within the plasma is included in D_M, so that if changes in diffusion resistance within the plasma are important in causing D_L to increase with exercise, this would be reflected as a marked increase in D_M. However, at high alveolar P_{O_2}, where almost all the diffusion resistance is in the capillary red cells, D_{LCO} also increases with exercise, indicating that V_c must increase.

Although D_I, and pulmonary blood flow both increase in exercise, (Figure 3) DL generally does not increase when pulmonary blood flow is increased by other means. Ross and associates (39) increased pulmonary blood flow in man with intravenous saline and albumin, and

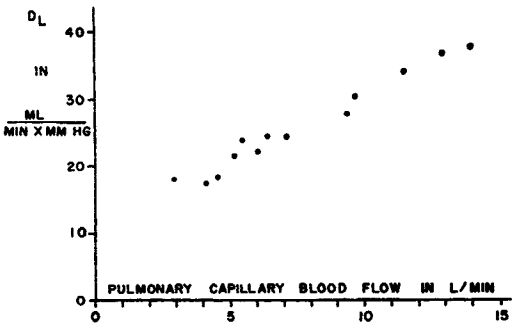


Fig.3. A graph of single breath D_{LCO} against against pulmonary blood flow as measured simultaneously with acetylene (adapted from 22).The lowest blood flow values were obtained during a Valsalva maneuver.

norepinephrine + atropine without causing an increase in D_L. Turino and associates (45) increased pulmonary blood flow unilaterally by occluding the contralateral pulmonary artery with a balloon and failed to find an increase in D_{LCO}. D_{LCO} is not increased in resting patients with hyperthyroidism although pulmonary blood flow is (43). Even with exercise D_L is not entirely dependent on the capillary blood flow. In Fig. 4 it can be seen that changes in D_L at the start and end of exercise lag the changes in pulmonary blood flow. To further complicate matters pulmonary vascular resistance and D_L can alter independently (21).

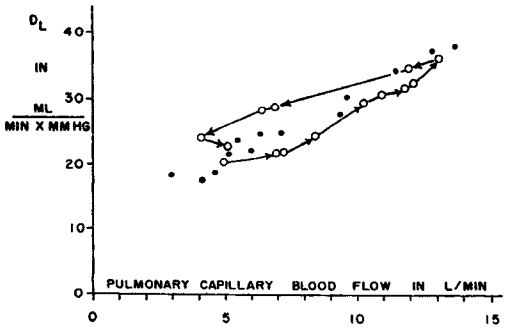


Fig.4. A graph of simultaneous D_L and pulmonary blood flow during the start and cessation of exercise (open circles). The arrows indicate the successive points starting with resting conditions before exercise. The solid points are the steady state data as in Figure 5 (adapted from 22).

Pulmonary vascular pressure should be important in controlling D_L, as an increase in transmural pressure causes an opening of the pulmonary capillary bed (38). Experimentally distension of the lesser circulation with blood displaced from the periphery by inflating a pressure suit around the lower half of the body causes an increase in D_L (26). Zechman, Musgrave, Mains and Cohn (24) found a reduction in D_L with negative pressure around the lower half of the body. However, it is extremely difficult to separate the effects of pressure and flow in controlling the size of the capillary bed. Increasing pulmonary blood flow causes an increase in D_L in the isolated perfused cat lung even with constant left auricular pressure at physiological flow rates as shown in Figure 5 (38). However, transmural pressures upstream from the left auricle must have changed to some degree if flow increased, and this slight increase in transmural pressure might be the important factor in regulating the capillary bed in this low pressure system.

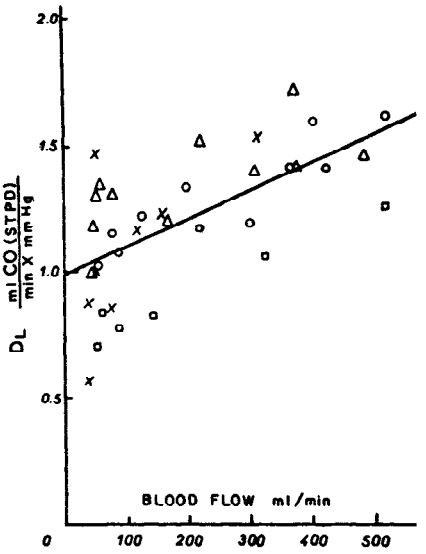


Fig.5. A graph of single breath D_{LCO} in the isolated perfused cat lung at constant left auricular pressure versus pulmonary blood flow. The different symbols represent different preparations (adapted from 38).

Exercise may increase D_L by some other mechanism than the obvious increase in cardiac output or pulmonary vascular pressure. For example, Krumholz and associates (26) found that D_L is increased more by pressure suit inflation after exercise than before, suggesting that some additional factor has altered the response of the pulmonary capillary bed.

One has the impression that there is a simple fundamental mechanism controlling flow through the pulmonary capillary bed, or through individual capillaries, that escapes us. One such mechanism that has received increased emphasis recently, is the Starling resistance role (24) of the pulmonary capillary bed or the "water fall effect". Because the capillary walls are not rigid whenever intracapillary lateral blood pressure falls below alveolar gas pressure, which approximates atmos-

pheric, the capillaries of necessity collapse. Under these circumstances the calculation of pulmonary vascular resistance as the quotient of [mean pulmonary arterial pressure less left atrial (or pulmonary venous pressure)] and flow has no meaning. The pulmonary capillary bed in the apex of the lung of the resting erect man should be collapsed, at least during certain parts of the cardiac and respiratory cycles. This appears to be the case as evidenced by external scanning studies of short lived radio isotopes at Hammersmith (12) and of radio xenon at McGill (11), which show that pulmonary blood flow per unit lung volume is reduced in the upper parts of the lung. This nonuniformity is increased by changes that would lower pulmonary capillary pressure, and decreased by factors that would raise the pulmonary capillary pressure. It is now being proposed that an important factor in the increase in D_L seen with various hydrodynamic maneuvers is the improvement in uniformity of pulmonary capillary blood volume per unit volume throughout the lung.

D_L is greater supine than sitting, and greater sitting than standing at least by the breath holding technique (14). This has been ascribed to parallel changes in pulmonary blood flow, which is greater supine than sitting, and greater sitting than standing. It is now known that the distribution of pulmonary diffusing surface becomes more uniform as the pulmonary blood flow increases, and the hydrostatic pressure gradients within the lung decrease and that this is a major factor in causing the changes in D_L with change in position. Gurtner and Fowler have findings pertinent to this question (19).

Training might be expected to alter the maximum D_L that an individual can attain. Mostyn and associates (32) have reported studies showing that Olympic caliber swimmers have a greater D_L than normal nonathletes under the same conditions. Reddan, Burpee, Reuschlein, Gee, and Rankin have investigated this same question at the University of Wisconsin (37).

Diffusion exchange in the lungs is most efficient if D_L/alveolar volume and D_L/alveolar ventilation are uniform throughout. Forster, Fowler, Bates and Van Lingen (16) obtained measurements of alveolar P_{CO} during breath holding which were not exponential with time as would have been expected if D_L/V_A were uniform throughout the lung (Fig. 6). Although the alveolar CO disappearance curve could be separated into two "phases" it is questionable as to what these "phases" represented. The findings were interpreted as indicating that D_L/V_A varied in different parts of the lungs. Fowler (18) and others have shown that the first and last parts of the expirate appear to derive from different parts of the lung. The last of the expired breath comes from regions with poorer alveolar ventilation/alveolar volume than the first part of the expirate. Knowing that D_L/V_A was uneven, Spicer and associates (42) measured D_L in the first and last parts of the breath in normals and in patients with abnormal distribution, but found no difference in D_L/V_A, provided differences in the time the gas in the alveoli were taken into account. This apparent paradox was explained on the assumption that the distribution of D_L/V_A and $\dot{V}_A/V_A$ are independent of each other. In other words that a sample from a region of good $\dot{V}_A/V_A$ would have

the same distribution of average D_L/V_A as a region with poor $\dot{V}_A/V_A$.

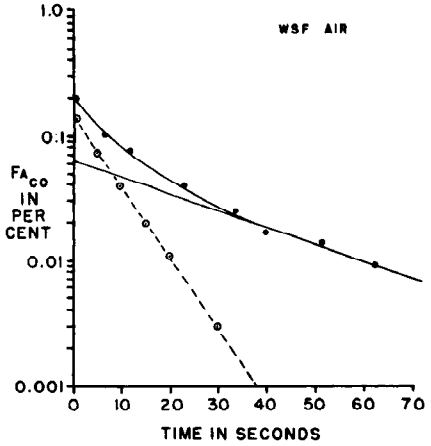


Fig.6. A semi logarithmic graph of expired alveolar CO concentration ($F_{A\ CO}$) against time of breath holding in a normal subject. The alveolar CO concentration at time zero, before any CO have been absorbed by the blood was 0.2 percent. The curve has been separated into two exponential phases.

Michaelson et al. (30) provide a better explanation in their paper, based on findings of Dollfuss et al. with radio xenon (11) that, starting from residual volume, the first part of an inspiration goes to the upper parts of the lung where the capillary bed is smaller in the erect position, and the later parts of the inspiration go to the lower regions of the lung, where the capillary diffusing surface is greater. Thus a sample of expired alveolar gas from the first part of a maximal inspiration would give a smaller value of D_L/V_A than a sample inspired at the end of a maximal inspiration. Spicer et al. (42) did not find any such difference possibly because their gas samples were too large. We now have the advantage of knowing the spatial distribution of inspired gas in the lung, which is an indispensable asset in interpreting measurements of D_L (11, 12).

Burrows and Harper (3) developed a technique of studying nonuniformity of $D_L/\dot{V}_A$ which involves following expired alveolar concentrations of CO and an inert tracer gas immediately after a subject or animal stops breathing a mixture containing these two gases and starts breathing air. Theoretically, assuming uniformity in the lung,

$$F_{A_{CO}} = \frac{F_{I_{CO}}}{1 + \frac{D_L\,(P_B - 47)}{\dot{V}_A}} \quad e^{-t\left(\frac{\dot{V}_A}{V_A} + \frac{D_L\,(P_B - 47)}{V_A}\right)} \qquad (2)$$

$F_{A_{CO}}$ is the mean expired alveolar (CO), $F_{I_{CO}}$ the (CO) that was inspired in the previous steady state. t is time in minutes. The multiplier in front of the exponent is the steady state value of alveolar (CO) that existed before the subject started breathing air. In the case of the inert gas, the terms containing D_L vanish and the initial steady state value equals inspired concentration of inert gas. The exponent contains

only the term t $\dot{V}_A/V_A$. Expired CO and inert gas concentrations can be plotted against time on semi-logarithmic paper and the inert gas curve subtracted from the CO curve to give a curve with only t D_L (P_b - 47) /$\dot{V}_A$ as an exponent. An example of such a curve in a dog (5) is presented in Figure 7. If $D_L/\dot{V}_A$ is not uniform as assumed, this corrected CO washout curve is not logarithmic and an obvious curvature appears as demonstrated in the experiment during shock, when presumably some parts of the pulmonary capillary bed were collapsed. Mittman, Edelman, and Shock (31) have used this and the steady state end tidal method to study uneven distribution of D_L.

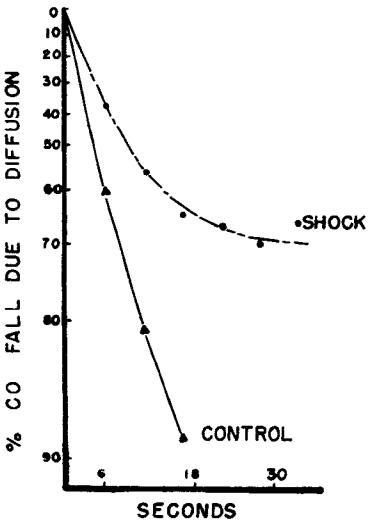


Fig. 7. A semi logarithmic graph of percentage fall in expired alveolar CO concentration due to diffusion alone into the blood in an anesthetized dog (equilibration technique) uneven control conditions and in post-hemorrhagic shock (adapted from Burrows & Niden (5). See text for more detailed explanation.

Nonuniformity in the lung generally presents problems that are mathematically insoluble without simplifying assumptions. Taking advantage of electronic computation, models have been constructed in which the effects of different distributions of the variables pertinent to gas exchange upon overall D_L have been studied (41). Approaching the problem from the other direction, that is attempting to calculate the distribution of the pertinent variables from measurements of overall D_L or of gas exchange, is strictly speaking mathematically insoluble, but with reasonable assumptions one can reach reasonable conclusions. Briscoe (2) has computed discontinuous distributions of blood flow and ventilation that would explain the values of expired, arterial and mixed venous gas tensions actually measured in a patient or subject. In the past, diffusion was assumed complete in a given alveolus. In their paper, King and Briscoe add a finite D_L to the variables considered in their calculations (23).

A great deal of interesting information can be obtained from measurements of gas diffusion in different species. In fact, it is sometimes more convenient to measure D_L as with CO than to measure requisite

O_2 tensions. This is certainly the case in the catfish, whose gill diffusing capacity has been measured by Coburn, Fisher, and Forster (9). For the same reasons as those advanced earlier in the consideration of variations in D_L with body size, we would expect the pulmonary capillary surface area to be proportional to O_2 consumption. In Figure 8 are presented results measured and collected by Tenney (44) for a variety of species of a range of body size showing that this simple relation exists. The CO diffusing capacity for the sheep placenta near full term is of the order of 0.5 ml/(min x mm Hg x kg of fetus) (29), which is very similar to the value of about 0.4 ml/(min x mm Hg x kg) for the lungs of a normal man. Both lungs and placenta are mainly gas exchangers and need about the same transfer properties for each gram of tissue supplied.

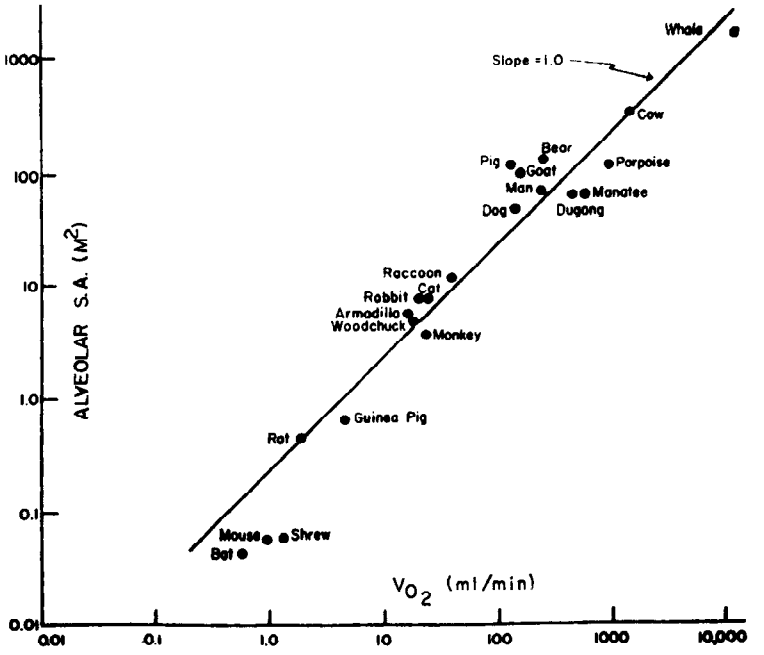


Fig. 8. A graph of pulmonary capillary surface area, obtained from anatomical studies, against O_2 consumption in different mammalian species. (After Tenney & Remmers)(44).

The lung fish should provide an unusual opportunity to compare exchanges in air and in water in the same animal. Rahn (35) has pointed out that the much greater solubility of CO_2 in water as compared to O_2, demands that water breathers have a lower blood P_{CO_2} than air breathers for approximately the same P_{O_2}. Lenfant (27) reports on his findings in this fish in water and air.

After this brief review, we should turn to the first of the presentations which dovetail together unusually well.

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COENOTHERMIA AND MESOTHERMIA, TWO NEW TERMS FOR PHYSIOLOGISTS

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Until about two years ago the term "normothermia" was widely used for the mean body temperature of homoiotherms. The term is a hybrid since it is a compound of the Greek work "therme" (heat) and the Latin word "normalis" (average). Recently there has been an increasing tendency to replace this term with one of purely Greek ancestry, "euthermia", which literally means "the good or true temperature". Although no one can cast aspersions on the origins of the latter term, the author has reservations concerning calling any temperature "good" or "true".

Euthermia is thus a colored term which carries implications which have not been demonstrated for all circumstances. For example, the experiments of Badeer (1) and others show that for the isolated perfused dog heart, the "good temperature" as measured by stroke volume, pulse pressure and electrocardiogram is about 26°C rather than 39°C, the temperature of the untreated dog. Likewise, the "good temperature" in rats for learning bar pressing for heat is 29°C not 37°C (4). In neonatal rabbits, cats and dogs it is 15°C core temperature if they are to be asphyxiated (under these conditions puppies live 7-1/2 times as long as their "eithermic" littermates (3).

A search for a neutral Greek word carrying a meaning of "average" "usual", or "customary" to join to "thermia" disclosed the following candidates:

1. gnorimos, meaning well-known
2. koinos, meaning common or usual
3. koinonikos, meaning average
4. metrios, meaning moderate
5. mesos, meaning in the middle

Since gnorimos is the source of the Latin word "norma", it was the first word to be considered. However, its union with thermia produced the monster "gnorimothermia" which sounded entirely too much like "a g'nother g'nu" (2) to be seriously considered for a scientific term. An even more monstrous monster could be made from koinonikos - "koinonikothermia"; and it also was discarded. Metriothermia also was rejected. The term sounds much like a "measured temperature", (from the Greek metron) and, in addition, its origin also might be confused with the word "metra" for uterus. "Mesothermia" represents the marriage of two well-known members of etymological aristocracy (words derived from the Greek). However, because it has the meaning of moderate, mesothermia too was passed over in favor of the final choice derived from "koinos" which conveys the connotation of the "usual" temperature.

None of the criticisms of the other candidates applies in the case of koinos, whose root "koine" denoted the language which was common to

the Greek-speaking peoples of the eastern Mediterranean from the Hellenistic period until the end of the Roman Empire in the 6th Century A.D. The anglicized form of this root, "coeno" is a very respectable term which has been used by a variety of subsciences of biology, for example, coenoblast of embryologists, coenocyte of histologists, coenuran of parasitologists, coenosarc of invertebrate morphologists and coenotrope of psychologists.

Therefore, since coenothermia represents the union of two well-known families with impeccable ancestry, and conveys, as it properly should, the concept that the temperature is common to a large number or to a species, the writer would like to suggest that the following words be added to the armamentarium of physiologists:

coenothermia (Gr. koinos = common + therme = heat) the condition in which the body temperature of homoiotherms is within the average range for the species.

coenothermic (Gr. koinos = common + therme = heat) pertaining to or characterized by the normal temperature for the species of animal in question.

There is a second problem of terminology in the field of hypothermia. This is the lack of precision regarding the use of the term itself. As used by physiologists it generally refers to body temperatures from normal down to 0°C, whereas surgeons often limit it to temperatures down to about 28°C with "deep" and "profound" used as modifiers for the lower temperature ranges.

In order to clarify and define more precisely the three temperature ranges, it is proposed to call the temperature from 20°C to 0°C as truly "hypothermic" and the middle range, between the normal body temperature and 20°C as the "mesothermic" range. This is a stressful zone in which thermogenesis is active and unanesthetized mammals expend large amounts of energy in attempting to elevate their temperatures. By contrast, in true hypothermia these mechanisms are inoperative and the metabolism varies with the temperature. Accordingly, we are proposing two additional terms:

mesothermia (Gr. mesos = middle + therme = heat) the condition in which body temperatures are within the range between normal (coenothermic) and truly hypothermic temperature (i.e. 37.5° - 20°C).

mesothermic (Gr. mesos = middle + therme = heat) pertaining to or characterized by the range between normal (coenthermic) and truly hypothermic temperatures (37.5° - 20°C).

With the additions listed above, the terms which are now available for describing various temperatures would be:

hyperthermia - temperatures from 37.5°C to lethal heat.

coenothermia - temperatures which are common to the species (from about 36.5° - 37.5°C).

mesothermia - temperatures below the coenothermic range but above 20°C.

hypothermia - temperatures from 20°C to 0°C.

cryothermia - (from the Greek "kryos" = cold) temperatures below 0°C. Although "crymothermia" would perhaps be preferable, since it is derived from krymos, the Greek for "frost", cryothermia is generally accepted and is an acceptable term.

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DR. I. L. CHAIKOFF
1902 - 1966

Dr. Israel Lyon Chaikoff died on January 25, 1966, in Berkeley, California. He was born in London, England, on July 2, 1902, and he grew up in Toronto. He graduated from the University of Toronto in 1924 and immediately embarked on a scientific life of research in physiology, which started in association with the late Professor J. J. R. MacLeod in the Department where insulin had recently been discovered by Banting and Best. The impact of this discovery had many effects, and undoubtedly led to sanguine feelings towards the potential ability of science to overcome the degenerative diseases of mankind. One of the effects was to shape the lives of contemporary young research workers towards careers in the medical sciences. One of the most distinguished of these young men was I. L. Chaikoff. He received the degrees of Ph.D. in 1927 and M.D. in 1930 from Toronto, following which he joined the faculty of the University of California at Berkeley. Here he became full professor in 1942. His laboratory maintained an unbroken flow of eminent contributions to biochemical endocrinology and metabolism. Many of his students continued their work in these fields as prominent members of the faculties of other universities.

Chaikoff was an originator in metabolic research, with the broadest of interests in biochemistry, medicine and nutrition. He quickly realized the potentialities of the cyclotron as a source of radioactive tracers; he was one of the very first to introduce radioisotopes in biology and medicine; he pioneered with I^{131}, P^{32}, and C^{14} in research on the thyroid, the pancreas, and the liver. For years he studied the biochemical changes following experimental pancreatectomy, especially as regards the etiology of fatty infiltration of the liver. He made numerous investigations in arteriosclerosis, phospholipid metabolism, cholesterol biosynthesis (including the role of squalene as a precursor), lipogenesis, the role of insulin in intermediary metabolism, fatty acid oxidation, carbohydrate metabolism, the action of estrogens, anterior pituitary hormones, and adrenal steroids.

Chaikoff shunned publicity, preferring to devote himself to his laboratory, to teaching and training students, and to the encouragement of his large staff of scientific associates and collaborators, among whom he inspired many loyal friendships. His scientific counsel was sought by numerous visitors of distinction in physiology. He objected strongly to any form of pretentiousness and he had wide literary interests. A man of the highest standards in research and scientific writing he was keenly conscious of the history and progress of the biological sciences. He was a prolific contributor to leading scientific journals in his field, with more than 400 publications, a record that is almost unparalleled in terms of productivity combined with excellence. He joined the American Physiological Society in 1932, and became a U.S. citizen in 1938. He held a Guggenheim fellowship in 1941-42, and a Miller Research Professorship in 1963-65. He was co-chairman of his department in 1960-61, a Harvey lecturer in 1952, received the medal of the Endocrine Society in 1958, and was Faculty Research Lecturer at the University of California in 1958. His wife, the former Isabelle Rawls survives him.