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The Physiologist

A Publication for Physiologists and Physiology
Orr E. Reynolds, Editor

Volume 22, No. 5, October 1979

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FUTURE MEETINGS

Spring

April 13-18, 1980	—	Anaheim, CA
April 12-17, 1981	—	Atlanta, GA
April, 1982	—	New Orleans, LA
FASEB - 15-23		
APS - 20-23		

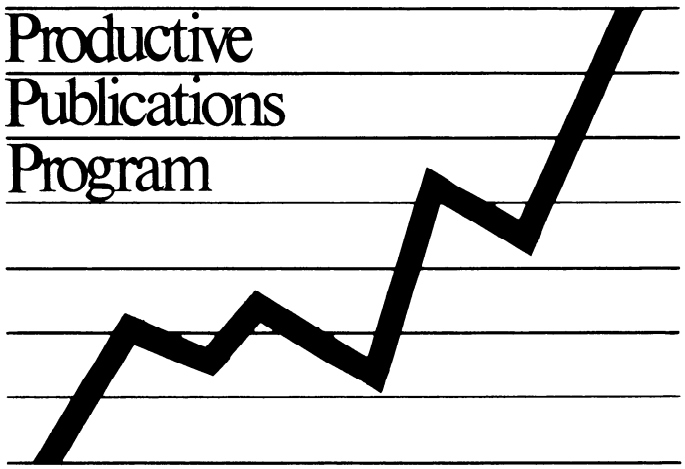
Fall

October 12-17, 1980	—	Toronto, Canada
November 1-6, 1981	—	Boston, MA
October 12-15, 1982	—	San Diego, CA

28th International Congress

July 13-19, 1980	—	Budapest, Hungary

Deadline for receipt of abstracts - December 31, 1979
(December 10, 1979, as per postmark)



The first half of 1979 was a most productive period for the publications of the American Physiological Society. Sixteen percent more journal text pages were published than in a comparable period in 1978 (Table 1).

Table 1. Journal Pages Published

	January - June		
	1978	1979	Change
A: Cell	226	321	+ 95 (+42%)
A: Endo	720	851	+ 131 (+18%)
A: Heart	799	969	+ 170 (+18%)
A: Regu	257	366	+ 109 (+42%)
A: Fluid	591	624	+ 33 (+ 6%)
Total AJP...	2593*	3131*	+ 538 (+21%)
JAP	1056	1284	+ 228 (+22%)
JN	828	936**	+ 108 (+20%)
PRV	527	448	− 79 (−15%)
Grand Total	5004	5799	+ 795 (+16%)

* Plus
\+ AJP front and back matter, 100 pages.
** Plus Cumulative Index, 173 pages.

In addition, two books were completed: *Pulmonary Edema* (in the Clinical Physiology Series) with 269 pages and *The Heart* (in *The Cardiovascular System* section of *Handbook of Physiology*) with 978 pages. The total number of pages published from January to June 1979 in the journals (including the *Journal of Neurophysiology* cumulative index) and books was 7319 pages.

"HELP WANTED" REPLIES

Since 1977 the *American Journal of Physiology* has been published as a series of specialty journals and in a consolidated form. The reorganization has given new vitality to the publications of the Society. Invited articles and discussions have been added to the high quality scholarly articles that have always appeared in the journal. A strong rapport is developing between authors and the individual journal in their area of special interest. The number of new manuscripts submitted to the journals and the number of pages published has increased dramatically. Despite inflation, the prices of the new journals have not been increased. The first price increase of the consolidated journal will occur in 1980 when the combination will include 6 rather than 5 journals.

An identical article is published in a specialty journal and in the consolidated journal. The page numbers, preceded by a mnemonic code letter to the title of each journal, are the same. However, the journal title, volume number, and issue number are different so that the article can be located in a collection composed of either form of the publication. Therefore, two forms of citation are possible and two have been used in the journals. The Publications Committee recognized that this system was cumbersome so it asked the readers of *The Physiologist* (22:12, 1979) for their suggestions for improving the method of citation. Many thoughtful replies were received. Most responders favored a method that combined the citation into a single item rather than leaving it in its present dual form. The citation will be simplified further with the removal of the issue numbers. In the future the journal part of a citation will appear as follows:

Am. J. Physiol. 238 (Cell Physiol. 7): C103-C110, 1980.

This form retains the essential elements needed to locate an article that may be in either of two places.

The Publications Committee wishes to thank the many people who responded to the "Help Wanted" announcement that appeared in *The Physiologist*. A journal subscription for 1980 will be sent to the person who came closest to the final form of the new citation.

The Publications Committee

Alfred P. Fishman, Chairman
Robert M. Berne
Howard E. Morgan

ARE CUMULATIVE TABLES OF CONTENTS USEFUL?

The January and July issues of the individual journals of the American Journal of Physiology* contain the entire table of contents from the consolidated *American Journal of Physiology* (AJP) for the previous six months. This feature has been added so that a subscriber to an individual AJP journal can scan this cumulative contents for articles of interest from the other journals.

The Publications Committee would welcome comments and advice about this new feature. Is it worth the cost and effort? Is it of practical use? Is it simply a needless venture that should be eliminated?

---

* AJP: Cell Physiology
AJP: Endocinology, Metabolism and Gastrointestinal Physiology
AJP: Heart and Circulatory Physiology
AJP: Regulatory, Integrative and Comparative Physiology
AJP: Renal, Fluid and Electrolyte Physiology

HALF-PRICE SALE - CIRCULATION HANDBOOK

The Heart, the first volume of the *Handbook of Physiology* section on the cardiovascular system was published this year. It will be followed by volumes on vascular smooth muscle, microcirculation, and peripheral and organ system circulation. These volumes will succeed the *Handbook of Physiology* section entitled *Circulation.*

A limited number of the original volumes, published in the 1960's, are available to members of the Society at half price.

Volume - Covers the physiology of the heart and its controls; blood volume. Sale price, $12.00

Volume II - Covers the functional morphology of vessels; blood flow. Sale price, $16.00

Volume III - Covers integrated aspects of cardiovascular regulation. Sale price, $16.00

Orders should be sent to the Subscription Office, American Physiological Society, 9650 Rockville Pike, Bethesda, MD 20014.

FEDERATION MEETING
64th Annual Meeting
Anaheim, California
April 13-18, 1980

Deadline for receipt of abstracts, Monday, December 3, 1979

GUEST SOCIETIES:

The Biomedical Engineering Society
The Reticuloendothelial Society
The Society for Experimental Biology & Medicine
The Society for Mathematical Biology

ASBC members are invited to participate and may submit abstracts to APS.

Tentative Symposia Titles for APS and its Guest Societies are:

New Advances in Cerebellum
Biophysical Aspects of Transmitter Action
Ionic Calcuium Currents in Nerve and Muscle
Acute and Maintained Changes in Reflex Excitablility
Brainstem Monamine Systems
Ways of Seeing Metabolism
Neural and Humoral Regulation of Gastric and Colonic Motility
Isolated Cell Models for G.I. Function
Muscle Energetics (Skeletal Muscle and Cardiac Muscle)
Central Respiratory Rhythmicity
Bioengineering for the Pulmonary Physiologist
Extra Pituitary Functions of Hypthalamic Hormones
Role of Electrical Potentials Across Membranes in the Functions of Living Systems
Potassium Handling in the Nephron
Transepithelial Transport in Cell Cultures
Role of Mg++ in Control of Muscle Activity
Disturbances in Neurogenic Control of Circulation
Regulation of Cerebral Circulation
Reticuloendothelial System in Physiologic and Pathophysiologic Events (cosponsored by the Reticuloendothelial Society)
The Cell Biology of Aging (cosponsored by the Society for Experimental Biology & Medicine)
Cardiac Shape and Structure (Satellite Symposium)
Space Biology and Medicine in the Shuttle Era (BMES President's Symposium)

NEWSLETTER FROM THE COMPARATIVE PHYSIOLOGY SECTION

The second meeting of the newly-formed Comparative Physiology Section, APS was held in Dallas, Texas and attracted 60 contributed papers of interest to comparative physiologists. Three important and interesting symposia were also presented and each attracted an impressive array of scientists. The titles and organizers of the symposia were: 1) "Muscles: How Do They Function During Normal Locomotion" organized by Dr. C.R. Taylor, Harvard Univ.; 2) "Chloride Transport in Biological Membranes" organized by Dr. J. A. Zadunaisky, New York Univ.; 3) "Physiological Regulation During Exercise" by Dr. E. R. Nadel. It is anticipated that the symposia will be published in *Federation Proceedings.*

The results of the CPS Business Meeting are summarized as follows:

1. Councilor Knut Schmidt-Nielsen proposed that in order for the membership to exercise maximum participation at our future scientific meetings, we should identify only one meeting each year as our official meeting. It was further proposed that the joint Fall Meeting with ASZ/DCPB shall be the annual meeting of APS/CPS and will be held on even-number years. Whereas, in the odd-number years, APS/CPS will meet in regular fashion as part of APS in the FASEB conclave. The motion was passed unanimously.
2. Councilor Knut Schmidt-Nielsen reported on the activities of the IUPS. The current advance registration for the IUPS to be held in Hungary in 1980 is nearly 6400 with approximately 1100 US registrants. All registrants under 35 years of age are to receive compensation for living expenses in Budapest (travel and registration fee not included) which is a very generous offer. Meanwhile, support for a travel grant program is being developed from several sources by the U.S. Committee for IUPS. Additional information is available in the August issue (1979) pp. 143-167 of *The Physiologist.*
3. Chariman-Councilor Conte appointed a nominating committee composed of Dr. Conte, Dr. Thomas H. Dietz, Louisiana State Univ., and Dr. Ronald W. Millard, Univ. of Cincinnati to prepare a nomination ballot for a new Councilor to replace Dr. Conte. The ballot, prepared by the Committee was mailed in September 1979. The ballot must be returned to the APS office before *December 1, 1979.* Results will be published in the February 1980 issue of *The Physiologist.*
4. Chairman-Councilor Conte appointed a publications committee comprised of Bodil Schmidt-Nielsen, Charlotte Mangum, Bill Dantzler, John Phillips, John Crowe, and Frank P. Conte to advise the APS publications committee on matters of nominations of editorships, editorial board nominations and other matters dealing with publications as appropriate in relation to sectional interests. Councilor Conte will act as Chairman of the Committee.

The 1979 Fall Meeting of APS in New Orleans contains a symposium entitled "Protein and Fat Metabolism during Mammalian Hypophagia and Hibernation" organized and chaired by Dr. G. Edward Folk, Univ. of Iowa. Additionally, there will be 11 contributed papers on Comparative Physiology of Respiration and Exercise, 11 papers on Comparative Physiology of Temperature Adaptation and 10 papers on Comparative Physiology of Osmoregulation, Feeding, Digestion and Nutrition.

The 1980 Fall Meeting in Toronto, Canada will contain a joint APS/ASZ symposium entitled "Physiology of Arthropods" and is being organized by Dr. F. P. Conte, Oregon State Univ. and Dr. John Crowe, Univ. of California, Davis. The program will cover some physiological aspects of insects, arachnids and crustaceans. Those persons interested in participating in the symposium should contact Dr. F. P. Conte, Dept. of Zoology, Oregon State Univ., Corvalis, Oregon 97331. Members interested in conducting future symposia at CPS meetings for 1981 and 1982 should contact Dr. Bruce Umminger, 4087B South Four Mile Run, Arlington, VA 22204.

The symposium proposers should include the names of the organizer(s), tentative title and identify the proposed meeting for conducting the symposium.

Lastly, members who wish to submit manuscripts to be published in AJP:RICP can request this by stating in his/her cover letter to Mr. S. R. Geiger, APS Publications Manager and Executive Editor, that the manuscript belongs in the field of Comparative Physiology.

Frank P. Conte, Councillor, Chairman
William R. Dawson, Councillor
Knut Schmidt-Nielsen, Councillor
Bruce L. Umminger, Program Officer
Roger A. McNabb, Secretary

XXVIII INTERNATIONAL CONGRESS OF PHYSIOLOGICAL SCIENCES

BUDAPEST, JULY 13—19 1980

CONGRESS SECRETARIAT

MOTESZ CONGRESS BUREAU

H-1361 BUDAPEST, P.O.B. 32 - HUNGARY

Budapest August 27 1979

Prof. Orr E.Reynolds

9650 Rockville Pike
Bethesda, M.D. 20014
U.S.A.

Dear Professor

On behalf of the Hungarian Physiological Society may I extend once more our cordial invitation to the members of your Society, to attend the XXVIII International Congress of Physiological Sciences, July 13-19, 1980 in Budapest.

I would like also to inform you that 1052 of your members have already preregistered. We shall forward for all of them, personnally, the 2nd Announcement before August 31, 1979. At the same time we send you also enough copies of it, and requesting you to distribute them among those members of your Society, who have not announced yet their intention of participation to the Congress Secretariat. The final dead-line of registration and date by which abstracts have to be submitted is: December 31, 1979 /December 10, 1979 as per postmark/.

It is our mutual interest to enable as many as possible members of your Society to attend the Congress and this is why I request your kind support and assistance as well. The Organizing Committee will do its best to provide an interesting scientific programme and memorable experiences for all of the participants during their stay in Budapest.

Should you have any problem, or would you need more detailed information, please contact me directly.

I thank you for your kind efforts

Sincerely yours,

Prof.L.Harsing
Secretary General

Correspondence: Congress Secretariat
Budapest H-1445, P.O.B. 370 Hungary
Telex: 225070 SOTE H

COMROE RECIPIENT OF FLEXNER AWARD FOR 1979

The Association of American Medical Colleges (AAMC) notified APS on September 17 that its Flexner Award nominee, Julius H. Comroe, Jr., had been selected to be the 1979 recipient. The citation accompanying his selection indicated that he was selected "for extraordinary contributions to medical schools and to the medical education community as a whole."

The presentation of the Flexner Award medal will take place at the AAMC Annual Meeting in Washington, D.C. on Tuesday, November 6, 1979.

Dr. Julius H. Comroe, Jr. has been awarded the 1979 Eugenio Morelli International Prize of the Accademia Nazionale dei Lincei of Rome for his contributions to the studies of the lungs and respiration. This Academy was founded in 1603, with Galileo as an early member.

The Board of Foreign Scholarships and the U.S. International Communication Agency announced over 500 Fulbright awards to American scholars for university teaching and advanced research abroad in a variety of disciplines for 1979-80. Two APS members are recipients of this honor.

Lawrence L. Espey, Prof. Environmental Studies, Trinity Univ., San Antonio, Texas. Research on physiology: mammalian reproduction; Institute Agronomy "N. Balescu" Bucharest, Romania.

Mohamed K. Yousef, Prof. and Director, Desert Bio Res. Ctr., Univ. of Nevada, Las Vegas. Courses in environmental and general physiology and endocrinology; research on comparative mechanisms for thermal tolerance; Gezira U, Wad Medani, Sudan.

Five APS members were elected to the National Academy of Sciences this past Spring.

Frederic C. Bartter, Chief, Hypertension-Endocrinology Branch, National Heart, Lung and Blood Institute, NIH.

Karl H. Beyer, Jr., Professor of Pharmacology, Milton S. Hershey Med. Ctr., Pennsylvania State Univ., Hershey.

Jared M. Diamond, Professor of Physiology, Univ. of California, Los Angeles.

Mark R. Rosenzweig, Professor of Psychology, Univ. of California, Berkeley.

Cornelis A. G. Wiersma (Netherlands), Professor of Biology, California Inst. of Technology, Pasadena, was honored as a Foreign Associate of the Academy.

GERONTOLOGICAL SOCIETY ANNOUNCES NAMES OF BROOKDALE AWARDEES FOR RESEARCH IN GERONTOLOGY

APS Member Dr. **Nathan W. Shock,** former Director of the Gerontology Research Center of the National Institute on Aging and presently Scientist Emeritus of the National Institutes of Health, has received the first Brookdale Award for Research in Gerontology of the Gerontological Society. Two awards, of $20,000 each, one in biological and clinical research and the other in social and behavioral research are given annually by the Society. The latter award was given to Dr. Robert J. Havighurst, Professor Emeritus of Education and Human Development of the University of Chicago.

The awards will be presented at the Gerontological Society's annual scientific meeting to be held in Washington, D.C., November 25-28, 1979 at the Washington Hilton.

Dr. Nathan Shock is one of the world's pioneers in physiological research in aging. He has had a 50-year career in this field. One of the founders of the Gerontological Society and a past president of that organization, he has been instrumental in the research program within the National Institutes of Health which culminated in the establishment of the National Institute on Aging in 1974.

The Gerontological Society, founded in 1945, is the national multidisciplinary organization of researchers, educators, and practitioners in the field of aging. Society members affiliate with one of four professional and/or disciplinary sections appropriate to their individual interests and activities in aging: biological sciences; clinical medicine; behavioral and social sciences; and social research, planning and practice. The Society publishes two bimonthly journals, the *Journal of Gerontology* and *The Gerontologist,* and holds an annual scientific meeting in November and a mid-year conference on aging research in June.

INSTITUTE OF MEDICINE

Members elected to the Institute of Medicine are chosen for major contributions to health and medicine, or to such related fields as the social and behavioral sciences, law, administration, and engineering.

Among the newly elected to the Institute are three APS members:

John C. Beck, The Rand Corporation, Santa Monica, California; **Carmine D. Clemente,** Brain Research Institute, UCLA; and **Howard S. Frazier,** Harvard School of Public Health.

APS ASSOCIATE MEMBER NAMED TEACHER OF THE YEAR

Karam F. A. Soliman was named Teacher of the Year, 1978-79 by the Florida A and M University School of Pharmacy on the basis of outstanding performance in teaching and youth leadership. Dr. Soliman was born in Cairo, Egypt and at the age of nineteen years, graduated with honors from Cairo University. Upon completion of his doctoral degree in 1972, he was appointed as Assistant Professor of Physiology and Pharmacology at Tuskegee Institute School of Veterinary Medicine. In 1975, he joined the School of Pharmacy at Florida A & M University as Associate Professor. He is involved in teaching twelve undergraduate and graduate courses each year. During the past year he supervised six graduate students in the Master's Program in Pharmacology and Toxicology. He has assisted in the editing and revision of three books. Dr. Soliman is married and is the father of two children.

MEDICAL GROUP TO VISIT CHINA

Fourteen physicians from the United States will spend 3½ weeks in China this Fall in an effort to accelerate the exchange of medical knowledge between the two countries.

Sponsored by the Chinese Medical Association, the trip will be a period of work for the medical specialists, most of whom are members of the American College of Physicians. The trip will serve to exchange medical information, especially information about the technical aspects of medicine; to look at Chinese medical practice and medical education; and to serve as the beginning of long-range exchange programs between medical institutions in the two countries.

The compostion of the U.S. delegation reflects both the new Chinese interest in Western technology and the nature of China's major health problems. Cardiovascular disease is the main cause of death in China, and most of the members of the group are cardiologists. The group also includes experts in nuclear medicine, cardiovascular surgery, and immunology. Three APS members are members of the group:

APS President-Elect, **Earl H. Wood,** Mayo Clinic, Rochester, MN (cardiac physiology); **Aldo R. Castaneda,** Harvard Medical School, Boston, (pediatric cardiac surgery); **Robert M. Rogers,** University of Oklahoma, Oklahoma City, (pulmonary disease).

SECOND INTERNATIONAL SYMPOSIUM ON THE MANAGEMENT OF STRESS

APS member Hans Selye has asked that readers of *The Physiologist* be notified that the largest Stress Congress ever is to be held in Monte Carlo, Principality of Monaco, Loews Monte-Carlo Hotel, between Novermber 18 and 22, 1979. The Congress will deal with the ever-increasing detrimental effect of distress in every major area in our Society. Among the participants will be four Nobel Laureates (Linus Pauling, Roger Guillemin, Christian de Duve, Sir Hans Krebs), Roger Mallet, Rector of the Sorbonne, Jonas Salk and numerous others.

Two offices have been established for interested people to contact:

Paris:	Centre Medical Francois 1er 23, rue Francois 1er 75008 Paris, France Tel: 359.42.38 - 225.74.10
USA:	International Health Resorts Inc. 144 S. Beverly Dr. - Suite 500 Beverly Hills, CA 90212 Tel: 213-273-3550

"RETIRED" PHYSIOLOGIST BREAKS OWN RECORDS*

Boulder City Nevada - America's premier exercise physiologist is breaking his own track record. Off and pedaling past his 88th birthday in 110° desert air, Dr. **David Bruce Dill,** who has been monitoring his own vital signs for over 50 years, has taken on a new grant to study the effects of aging on physical performance.

At the University of Nevada's Desert Biology Research Center here, Dr. Dill is giving a bicycle ergometer stress test to himself and 50 volunteers over 60 years old in a research project sponsored by the National Institute on Aging. Those who pass the preliminary trial by bicycle - which records heart rate, ECG, oxygen consumption and CO_2 output as the load on the brake increases - are sent on three one-hour walks around a closed track in the desert while being monitored.

Rectal temperature and nude body weight are compared at start and finish and palmar sweat collected. Body fat is measured and blook analyzed. His earlier research, in which he was both subject and investigator, suggests that old people can handle high ambient temperatures better than young ones.

"Our 50 volunteers represent a biased sample," Dr. Dill told MWN, "as they are people who appreciate keeping fit." Many are retirees who've kept up their jogging, including several dealers from the casinos of nearby Las Vegas.

Dr. Dill has been conducting human physiological research at the desert site since 1966, when he retired from the University of Indiana at 75. His first retiredment was from Harvard in 1961, at 70. At Harvard's Fatigue Laboratory and at Massachusetts General Hospital he led research in the physical chemistry of blood proteins and in exercise physiology for some 36 years.

While at Harvard in 1932, Dr. Dill read in a ship's newspaper, en route home from Europe, that 13 men had died of heat prostration while building Boulder (now Hoover) Dam on the Colorado River. Assembling a team of scientists under an emergency appointment from the U.S. Secretary of the Interior, he hastened to the work site to conduct crash studies of how people and animals deal with high and dry desert temperatures. After determining the effects of fluid and electroyte depletion, he posted signs in the workmen's mess halls urging them to drink lots of water and to salt their food liberally. "No one died that summer of the heat," Dr. Dill recalls.

A symposium on "Life, Heat, and Altitude" at the University of Nevada in Las Vegas honoring Dr. Dill's 88th birthday this year recalled that his exercise-physiology research over the past half century has specifically benefited medical practice - from hs early description of the oxygen-dissociaton curve to fundamental studies of artificial respiration leading to modern cardiopulmonary resuscitation.

But Dr. Dill still has plenty to look forward to. He has just been appointed to the advisory committee for the Himalayan medical research expedition of 1981, the year he turns 90.

*Reprinted from Medical World News/August 20, 1979.

D. B. DILL SCHOLARSHIP FUND

A Symposium was held earlier in the Spring to honor David Bruce Dill on his 88th birthday. At the conclusion of the meetings, it was agreed to give any associate or student or friend of Dr. Dill the opportunity to contribute to the D. B. Dill Scholarship Fund at the University of Nevada, Las Vegas. Any such contribution should be assigned to the Board of Regents, University of Nevada at Las Vegas and sent to:

M. K. Yousef, Ph.D.
Biological Sciences Dept.
University of Nevada at Las Vegas
Las Vegas, NV 89154

THOMAS WILLIAM SALMON LECTURES

The Salmon Committee on Psychiatry and Mental Hygiene announces the Forty-Seventh series of Thomas William Salmon Lectures to be given by Michael L. Rutter, M.D., Professor of Child Psychiatry, University of London. The lectures will take place at the New York Academy of Medicine, 2 East 103rd Street, New York, NY 10029 on Thursday, December 6, 1979, afternoon and evening.

Lecture I - Psychological Sequelae of Brain Damage in Childhood.

Lecture II - Syndromes Attributed to "Minimal Brain Dysfunction" in Childhood.

The Committee, appointed by The New York Academy of Medicine, selects as the Thomas William Lecturer each year the specialist in the field of psychiatry, neurology, or mental hygiene, in this country or abroad, who has currently made an outstanding contribution to his specialty. These lectures are designed to be permanent contributions to the field of medicine and are usually published in book form.

COUNCIL OF ACADEMIC SOCIETIES BRIEF

ASSOCIATION OF AMERICAN MEDICAL COLLEGES • 1 DUPONT CIRCLE NW • WASHINGTON DC
(202) 828-0400 FALL, 1979 VOL. 5., NO. 1

The CAS Brief is prepared by the staff of the AAMC Council of Academic Societies and is distributed through the auspices of your member society.

NIH ANNOUNCES SHORT TERM RESEARCH AWARDS FOR MEDICAL STUDENTS. Spurred by recent evidence of a disturbing decline in the number of medical students who are interested in research careers, the NIH has mailed to deans an announcement of a new program which will provide, on a competitive basis, a research training program for students in each medical and other professional schools. These new grants will support from 4 to 32 medical (or other professional) students each year for three months of training. An important change is that the students will not be required to pay back the government in research or teaching in return for the experience. Each school will work out the details of its own program which may be in a single department, interdepartmental or school wide. Formal recruiting and research training efforts (e.g., research seminars) must be mounted as a condition of the award and evaluation of impact of the program is highly desirable. Grants will be awarded to those institutions which show the best programs to place highly motivated students in training with those faculty who have the best research and training records.

The grants may be awarded for up to five years and provide $325 monthly for each student and up to a total of $750 in institutional training funds. Higher stipends ($420) may be provided if trainee stipends are generally increased in 1980. The grant is made possible by a 1978 change in the research training authority (NRSA). Applications must be received by November 19 for awards in the Spring of 1980.

APPROPRIATIONS PROCESS TAKES A CURIOUS TWIST. The NIH 1980 appropriations were approved in late summer by both House and Senate at $3.405 billion, an 8.1% increase over the President's recommended 1980 budget. The apparently successful attempt to sustain the biomedical research budget at levels nearly equal to inflation was dealt an unprecedented blow when the traditional appropriations process defied the new Congressional budget-setting process. Members of the House and Senate Budget Committees were unwilling to "take the blame" for appropriations which exceeded the budget ceilings imposed earlier by the Congress. This led to a confrontation between Senators Muskie and Magnuson, Chairmen of the Senate Budget and Appropriations Committees respectively, and threatened to cut previously passed appropriations bills. This was narrowly averted by the Senate leadership but the scenario has introduced a new reality and uncertainty for the budget process in the future. Meanwhile, as of this writing, final Labor-HEW appropriations are being held up past the beginning of the new fiscal year by the annual debate on what abortions may be paid for by HEW funds.

LIAISON COMMITTEE ON CONTINUING MEDICAL EDUCATION WILL MAINTAIN ACCREDITATION SYSTEM. The House of Delegates of the American Medical Association approved a recommendation of its Council on Medical Education that the AMA should withdraw from the Liaison Committee on Medical Education. In late July the AMA announced that it was

withdrawing from the LCCME and that it was resuming its accreditation of institutions which provide continuing medical education. The other sponsors of the LCCME, which are the AAMC, The Council of Medical Specialty Societies (CMSS), the American Board of Medical Specialties (ABMS), the Federation of State Medical Boards (FSMB) and the Association of Hospital Medical Educators (AHME) have determined that they will continue the accreditation process which the Liaison Committee has developed during the two years that it has been functioning. This unilateral disruption by the AMA of a liaison committee established for the purpose of involving other professional organizations in the accreditation policies and process for medical education has disturbed many. Of particular concern is an intimation in the Council on Medical Education report that similar action should be considered by the AMA for the Liaison Committee on Graduate Medical Education. For several years the AAMC, CMSS and ABMS has been critical of the support provided to the LCGME by the AMA staff, and have recommended that LCGME have its own staff and that it be financially independent of the AMA. The AMA is in the process of examining its relationship to the LCGME. Should it withdraw and attempt to resume the accreditation of graduate medical education on its own it is likely that the sponsoring organizations of the LCGME will continue the accreditation program which the LCGME has developed with the Residency Review Committees during the past seven years.

AAMC TO WITHDRAW MCAT FROM NEW YORK STATE. In July Governor Carey of New York signed into law a bill requiring agencies administering standardized tests utilized for the evaluation of students for admission to institutions of higher education to file copies of each test for public inspection and provide to students their own answer sheets and the correct answer key. The law's supporters claim that it is intended to protect the interests of examinees. The AAMC, after assessing the potential impact of the disclosure of test materials in the long-term quality and viability of the New MCAT determined that present standards for the development of new questions could not be maintained. Therefore, the Association announced that it will not give the examination in New York State after January 1, 1980. Similar efforts to require disclosure of secure test items are underway in Congress in the form of H.R. 4949 introduced by Representative Weiss (D-N.Y.). H.R. 3564, introduced by Representative Gibbons (D-Fla.) also seeks to regulate testing. Both bills are being considered by the House Subcommittee on Elementary, Secondary and Vocational Education.

These efforts to regulate the standardized tests used for the evaluation of candidates seeking admission to college and professional schools are disruptive and threaten the quality of tests. To date sponsors have failed to produce evidence that the alleged problems are the result of testing or that the benefits claimed will be achieved through the proposed legislation.

H.R. 2222 VOTED OUT OF COMMITTEE. H.R. 2222 was approved by the House Committee on Education and Labor by a 23 to 9 majority. The bill, which would authorize the inclusion of residents as employees in the National Labor Relations Act and permit their unionization for the purpose of collective bargaining, must go to the Rules Committee before being presented to the House. It is important that the academic community continue its efforts to inform the Congress that H.R. 2222, if passed, will jeopardize the teaching-learning relationships between residents and faculty.

AAMC ANNUAL MEETING. The 90th AAMC Annual Meeting will take place at the Washington Hilton Hotel in Washington, D.C. from November 3 to November 8. The theme of the meeting is "The Allocation of Medical Resources and Services: The Role of the Academic Medical Center." The CAS Business Meeting will take place on Monday, November 4.

McKnight Scholars Awards

In 1976, the McKnight Foundation announced the initiation of a program to stimulate research in neuroscience, especially as it pertains to memory and, ultimately, to a clearer understanding of diseases affecting memory and its biological substrates. To accomplish its goal, the Foundation announced five McKnight Scholars Awards in 1977 and 1978 and is now eliciting applications in order to process five more McKnight Scholars Awards in 1980.

McKnight Scholars will be selected from applicants who hold the M.D. or Ph.D. degree and who have not completed more than five years of postdoctoral research (exclusive of Clinical Training—M.D., etc.) Applications may be submitted after two or more years of postdoctoral research.

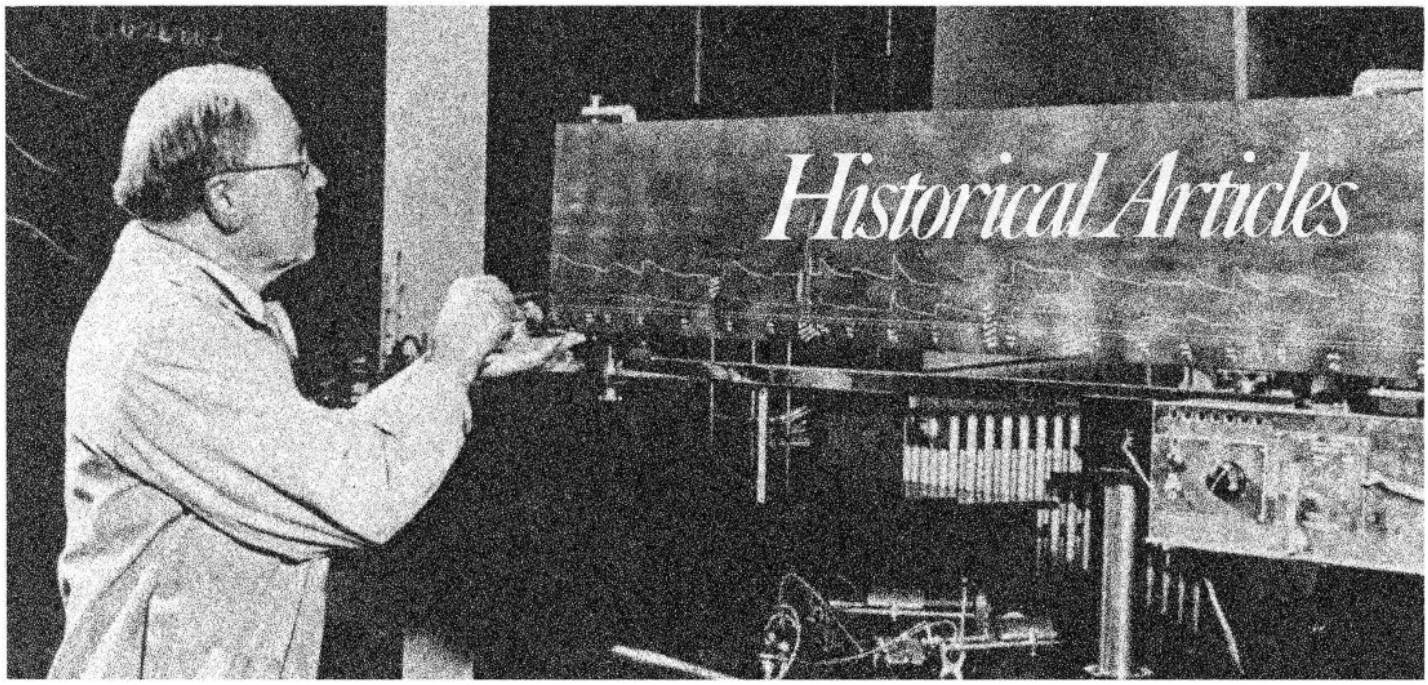
Candidates should have demonstrated meritorious research in areas pertinent to the interests of the McKnight Foundation and should be embarking on an independent career. Evidence of a commitment to a continuing career in neuroscience should come from the candidate's record, as well as statements from the sponsoring institution.

Five McKnight Scholars were selected in each of the years 1977 and 1978 and five additional Scholars will be selected in 1980. Each McKnight Scholar will be supported with an award to the sponsoring institution of $25,000 for each of three successive years. Funds may be used for salary and direct costs but not indirect costs.

Applications will be evaluated by a Review Committee which will recommend candidates to the Foundation for appointment. The Awards will be effective July 1, 1980, with the deadline for submission of applications being March, 1, 1980. Award announcements will be made on June 1, 1980.

Requests for further information and instructions about applications should be directed to Mr. Russell V. Ewald, Executive Vice-President, The McKnight Foundation, Suite 1701, Shelard Tower, Minneapolis, Minnesota 55426.

THE McKNIGHT FOUNDATION
Suite 1701, Shelard Tower, Minneapolis, MN 55426
(612-546-8814)



GROWING UP IN THE AMERICAN PHYSIOLOGICAL SOCIETY

Edward F. Adolph
The University of Rochester,
Rochester, New York 14642

A society of scientists ties together those who share incentives in their chosen work. Few scientists create major advances alone; whereas cross stimuli may enhance the accomplishment of each individual.

Here I will mention some of the incidents that aided my generation to develop as citizen physiologists. My story will focus on the role of the Society in our careers. I omit most of the events that are already recorded in the two volumes of A.P.S. histroy (Howell and Greene, 1938, 1938; Fenn, 1963).

First Exposure

While in school I wanted to become a biologist. In Harvard College I was attracted to physiological studies of animals by some happy reading, and by the person of George Howard Parker. He was the first APS member that I knew. In my third college year he accepted me as a research student, and that settled my outlook on careers. I listened to several lectures in an undergraduate course on organ physiology given by Ernest G. Martin; they did not interest me. I listened to Walter B. Cannon giving his Lowell lectures (1914) on "Bodily Changes in Pain, Hunger, Fear and Rage". Some of Cannon's intensity came across, but I was not impressed with cat-and-dog physiology. I thought the processes in invertebrate animals could be more readily understood.

Here I may say that in the 1930's I changed my focus of interest from invertebrates to highly differentiated processes in vertebrates. I became interested in regulatory physiology, and began to recognize that specialized processes were exemplary.

First Meeting

In 1916 I was a graduate student at Yale University, where I became acquainted with half-a-dozen more members of APS. In December I attended the Society meeting, held at Cornell Medical College in New York. This was the 29th annual meeting of APS; my first. Cannon was president; and since Society sessions were few, his duty was to preside at all of them. In one session I heard the young Cecil K. Drinker and wife report on certain bone-marrow perfusions. They were looking for factors in blood coagulation. As I now view the program of that 3-day meeting, I find there were 67 papers listed (some "by title") and 14 demonstrations. What impressed me most was the friendly atmosphere in which attendees, both in public and in private remarks, spoke of the papers given.

First Paper

In 1921 the APS became important to my career. I had received the Ph.D. at Harvard University in a novel program termed General Physiology. My thesis advisor was Lawrence J. Henderson; Cannon attended my examination. Thereafter I had worked for a few months at Oxford in J.S. Haldane's laboratory, and passed through the embarrassing but welcome experience of presenting two papers before the Physiological Society in London. Now in December in New Haven I gave my first paper at an APS meeting, and also was elected to membership. Henderson sponsored both paper and candidacy.

How did I prepare my presentation? Projection slides for the paper, on "Excretion of chloride urea and water by the human kidneys", I made by lettering and drawing with water-color paint

on blank glass slides. The abstract of my paper was pre-written, but was revised in the light of discussion at the meeting. I retyped it and handed it to the Society secretary (Charles W. Greene) before the last session, as was the custom. All abstracts appeared in the *American Journal of Physiology* two months later. Abstract lengths were not limited.

My paper received a kindly criticism from E. K. Marshall, whom I already knew. Most grateful to me were the personal greetings of Cannon, Drinker, A. N. Richards and G. N. Stewart. There was no chance for the novice to feel neglected in that friendly Society gathering.

In that year J.J.R. Macleod was president, and chaired all Society sessions. The program also featured two "Joint Sessions" under auspices of the four Federation societies. In one of them Frederick G. Banting presented evidence for the isolation and potency of insulin; Macleod and Charles H. Best were co-authors of the paper. The discussions were impressive, though the points at issue have been long forgotten. The Federation program also included a laboratory tea, and a customary Federation dinner. In 1921 the Society had 300 members, of which about 100 attended.

Travel

Today we go to meetings by airplane or by automobile. Before 1946 airline services were almost unavailable. For example, in 1921 travel was by railroad. Each attendee was urged in advance to secure a "railroad certificate" along with his train ticket. This certificate allowed him to return home for half fare, if the ticket agent at the terminus was given 150 or more certificates for approval. But travellers attending the four societies of the Federation provided barely enough certificates. Whether at the 1921 meeting or some other, the society secretaries had to ride to the nearest rail stop to buy the 2, 3 or 4 tickets and certificates still needed to reach the 150 count, thus enabling everyone to benefit by the reduced fare. Railroad certificates went out of existence with the 1941 meeting; thereafter railroads were busy hauling soldiers and sailors.

Travel funds were scarce. In my School, however, faculty members were allowed railroad fare to one meeting annually. In the early post-war years, research grant funds were not considered usable for trips to meetings; but by 1952 they were, and the great build-up of attendance had begun.

I wish it were possible to gather together the travel stories based on unscheduled happenings. One incident that impressed me was a snowstorm of 1930. We alighted from the railroad cars at 63rd street station in Chicago early on 27 March to find the city silent. Taxicabs were not running; all streets were blocked by snowdrifts. Travellers, just arrived, perforce walked by detouring drifts, carrying luggage. With effort, both young and old reached the Shoreland Hotel for shelter, and later the University of Chicago Campus for the sessions.

Early meetings were limited to the North-East. But in March 1940 a southern meeting was staged at Tulane University and Louisiana State University. A colleague arranged for travel to New Orleans in a special car by a group from Syracuse, Rochester, Buffalo and Toronto. This proved to be a friendly trip. At the end of the first day's ride, the travellers transferred from coach to sleeping car. Return was by the same route, requiring 37 hours each way.

Spring meetings

I recall attending the Christmas-week meeting of 1924 in Washington. The Society sessions were held in a high school. Anton J. Carlson was president and chaired all of them. Walter J. Meek collected the abstracts in his role as secretary. It may be said that these two were outstandingly responsible for the increase in quality of the researches reported over the years. (Carlson: "What is the evidence"? Meek: "manuscripts for publications must be refereed".)

As a result of the "crowded" program at Washington, the next meeting initiated the scheduling of concurrent APS sessions. Now the president delegated other Council members to preside. And a year later the Society decided to test the plan of holding future meetings in spring.

The spring meeting (1927) was held in Rochester. Members were curious to see our new medical building, with some areas still unoccupied. John R. Murlin made local arrangements. The entire attendees of four societies at the joint sessions just filled the 300 seats in the amphitheater of the School of Medicine and Dentistry. Wallace O. Fenn accommodated the demonstrations from the four Federation Societies in the Department of Physiology. The two classes of medical students, all 55 of them, had vacation during the sessions; several ran projection lanterns, some of which were borrowed. Ray G. Daggs was one of these medical students, soon to be diverted into becoming a physiologist.

Joseph Erlanger presided over the Society and some of the sessions. I recall that when the program came to my paper, he glanced around the room of about 40 people and did not notice me; so he called for the next following paper. During the discussion of that paper he spied me, and proceeded to announce my title, with profuse apology for the previous oversight. I mention this incident to indicate how informal the sessions were.

Up to 1941, a local Federation committee made all meeting arrangements. The local committee provided blackboards, pointers, timing devices, facilities for demonstrations. It arranged an evening "smoker". In three enviable instances a banquet was also tendered by the host university or city.

In addition, the Federation regularly scheduled a semi-formal dinner. There one became acquainted with those who chanced to sit nearby. I recall an evening with Percy Dawson and Peyton Rous, both voluble. They had been members of the first class to graduate from Johns Hopkins Medical School. Both attained prominence in physiological research and teaching by their devoted efforts.

It should be recalled that the Federation (FASEB) was founded in 1913. Before that date the three societies were already meeting concurrently. A "yearbook" list of all members was issued annually. The Federation had no permanent office or secretary until 1935, when D.R. Hooker was appointed to look after Federation affairs at his Baltimore office for publication of American Journal of Physiology and Physiological Reviews. In 1947 Milton O. Lee assumed the tasks of executive secretary for both APS and FASEB.

Registration at meetings was first arranged in 1930; before that date one was simply a brother phsyiologist. In 1933 a fee was required and a name badge was furnished. Attendance did not increase greatly from 1930 to 1940, since financial depression forbade increases of faculties, graduate students and travel funds in most institutions.

I was able to attend all the spring meetings of the Society between 1927 and 1978. Actually there were not 52 meetings, since three were omitted in 1943-45. In 1929 also the Society meeting was skipped; instead the International Congress of Physiology convened in August at Harvard Medical School in Boston. Of course, members of our Society and Federation attended the Congress in large numbers. William H. Howell was president of the congress, and Cannon was chief organizer.

Programs

In the early decades of the Society, the meetings aimed primarily to give each member or guest an opportunity to present his researches for discussion. This privilege has been preserved and fostered. Demonstrations of methods and results were also highly valued. To a certain extent this value has been revived in present-day poster sessions.

Only rarely were Society speakers actually invited. When the Federation formed, general Federation sessions were held, at which each speaker presented a comprehensive topic. About 1940 the Society began to invite groups of its members to organize symposia, each upon a selected topic. These have burgeoned.

Additional attempts to vary the lock-step of ten-minute papers have been tested. The most notable was the 30-minutes "Introductory remarks" which were invited from selected session chairpersons. This procedure had highly variable results. Who will invent a new and attractive type of session?

In the 1920's the limitation of each paper to ten minutes of session time was counted as a hardship by both speakers and chairpersons. Time overruns were frequent; discussions were cut short; papers were deferred. Gradually all concerned learned to adhere to the stop-clock.

In 1928 a speaker (E.G. Martin) from the west coast was asked to truncate his presentation when the assigned time had been exceeded. But the speaker reminded the chairman that he had travelled for several days to come to the meeting, and intended to finish his paper. If I recall correctly, the chairman acceded to the speaker's plan.

Some years later a speaker (R. Gesell) began his paper by announcing that he would show 32 slides in the 10 minutes allotted. His own projectionist handled the glass slides while he himself read his timed manuscript. And he finished the presentation just as the bell rang! Of course, the audience was so intent on the performance that no one knew what was said or shown.

In the spring of 1932, and for several years thereafter, abstracts of papers to be presented at the annual meeting were printed and precirculated to APS members. Corrections could be made before the same abstracts appeared after the meetings in a regular issue of the *American Journal of Physiology*.

In 1942 *Federation Proceedings* was founded, designed to contain the programs of all five (later six) societies.

How were Society programs prepared, before the coming of computers? In 1953 my duty as president-elect was to compose the APS program from the 522 submitted abstracts. One copy of each abstract went from the Washington Office to the printer, who converted the typewritten scripts into type-set, and printed the issue of *Federation Proceedings* in time for distribution to members before the April meeting. Meanwhile, carbon copies of the 522 abstracts came to Rochester. With the valiant assistance of one typist the titles and names of authors were typed in 50 lists; a chairperson (preselected by the society president) and a specific half day were assigned to each list. I carried these lists to the meeting in Washington of the six Federation program officers, where each such officer bespoke meeting rooms for his sessions. Then the combined list of all sessions went to the printer for typesetting of the definitive program, to be promptly distributed as another issue of *Federation Proceedings*.

Membership

A professional society expresses its purposes in the qualifications it sets for membership. Up to about 1950 there were two fixed features of new APS members: they had done publishable research, and they occupied positions where more researches could be expected. In the ensuing years the Society's views broadened: the candidate might be any person who would be aided by attendance at meetings and by recognition as a colleague. He could be a teacher or an administrator who did no research, or a researcher who did no teaching. To further this end still more, a compromise measure was the creation of associate membership in 1957. Especially, associate members could actively participate in autumn meetings, which had already been established in 1948. Eventually, the addition of numerous comparative physiologists to APS membership, erased what some colleagues had considered a barrier between members of medical faculties and members of non-medical faculties. The Society has come to serve nearly all physiologists who wish to belong.

I note that, although the first 28 years of the Society's existence had passed before I attended a meeting, I have been acquainted with all its presidents except three: Mitchell, Bowditch and Meltzer. Even they were alive in my adolescence. These three were the leaders whose blessings I missed. The other two of the first five presidents were Chittenden and Howell. Chittenden served the Society as president for the longest term, 9 years. At Yale he conducted a weekly quiz class in nutrition, which I attended (1917) without being impressed by it. Chittenden, kindly and efficiently, directed the Sheffield Scientific School at Yale, in which I was listed as a graduate-student assistant in biology.

Howell was president of the Society for 6 years. He invited me to give a seminar talk (1925) in his department in the new School of Hygiene at Johns Hopkins. I recall that he had on his desk some flasks of blood plasma, and was still studying coagulation, in the midst of heavy administration tasks. I note now that Howell had been the first speaker on the first APS program in 1888; quite a span of years ago!

These five APS presidents pilotted APS through its first 26 years.

I once amused myself by putting together sample autographs from each of the Society presidents. The few from whom I had no letters, had their signatures reproduced in publications of one sort or another. These I photo-copied to complete the set.

One kind of question that interests some APS members is: how do council members and presidents-elect feel about their elections to office? A general answer is that they are anxious to serve the Society. I recall that Ralph Gerard and I joined the Council in the same year; and immediately set out to formulate a list of novel practices that seemed desirable and might be tested by the Society. Many of the items proved impractical when critically considered; but the making of the list manifested our feeling of commitment. Actually our concerns continued into some studies of the status of physiologists (see below under "Education").

The president-elect who may have appreciated most deeply the expression of the Society's confidence was H. Cuthbert Bazett. For years he felt unlike other members, due to his British background. In two special ways he labored for the Society: he chaired a committee on scientific aid to European physiologists after war II; and he informed the Society about the efforts of ICSU (International Council of Scientific Unions) to form IUPS (International Union of Physiological Sciences). He accompanied his goal in the Aid project; and he prepared the ground for APS to help activate IUPS; when he became president-elect (1949). He had almost reached age 65 when elected, and he privately expressed great but humble satisfaction in it. Tragically, he died of a heart attack after serving as president of the Society for but a month; the only one of our officers to die in office.

Publications

Present-day physiologists will be interested to learn that in the early days, manuscripts destined for publication in A.J.P. received little criticism. Ordinarily the first managing editor (William T. Porter) alone saw the paper before it was printed. The Journal came into control of the Society in 1914, but the editorial board was still advisory only (D.R. Hooker, managing editor). In my limited experience Hooker restricted his comments to requests for substantial shortening. In 1933, "publication trustees" were appointed; and at once critical appraisals of all manuscripts began. Looking back, I regard the submission of manuscripts to referees as a great step in the rise of research standards. No longer could an author substitute words for deeds. In 1933 I received guidance from Alfred N. Richards, who wrote a personal letter offering weighty suggestions concerning each paper submitted. Soon thereafter, referees became anonymous.

In 1921 the first issue of *Physiological Reviews* came into print. In its early years, the articles published tended to represent the life work of each senior physiologist. Customarily, physiologists exchanged reprints; one's shelves thus contained reports of most work done by a score or two of North American physiologists.

In 1947 the *Journal of Applied Physiology* was founded. Those who discussed the need for this journal. had done war-time studies that they would like to publish in the new journal. The belief of some that applied physiology could be demarked from other physiology did not eventuate.

My experience was, and still is, that refereeing of submitted papers proves rewarding. The referee is challenged to grasp the plan of the work reported, and to assess the reader's ability to understand the methods and conclusions offered. Most of all, refereeing gives an unparalleled opportunity to educate the author. Can he be led by specific suggestions to see more in his present work and future work than he has expressed? Is he developing his concepts as far as justified?

Education

Two unusual opportunities for work in the Society came my way. One: during World War II, discussions arose about the prospects for physiologists when peace should arrive. Would we go back to one-man researches? To no research budgets? To kymograph-type instruction? Four of (Philip Dow, Julius H. Comroe, Jr., T. E. Boyd, E. F. Adolph) were commissioned (1944) by the Society Council to survey physiologists' situations in terms of numbers, facilities, economics. The problems uncovered emphasized the education of future physiologists: age distribution, Ph.D. or M.D., types of experience, incentives. The conclusions and opinions were published in *Federation Proceedings* 3, 407-436, 1946. In short, we learned how physiologists stood in the eyes of students and public. But we failed to forsee the huge expansion of physiology and other sciences in the next decade. This Survey gave rise to an independent Study Committee (1946) that concerned itself with more specific teaching problems in physiology (Fenn, 1963, p. 146) and (1952-56) a second Survey of physiology (R.W. Gerard: "Mirror to Physiology", 1958). All reports were published by the APS.

Two: A permanent Education Committee (at first William R. Amberson, C. Ladd Prosser, Comroe, Adolph) was formed in the Society (1953) which chose, as its chief initial mission, to ascertain what aids could be given to the advanced education of teachers, especially those in colleges. Facilities and persons in medical faculties had expanded, but some colleges now offering instruction in the newly prominent science of physiology were manned by instructors with little research experience.

With federal funds, summer fellowships were made available to selected college teachers who came into university laboratories. Workshops in college teaching were held. Society sessions about teaching at various levels of sophistication were programmed. The stated aim was to make education and teaching as valued and respected in the Society as research and writing had been. For the first decade (1953-63) this seemed to be gradually approached. Thereafter organized efforts in other directions were pursued by the Society's Education Committee.

The above paragraph brings to mind an incident that shows how action is often unpremeditated. In reporting to the Council the thoughts of the Education Committee, I stated that the latter would like to emphasize effort in teaching through the founding of an annual award to be given to an outstanding teacher of physiology. But, the Committee had concluded that there was no acceptable way of choosing a recipient for such an award. Thereupon Louis N. Katz said: "Until a way is found, I suggest such an annual award be given to a young investigator who will present a research lecture to the Society. And I think I know where the money can be obtained." That is how the Bowditch lectureship was founded. It has proved to be a fruitful feature of the Society.

Fun

Dinner groups came to be formed especially in the years following World War II. Their informality and comraderie have brought joy to many. I participated in four of them. The Temperature Regulation dinners started in 1949 and continue to this date. The attendees served as a natural group to send a representative to the Society's program committee. The group controls an annual (Belding) prize which is granted to a student who gives a creditable paper at the regular sessions of the Society.

I think, too, of the Comparative Physiology dinner group. When it formed in 1951 the kind of physiology in which its participants were interested seemed underrepresented in APS. But when it disbanded 17 years later, researches were being pursued on a great variety of animals; and the kinds of comparative concepts that were being formulated commanded the attention of most physiologists.

Perinatal Biology was first represented by a dinner group in 1969. Amazing are the diverse disciplines represented by those who come together annually.

And so with the now defunct Regulatory Physiologists' group. The flexibility of the groups and regroups is an outstandingly favorable feature of our Society.

An APS Committee that has gained a marked response is that on Senior Physiologists. It arose in 1960 when Bruce Dill proposed that those who were retiring on account of age might be helped into useful jobs through a sort of senior placement bureau. Circular letters sent to oldsters also elicited personal news. These news-items were published in the *The Physiologist,* which had been established in 1957. The news proved so interesting to readers, and so appreciated by the semi-neglected seniors, that the communication arrangements have survived, while the placement plan turned out to be unneeded. There are now more than 600 members of the Society 65 years of age or older. Two-way communication with them benefits us all.

Coda

A physiologist climbs many steps as he matures in his profession. While ignorant of how his career will open, he becomes a candidate for a doctorate. He attends his first Society meeting. He writes a thesis. He delivers his first research paper. He plans his first independent research. He has his paper published. He

becomes acquainted with counterparts in other institutions. He is elected a Society member. He joins a dinner group. He chairs Society sessions. He is appointed a journal referee. He becomes a committe member. He is invited to participate in symposia. He is a senior physiologist. He becomes a professor-emertus. He enjoys chatting with old acquaintances and students at meetings. He realizes that he and the Society have grown old together. Such are the ages of a career-physiologist.

As I look back upon the Society's Anniversary at 50 years (1938) and again 75 years (1963), I dimly extrapolate froward to 100 years. Though I will not participate in that Anniversary, I enjoy the prospect of it now. Physiology will be different, the Society will be different, the members' personalities will be different. To my mind, the greatness of APS has consisted in its tradition of aspirations in research and teaching. Top satisfactions in my career came through the Society. I enjoy watching today's activities maintaining and promoting the flexiblity that makes the APS meaningful to its members.

W. O. FENN BIOGRAPHY

A Biographical Memoir on Wallace O. Fenn has been prepared by Dr. Hermann Rahn for the National Academy of Sciences.

Wallace Osgood Fenn, 1893-1971). *Biographical Memoirs,* Vol. 50, Natl. Acad. Sci., Washington, D.C., 1979, pp. 141-173.

PLAN FOR THE APS CENTENNIAL

The introduction of a new feature, the Historical Section, is a fitting occasion for presenting information about the Society's plans for a Centennial Celebration. The initial statement was made at the general meeting in Atlantic City in 1978. Since that time, the Commemorative Committee was activated and a Task Force was formed.

We believe it is appropriate to spell out the general concept of the Commemorative Celebration. As you will see, the full membership of the Society is invited to participate. Although many detailed activities are being planned, we believe we would benefit greatly from suggestions and proposals, consistent with the basic concept, from our readers.

An area of special interest to which we hope your attention will be drawn is the matter of raising funds. Any ideas, suggestions, even schemes for raising the funds required will be welcome.

This is also the time to call for volunteers to help make the Society's Centennial celebration a significant event in the history of American science.

The period for commemoration will begin with the 30th International Congress of Physiological Sciences in 1986 and end with a Centennial Meeting (the APS Fall Meeting) in 1987.

The objective of the Program is "to utilize the Centennial Year activities to make the scientific community and the lay public aware of the history of the American Physiological Society (and essentially the history of American physiology); aware of the nature of physiology and its role in understanding biological processes and in doing so, how physiology and physiologists promote human welfare, directly and through stimullating advances in medicine, agriculture, public health, environmental protection and other physiologically based sciences." (From: Organization, Duties and Responsibilities of the Committee for the Commemorative Program for the Centennial year of the American Physiological Society, 1986-1987).

It is our intention to publish in future issues, information on the organization of the Committee and its subcommittees, the Task Force, and various projects on: Publications, Meetings and Lectures, Promotional Activities, Exhibits, Funding and others.

Meanwhile, we urge members to begin active participation by sending their ideas and proposals and volunteering their services. Please address these to:

Dr. M.C. Shelesnyak, Task Force Director
Comittee on the Commemorative Program for
The Centennial Year (C.C.)

The early history of material transport in nerve[1]

BY SIDNEY OCHS

Inidana University, Indianapolis, IN 46223

As our knowledge of the nervous system expands before us with ever greater richness and meaning, curiosity leads us to take a brief look backward to its origins. One branch of our field, that of axoplasmic transport, has grown so quickly as to suggest that it has a short histroy, perhaps limited to the last quarter of a century or so. However, the idea of the movement of some influence in nerve is old (Bastholm, 1950; Brazier, 1959; Clarke and O'Malley, 1968; Rothschuh, 1973), reaching back to ancient Greece. Animal spirits moving in hollow nerves as the basis for sensation and muscle movement were an integral part of the physiological schematization of Galen in the 2nd centry (Siegel, 1973), a conception which, remarkably, remained viable for 1500 years (Clarke, 1968). After Harvey overturned Galen's views on blood flow, the theoretical modifications by Descartes (Descartes, 1972) and others of the part of Galenic Theory dealing with nerve function gave it added life and it lingered on even into the 19th century. A discussion of the various theories advanced in the 17th and 18th centuries to account for nerve action would take us too far afield at this time. Here we can only list some of them, such as the movement in the fibers of a spirit with a "fiery nature" (Descartes); a thin watery-like fluid (Boerhaave); a thicker fluid like egg albumin (Malpighi); an influence with a nature similar to that of light (Willis); and a more solid form of the nerve "capillamenta" responding to a vibration of the "ether" (Newton) or to mechanical vibration (Baglivi). (See Bastholm, 1950; Brazier, 1959; Clarke and O'Malley, 1968; Rothschuh, 1973).

Of particular interest were the views of Galvani regarding electricity as the agent of nerve influence. He wrote.

> "...that the electric fluid is produced by the activity of the cerebrum, that it is extracted in all probability from the blood, and that it enters the nerves and circulates within them in the event that they are hollow and empty, or, as seems more likely, they are carriers for a very fine lymph or other similarly subtle fluid which is secreted from the cortical substance of the brain, as many believe. If this be the case, perhaps at last the nature of animal spirits, which has been hidden and vainly sought after for so long will be brought to light with clarity" (Galvani, 1953).

To account for the retention of the electrical fluid within the nerve fibers (which he recognized as an electrical conductor), Galvani considered the hollow fibers to be sheathed with an oily (nonconducting) substance (Galvani, 1953).

Direct support for the presence of fluid in nerve fibers was given by Van Leeuwenhoek in his observations transmitted to the Royal Society (Clarke and O'Malley, 1968). He described how he placed freshly cut optic nerves under his microscope and found the fibers in cross-section to be circular. Then, within a few minutes, a pearly fluid was seen exuded from the center of each of the fibers, which became transformed into flattened bands (Figure 1).

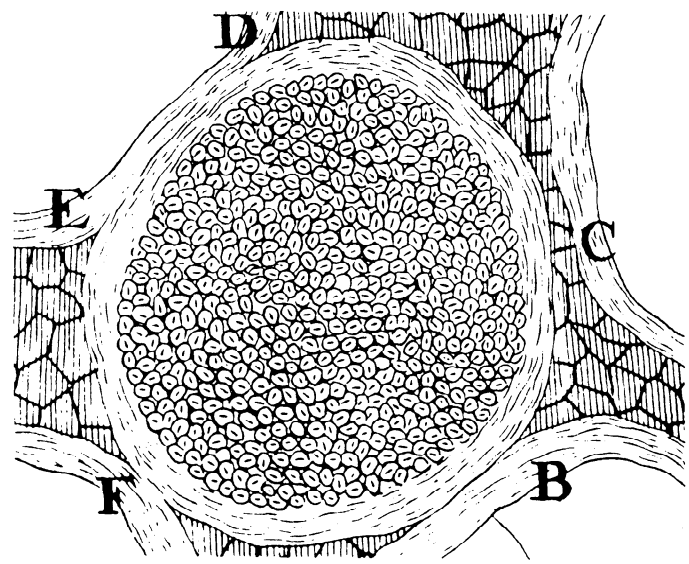


Fig. 1 We can readily interpret Van Leeuwenhoek's drawing from his 1719 paper to be a cross section of a small funiculus of nerve in the center with the letters B to E indicating the perineurial sheaths of other such funiculi. Within the central funiculus, the myelin sheaths of the fibers appear swollen with the axonal space squeezed down to a slit-like form. Van Leeuwenhoek found this to result from the loss of nerve fluid of cylindrical fibers as described in the text.

Van Leeuwenhoek explained this by considering that normally the nerve fluid distended the walls of the fibers. When the fiber was cut, the fluid escaped and the fiber collapsed. A favorite exercise of the early microscopists thereafter was to present drawings of fluid oozing from the cut ends of nerve fibers (Liddell, 1960).

(1) This paper was originally presented at a workshop on the Foundations of Modern Neuroscience, at the annual meeting of the Society for Neuroscience, St. Louis, Nov. 6, 1978, and published in *Society for Neuroscience, 8th Annual Meeting. Summaries of Symposia,* (BIS Conf. Rpt. #49). UCLA, Los Angeles, Brain Information Service/BRI Publications Office, 1979. 157 pp.

Microscopic progress was hampered by the chromatic and optical distortions of the lenses used until, in the early part of the 19th century, the achromatic compound lens became available. The clearer and enlarged view led to a rapid advance in the study of nerve.

Purkinje and Valentin identified the nerve cell bodies, characteristically containing a nucleus and nucleolus. Unfortunately, they considered that the cells and nerve fibers were two separate neural entities (Van der Loos, 1967; Ochs, 1975a). In their view, the cell body was an "active" element in close apposition to the fiber which either facilitated or inhibited the circulation of the nerve fluid within the hollow nerve fibers. The fluid was thought to flow continuously, the fibers forming a closed loop with one end of the loop in ganglia or in the central nervous system near the cell bodies, the other end at the periphery in sensory organs and muscles. [2] Remak (1838) was the first to advance the idea that the fibers and cells were in fact connected and constituted a single neural entity. As early as 1837 he concluded that

> "...the organic fibers originate from the substance of the nucleated globules itself. In spite of the fact that this observation is very difficult and requires great dexerity in preparation as well as in observation it is so well founded that it already would not be possible to doubt (it)" (Remak, 1838).

This "early neuron doctrine" of Remak's was, unfortunately, not widely accepted at the time and only toward the end of the centruy was the neuron doctrine on the way to becoming firmly established. The failure to recognize the source of the fibers led to confusion regarding the process of nerve regeneration (Ochs, 1977; Ochs, in press).

In spite of the varied views as to neuron structure in the middle of the 19th century, Waller inferred a close funtional relationship between the nerve cell body and fiber on the basis of his studies of degeneration (Ochs, 1975a). In a classical study, he transsected the roots and nerves of the 2nd cervical ganalia of kittens and found the patterns of fiber degeneration shown in Figure 2.

Only those parts of the fibers of the nerves or roots which were separated from the ganglion underwent degeneration. Waller concluded from these studies that

> "...the ganglion corpuscles (cell bodies) present in the dorsal root ganglion exert a trophic influence necessary to maintain the form and function of the fibers ascending in the dorsal root fibers as well as on the sensory fibers descending in the peripheral nerve."

Additionally, he wrote

> "...as long as the influence of the ganglion over the nerve fiber occurs, this equilibrium (forces of renewal as opposed to those of degeneration) is maintained, but as soon as the connecetion of the ganglion corpuscle with the nerve fiber is destroyed, its peripheral (severed) end is subjected to forces of degeneration."

Elsewhere, he stated

> "...a ganglion therefore, was to the fibers connected to it what a river was to the rivulet that trickled from it, a source of nutritive energy" (Waller, 1852).

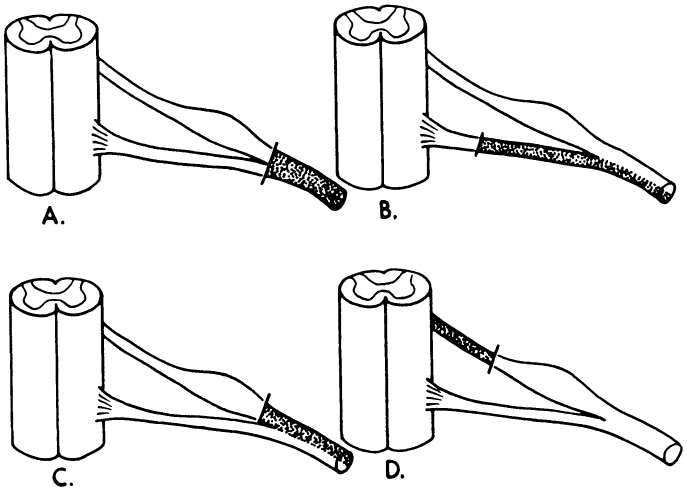


Fig. 2. The roots and nerves of the C2 segments of kittens were transected by Waller in various ways, as indicated by the transverse lines. This was followed later by a charcteristic pattern of fiber degeneration, as shown by the shading. In all cases, only those portions of the nerve fibers separated from their cells undergo such degeneration.

In apparent conflict with a movement of fluid in hollow nerve fibers was Remak's finding of fibrillary material in the primitive nerve fiber (Remak, 1838). The "nerve band", as Remak called it, was verified by Purkinje who renamed it the nerve axis or axon. Schultze (1871), who later observed the fibrillary material in more certain fasion in stained preparations, considered that the function of this organelle was to conduct the nerve impulse.

Later, when the axon membrane was recognized as the seat of the nerve action potential (Bernstein, 1912), it was clear that some other function had to be assigned to the neurofibrils. Parker proposed that the fibrillary elements were the means by which metabolic control was exerted by the cell body over its fiber (Parker, 1929). Considering the position of the unipolar T-shaped neurons of the dorsal root ganglion with respect to sensory inflow, Parker wrote:

> "In the ordinary sensory neurons, nerve impulses originate at the peripheral end, make their way centrally over the neurite, and without entering the body of the cell, pass on to discharge at the central end of the neuron. The metabolic in-

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[2] A most interesting discussion of the concept of a neural circulation introduced by Henricus Regius in 1646 was published by Clarke (1978), too late to be incorporated at the time this paper was written and presented. Regius believed he saw such a circulation in the sole of the garden slug which in actuality is an optical phenomenon caused by the wave-like locomotory movements of the animal. Clarke's paper is of particular value in showing the various factors influencing Regius, in particular Harvey's discovery of the circulation. After the 18th century Regius' concept of a nerve circulation mostly disappeared, though some remenants trailed on into the 19th century. The concept of a neural circulation used by Valentin was based on his faulty microscopical interpretations of looped sensory and motor nerve fibers in the periphery, with apparently similar loops also found in the CNS. His views were strengthened by the observations of looped peripheral nerve terminations by others (Prevost and Dumas, 1823). In Purkinje and Valentin's conception , cell bodies apposed to the fibers in the ganglia and in CNS act as a generator to cause the neural fluid to circulate in the closed fibers loops.

fluences on the other hand originate in the region of the nucleus of the cell body, pass down its neck to the tract of nervous transmission where they separate into two streams, one flowing peripherally over the neurite and the other centrally over the central nerve-fiber process."

He further stated:

"Thus, the course of the neurofibrils does not follow that of the nerve impulses but does duplicate exactly that of the metabolic influences. I conclude, therefore, that the neurofibrillary system in the neurone is concerned specifically with the distribution of the metabolic influences and not with the conduction of nerve impulses. These influences start in the region of the neuronic nucleus and spread over the lines of neurofibrils throughout the whole neurone."

Parker speculated on the nature of the materials transported.

"What the metabolic influences are, it is impossible at present to say. It seems hardly reasonable to think of them as streams of material in the nature of a hormone, emanating from the region of the nucleus and percolating throughout the neurone."

Gerard (1932), taking into account the then new evidence that nerve impulses depend on oxidative metabolism, proposed that the enzymes necessary to maintain metabolism were being continually transported in the nerve fibers from their origin in nerve cell bodies.

The loss of enzymes on cutting the nerve leads to Wallerian degeneration. A somewhat similar view had earlier been expressed by Goldscheider at the turn of the century, who suggested that the transport of a "ferment-like" substance moved down from the cell along the whole course of the axon to its extremity allowed the axon to make use of materials for its nutrition (Barker, 1899).

Ramón y Cajal (1928), basing his classical studies of degeneration and regeneration on Waller's concepts, used ligatures to partially compress nerves and after a time found a series of bulges in fibers above with narrowing in the region of the compression (Figure 3). These were interpreted by Cajal as a starting and stopping of the process of nerve fiber growth. Fine regenerating fibers were seen to pass through the region of compression. He considered that those fibers still retained their capacity for regenerative growth as shown by the sprouts (growth cones) emerging from them.

Later, Weiss and Hiscoe (1948) studied the effects of partial compression of nerve trunks and saw similar form changes in the fibers which they interpreted differently. The axoplasm was viewed as a column of highly viscous axonal material normally "growing" down within the nerve fiber (Weiss, 1967). When an obstruction was met, the axoplasm became "dammed up", causing the beading and tortuosities seen. By assessing the apparent increase in the volume of axoplasm in the bulged and beaded portion of the fibers, nerve axoplasmic growth was estimated to have a rate of 1 to 3 mm/day, a rate close to that of nerve regeneration.

At about the same time, the concept of a continual outflow of axoplasm within nerve fibers had also been advanced by Young (1945) on the basis of his observations of an oozing of axoplasm from the cut ends of giant axons. He also related degeneration in cut myelinated nerve fibers to the loss of axoplasm continually being produced by the cell body which is normally pushed down the axon to maintain its cylindrical form. The loss of fluid pressure inside the nerve fiber which is opposed by the surface tension in the walls of the fiber causes the beading and ovoid formation of degeneration. Lubinska (1964), however, described both an anterograde and retrograde movement of acetylcholinesterase in nerve, a finding inconsistent with a simple flow of axoplasm.

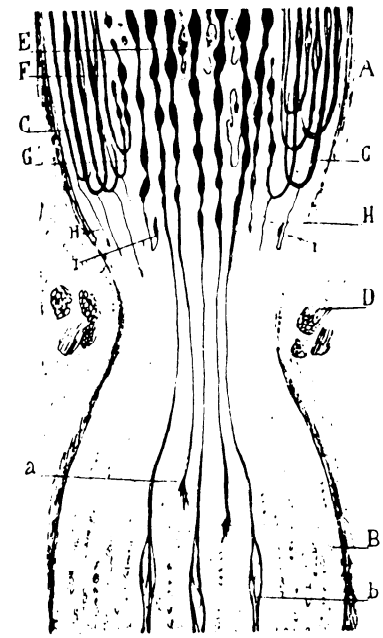

Fig. 3 A partial compression of a sciatic nerve produced by Ramón y Cajal (1928) shows beading of nerve fibers on the proximal side (A) of the ligature (D) and a thinning of fibers in the compressed region and in the distal portion (B). The capability of regeneration is evidenced by the growth cones (A), passing into the distal portion of the nerve.

With the introduction of isotopes as labels, our view of axoplasmic transport was radically transformed. In recent years it has become apparent that a much faster rate of axoplasmic transport is present in many if not in all mammalian fibers and other nerve fiber types at a constant rate close to 410 mm/day. The underlying mechanism appears to be a specific molecular process related to microtubules and/or neurofilaments with a constant supply of metabolic energy required to continuously move a wide range of molecular species and organelles both down and up the axon in order to supply its structural and functional needs (Ochs, 1975b). We are now, however, in the realm of the present and for contemporary views of transport and its mechanism the reader is referred to recent reviews (Cowan and Cuénod, 1975; Livett, 1976; Grafstein, 1977; Ochs and Worth, 1978).

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WILLIAM TOWNSEND PORTER*

PORTER, WILLIAM TOWNSEND (Sept. 24, 1862-Feb. 16, 1949), physiologist, was born in Plymouth, Ohio, the second son of Frank Gibson Porter, a physician, and Martha (Townsend) Porter. His father served as a medical officer in the Union Army during the Civil War and then practiced medicine in St. Louis, Mo. Porter's mother died when he was twelve years old, and he was orphaned at the age of seventeen. He supported himself by working nights while attending the St. Louis Medical College (later the Washington University School of Medicine). He received his medical degree in 1885 and then took a course in physiological chemistry in Philadelphia before going abroad for postgraduate studies in the universities of Kiel, Breslau, and Berlin under the tutelage of Walther Flemming, Karl H8urthle, and Martin Heidenhain. The striking contrast between the didactic methods used in teaching physiology at St. Louis and the experimental approach in the German laboratories was instrumental in shaping Porter's concepts of medical education.

Returning to St. Louis, Porter became resident physician and acting superintendent of the St. Louis City Hospital. In 1887 he was appointed assistant professor of physiology at the St. Louis Medical College; he was made professor the following year. Not only did he establish the first laboratory of physiology beyond the Eastern seaboard, but in addtion to physiology he taught bacteriology, laryngology, and physiological chemistry. His journal publications on ventricular filling and pressure, control of respiration, coronary circulation, and origin of the heartbeat and his monographs on the physical and mental development of children, drew the attention of eminent scientists, such as Charles Scott Sherrington, the English physiologist, and Henry Pickering Bowditch, Higginson professor of physiology at Harvard Medical School.

In 1893 Bowditch persuaded Porter to join his department to reorganize the teaching procedures and in particular to introduce the use of laboratory experiments as part of the routine instruction. Until then, physiology had been taught almost entirely by lectures, textbook assignments, and demonstrations. Since the apparatus needed to equip such laboratories was available only from Germany and was prohibitively expensive, Porter established a machine shop in the department to make simplified, less costly models of the existing apparatus and to develop and produce new instruments. The innovative techniques he devised for production in quanitity enabled him not only to supply Harvard's needs but to provide surplus apparatus for use by other schools. President Charles W. Eliot of Harvard, although sympathetic to Porter's mission, was concerned that such an enterprise would be viewed as a commercial venture operating on nontaxed property. In 1901 Eliot secured for Porter the original capital to found the Harvard Apparatus Company, which was moved off the campus.

By 1900 Bowditch had turned over to Porter essentially the entire responsibility for instruction in the physiology department. Porter planned a more extended course than medical students had ever been given. As his chief teaching associate he chose Walter B. Cannon, one of the most promising of his students, and energetically furthered Cannon's career at the medical school. Porter himself was a skilled experimenter and a master of laboratory technique. He was, however, a strict disciplinarian, and he set teaching standards for his students that were perhaps too high in view of their educational background, for the medical school at Harvard, unlike that at Johns Hopkins, did not then require a bachelor's degree for admission. In the years 1902 to 1904 roughly a third of Porter's students failed to pass the physiology course. Protesting students labeled Porter a martinet, while at the same time praising the teaching ability of Cannon. The revolt became so serious that in 1906 President Eliot appointed Cannon the Higginson professor and chairman of the department, to succeed Bowditch; Porter was made professor of comparative physiology. The resulting breach between Porter and Cannon continued for many years. Porter became professor emeritus in 1928.

Porter was elected a member of American Physiological Society at its fourth annual meeting in 1891. Members of the society were concerned that no journal existed in the United States for the publication of research in physiology but failed to agree on plans for such a journal, whereupon Porter in 1897 singlehandedly founded the *American Journal of Physiology,* assuming both editorial and financial responsibility; the first issue appeared in January 1898. As an editor, Porter set high standards in the publication of research. He continued to edit the *Journal* until 1914, when he presented it to the society, debt-free.

Porter maintained his his interest in supplying specialized physiological apparatus to educational institutions at minimum cost through his Harvard Apparatus Company, which in 1934 became a nonprofit organization. He had never accepted a salary from the company, and by 1921 it was amassing an annual surplus, which he used to establish the Porter Research Fellowship, to be awarded annually by the American Physiological Society to a young postdoctoral physiologist of promise.

In 1893 Porter married Alma Canfield Sterling of St. Louis. They had one child, Hildegard. During World War I, the Rockefeller Foundation chose Porter to do a study of the treatment of traumatic shock under combat conditions in Belgium and France; a personal account, entitled *Shock at the Front* (1918), was published for the general public. Porter received honorary degrees from the University of Maryland (1907) and Washington University (1915). The American Physiological Society in 1948 elected him an honrary member, an honor previously reserved for distinguished foreign physiologists. Physiology was Porter's religion; he had no other. In later years the Pokanoket Club in Dover, Mass., where he made his home, was his chief source of companionship. He died of bronchopneumonia in a nursing home in Framingham, Mass., and was buried in Dover.

[The chief sources are Am. Physiological Soc., *Hist. of the Am. Physiological Soc., Semicentennial, 1887-1937* (1938), pp. 78-83, 171-173, 193-194; A. J. Carlson et al., "The Harvard apparatus Co., the *Am. Jour. of Physiology* and Dr. W. T. Porter," *Science,* Dec. 8, 1944, pp. 518-519; Obituary by Carlson, *ibid.,* July 29, 1949; Eugene M. Landis in *Am. Jour. of Physiology,* 158 (1949), v-vii; A. C. Barger in *Physiologist,* 14 (1971), 277-285; and correspondence of Porter with President Charles W. Eliot, Harvard Univ. Archives. Information was provided by Harold Sossen, president of the Harvard Apparatus Co., and Hildegarde Porter Heffinger.]

A. Clifford Barger

*From *Dictionary of American Biography,* Suppl. 4, 1946-50. E. J. James, Ed., 1974. pp. 675-677. Charles Scribner's Sons, New York (Permission granted).

A.C. IVY - Reminiscences

D.B. Dill

The recent biography of A.C. Ivy in *The Physiologist* (3) provides a factual summary of his education and his scientific career. He was my good friend for the last 35 years of his life. I admired his ambitious drive engendered or at least strengthened by his outstanding record in contact sports in college. Working his way through college left its imprint. He seemed to have boundless energy, demonstrated by his spending twelve hours a day seven days a week in his laboratory or at his desk. Through his career he followed the example of devotion to students set by his teacher, A.J. Carlson. His patriotism was proved by making his talents available to the military services.

Two stories illustrate his combative spirit. He once told me that as a college student he worked one summer as foreman of a section gang on a railroad. I guess his boss had learned of his record as a boxer. The boss advised him that there was only one way to enforce discipline among the rude men assigned to him, "The first time a man fails to obey orders, knock him down. After you have knocked down two or three men you will have no more trouble." Ivy took his advice; after he had knocked down two men his orders were obeyed.

Many years later he was at his desk at the University of Illinois Medical School when an agitated laboratory assistant rushed in to tell him some woman had entered the laboratory, picked up an anesthetized dog from the operating table and carried it out of the building. Ivy caught up to Irene Castle at the foot of the stairs posing with the dog as a photographer was preparing to take a picture. In a well-coordinated movement Ivy kicked the camera from the photographer's hands and lifted the dog from Irene Castle's arms. Shortly, the dog was back on the table. During this period, with the backing of A.J. Carlson, he was waging an aggressive campaign against antivivisectionists through the National Society for Medical Research.

Ivy was recognized as an authority in the field of aviation medicine. About 1941 he became acquainted with Arthur H. Starnes who had a reputation as an expert at "free-falls" established at fairs. Together they planned an instrumented free-fall. Ivy sought the use of a high-altitude plane from Wright Field. I was in the Aero Medical Laboratory at the time and attempted, unsuccessfully, to arrange the loan. Ivy, not to be outdone, arranged for the use of a commercial aircraft with a ceiling above 15,000 ft. Starnes was fitted out with a motion picture camera, a tape recorder and other instruments. The free-fall from 15,000 ft was a success, the parachute opening on schedule. Ivy arranged for himself and Starnes to present the results at the next meeting of the Institute of the Astronautical Sciences, January 29, 1942. F.G. Hall and I were at the meeting to present a paper, later published (1). Ivy presented an impressive paper: "The physiologic aspects of a free-fall parachute jump."* After his presentation he asked the chairman to excuse him to meet an engagement in Chicago so he did not hear Starnes' presentation. In an aggrieved tone Starnes opened by saying, "Now, you are going to hear from the fellow who did the free-fall - I know what happened." Hall and I wondered how Ivy would have reacted.

Another illustration of the stressful life Ivy led was his acceptance of the Navy's invitation to become scientific director of the Naval Medical Research Institute in Bethesda, Md. He served in this capacity from October 1942 to July 1943. The Institute had been organized in 1939 by Albert R. Behnke, Captain in the Naval Medical Corps. Nello Pace and W.V. Consolazio helped them create an intra-navy test facility. In a personal communication Behnke comments that Ivy "was dynamic, an inspiration to all of us --- he did not relinquish his position as Head of Physiology at Northwestern. This was not too much of a handicap for a man who could run two shows at the same time ---."

Years later, Hall and I shared with Ivy the privilege of taking part in the first conference on " Biological Aspects of Space Flight." This was organized by Maj. Gen. Harry Armstrong, pioneer in aviation medicine, and was held at Randolph Field May 12, 1945. Events there provided another illustration of the stressful life Ivy led. He was scheduled to arrive at San Antonio late in the eveing before the meeting. Because of bad weather he was taken on to Corpus Christi. Eventually, he hired a limousine and reached Randolph Field in the early morning hours. After his talk he asked to be excused so he could hurry back to an appointment in Chicago.

In the early post-war years when I was scientific director of the Medical Laboratories of the Chemical Corps, a major problem was seeking the best means for treating the respiratory effects of nerve gas. One step was to explore the effectiveness of the various methods for artificial respiration. Knowing of Ivy's interest in military problems and his knowledge of respiratory physiology, I called on him for advice and possible cooperation. I found him eager to help; he recommended that one of his young assistants, Archer S. Gordon, be given primary responsibility. This advice was accepted. Along with several others, Gordon had a major role in research during the next several years, working with Army support. This research led first to acceptance of back pressure-arm lift as the preferred method of artificial respiration and later to adoption of the mouth-to-mouth method. Gordon organized a symposium to report their findings including the contribution by him and his associates (2). Gordon has played a leading role ever since in developing Cardio Pulmonary Resuscitation (CPR) and in perfecting teaching techniques. It is to Ivy's credit that he gave full support to his young assistant in the conduct of those studies.

That was the Krebiozen period, a sad affair for Ivy's friends. At the Federation meeting in Chicago in 1953 I had Gordon with me one day and had an opportunity to introduce him to A.J. Carlson. When I mentioned Gordon's association with Ivy, Carlson interrupted, "Oh, Ivy, that hurt me worse than my coronary." At the fall meeting at Urbana in 1959 I met Ivy entering the "Cow Palace" for the barbecue. As usual, Ivy talked at length about Krebiozen. We stood in the wide doorway, he with his back to those entering. I noticed several coming in whom I knew had been Ivy's friends and admirers. None stopped to speak to us; it seemed to me they were intent on avoiding Ivy. No one has been able to explain Ivy's continued defense of Krebiozen. I put it down as and emotional quirk and did not allow it to blot out my great admiration for Ivy's achievements and the fact that he had been chosen by his fellow physiologists to be President of the Society. I am confident that one factor that prevented him from supporting the weight of negative evidence was his innate combativeness. I see some parallel to our long-continued involvement in the Viet Nam affair.

*I can find no record of publication of the paper.

Acknowledgements

In assembling these reminiscences I had the invaluable assistance of Harry G. Armstrong, Sarah A. Nunneley, Albert R. Behnke and Archer S. Gordon.

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2. Gordon, A.S., C.W. Frye, L. Gittelson, M.S. Sadove and E.J. Beattie, Jr. Mouth-to-mouth versus manual artificial respiration for children and adults. *J. Am. Med. Assn.* 167:320-328, 1958.
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NSCPT 5th ANNUAL FALL SEMINAR

The National Society for Cardiopulmonary Technology, Inc. will hold its 5th Annual Fall Seminar on November 29 and 30, 1979 at the San Diego Sheraton Harbor Island Hotel. The theme of the Seminar will be "Exercise Physiology in Health and Disease." November 29 will be a full day of formal presentations by experts in the field. November 30 will include live demonstration workshops: Cardiovascular Exercise Testing; Pulmonary Exercise Testing; Computerization of History Taking; and Echocardiography.

For more information and registration forms, contact: NSCPT, Suite 307, 1 Bank St., Gaithersburg, MD 20760.

DWIGHT J. INGLE MEMORIAL AWARD

Perspectives in Biology and Medicine announces the Dwight J. Ingle Memorial Award for authors under 35 - a $500 award for the best essay (in English) submitted in competition between March 1, 1980 and December 31, 1980. For details, see Autumn 1979 issue or write the Editorial Office, Perspectives in Biology and Medicine, Culver 403, 1025 E. 57th St., Chicago, IL 60637.

THIRD INTERNATIONAL SYMPOSIUM ON GASTROINTESTINAL HORMONES

This Symposium will be held in Cambridge, England, September 15-18, 1980. The Symposium will cover the conventional circulating hormones, as well as the locally acting paracrine peptides and the peptidergic innervation.

The program will consist mostly of submitted papers with review talks by invited authorities. Deadline for receipt of abstracts, *March 31, 1980.* For further details write to:

Dr. S. R. Bloom or Dr. J. M. Polak
Royal Postgraduate Medical School
Du Cane Road
London, England W12 OHS

NORTH AMERICAN SOCIETY FOR CARDIAC RADIOLOGY

The North American Society for Cardiac Radiology will hold it's annual meeting April 23, 1980 through April 29, 1980 in San Francisco at the Mark Hopkins Hotel. For further information, please contact:

Dr. Erik Carlsson
Dept. of Radiology
University of California
San Francisco, CA 94143

INSTRUCTIONS FOR APPLYING FOR APS MEMBERSHIP

CURRENT APPLICATION FORMS

Most issues of The Physiologist routinely carry one copy of the current application form (following). This form will serve for all categories of membership. Any member desiring to sponsor more than one applicant may use a Xerox copy of this form. Any application submitted on an out-dated form will be redone on the acceptable form.

One application form serves all membership categories. There are, however, specific sets of instructions for each category. Therefore it is essential that sponsors and applicants carefully attend to those instructions specific to their desired category.

GENERAL INSTRUCTIONS

FOR ALL CATEGORIES:

Use only the current application form. Check the box indicating the category of membership for which you are applying. Use the SPECIAL INSTRUCTIONS for that category when filling out the form. Type the Application. Fill out all applicable spaces. Only completed applications will be reviewed.

The Bibliography must be submitted in the form found in the Society's journals. An example of the correct form is:

JONES, A.B., and C.D. Smith. Effect of organic ions on the neuromuscular junction in the frog. Am. J. Physiol. 220:110-115, 1974.

Send no reprints.

Deadline Dates: Completed applications received between February 1 and July 1 are considered for nomination by the Council at the Fall Meeting. Applications received between July 1 and February 1 are considered for nomination by the Council at the Spring Meeting. Applications are not complete until all materials, including sponsor's letters, are received.

QUALIFICATIONS (Except Students):

The Membership Advisory Committee uses the following 5 categories in evaluating an application:

1. Educational History. Academic degree and postdoctoral training are evaluated and assessed with regard to how closely the applicant's training has been tied to physiology.
2. Occupational History. Particular emphasis is given to those applicants who have a full time position in a department of physiology, or are responsible for physiology in another department. Relatively high ratings are given to people with positions in clinical departments and to people functioning as independent investigators in commercial or government laboratories.
3. Contributions to the Physiological Literature. This category is of major importance. The applicant's bibliography is evaluated on the basis of publications in major, refereed journals which are concerned with problems judged to be primarily physiological in nature. Emphasis is given to papers published as the result of independent research. Special note is taken of publications on which the applicant is sole author or first author.
4. Interest in and Commitment to Teaching Physiology. This evaluation is based on: (1) the fraction of the applicant's time devoted to teaching, (2) publications related to activities as a teacher including production of educational materials, and (3) special awards or other recognition the applicant has received for outstanding teaching effectiveness.
5. Special Considerations. This category permits the Membership Advisory Committee to acknowledge unique accomplishments of an applicant. These might be excellence in a specific area, or unusual contributions to Physiology resulting from talents, interest or a background substantially different from the average.

SPONSORS:

Primary responsibility for membership rests with the two sponsors who must be regular members of the Society. Sponsors should discuss the appropriateness of the selected category of membership in this Society with prospective applicants.

Each sponsor should write an independent confidential letter about the candidate using the five categories listed above to evaluate the candidate.

CHECK LIST:

1. Original copy of application signed by both sponsors.
2. Application on a current form, including the bibliography (1 original and 7 copies).
3. Mail the original, which has been signed by the two sponsors, plus 7 copies to:

Executive Secretary
American Physiological Society
9650 Rockville Pike
Bethesda, Maryland 20014

SPECIAL INFORMATION AND INSTRUCTIONS

FOR REGULAR MEMBERSHIP

Bylaws of the Society:

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

IF ALIEN: Please attach a letter and 7 copies stating visa status and type of passport and giving evidence of intent to stay in North America.

Duties and Privileges:

1. Hold Elective Office.
2. Vote at Society Meetings.
3. Serve on Committees, Boards and task forces.
4. Serve on Federation Boards and Committees.
5. Sponsor New Members.
6. Orally present or co-author a contributed paper and sponsor a non-member authored paper at the Fall scientific meeting.
7. Orally present or co-author one contributed scientific paper at the annual Federation meeting or sponsor one paper.
8. Receive The Physiologist.
9. Receive Federation Proceedings, Public Affairs Newsletters and annual Membership Directory.
10. Subscribe to handbooks and periodicals published by the Society at membership rates.
11. Register to attend scientific meetings of the Federation and the APS Fall meeting at membership rates.
12. Participate in FASEB Member's Life Insurance Program, Disability Program and in Hospital Protection Plan. (For Residents of the United States, its territories or possessions).
13. Eligible to receive the Daggs Award.
14. Eligible to be selected as Bowditch Lecturer (members under 40 years of age).

FOR CORRESPONDING MEMBERSHIP

Bylaws of the Society:

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

Duties and Privileges:

1. Serve on Society Committees, Boards and Task Forces.
2. Serve as one sponsor of new Corresponding Members (One regular member must be sponsor of a new Corresponding Member).
3. Orally present or co-author a contributed paper and sponsor a non-member authored paper at the Fall scientific meeting.
4. Orally present or co-author one contributed scientific paper at the annual Federation meeting or sponsor one paper.
5. Receive The Physiologist.
6. Receive Federation Proceedings, Public Affairs Newsletters and annual Membership Directory.
7. Subscribe to handbooks and periodicals published by the Society at membership rates.
8. Register to attend scientific meetings of the Federation and the APS Fall meeting at member rates.

FOR ASSOCIATE MEMBERSHIP

Bylaws of the Society:

Article III, Section 5 - Associate Members. Persons who are engaged in research in physiology or related fields and/or teaching physiology shall be eligible for proposal for associate membership in the Society provided they are residents of North America. Associate members may later be proposed for regular membership.

Duties and Privileges:

Same as for Regular Members except for the privilege of:

1. Holding Executive Office, or membership on certain committees.
2. Voting at Society Meetings.
3. Sponsoring New Members.
4. Receiving the Daggs Award.
5. Selection as Bowditch Lecturer.

FOR STUDENT MEMBERSHIP

Not all questions on the application form may be appropriate – Please place NA next to any such question.

Bylaws of the Society:

Article III, Section 7 - Student Members. Any student who is actively engaged in physiological work as attested to by two regular members of the Society and who is a resident of North America. No individual may remain in this category for more than five years, without reapplying.

Duties and Privileges:

1. Present one contributed paper at the Fall Scientific meeting with the endorsement of the student's advisor.
2. Receive The Physiologist.
3. Subscribe to Handbooks and Periodicals at member rates.
4. Register to attend scientific meetings of the Federation and the APS Fall meeting at student rates.

Submit original and 7 copies of application and supporting documents.

APPLICANT'S LAST NAME _____

Date _____

THE AMERICAN PHYSIOLOGICAL SOCIETY
9650 Rockville Pike, Bethesda, MD 20014

MEMBERSHIP APPLICATION FOR:

REGULAR ☐
CORRESPONDING ☐
ASSOCIATE ☐
STUDENT ☐

CURRENT MEMBERSHIP CATEGORY; YEAR ELECTED _____

See Instructions

Name of Applicant: _____
First Middle Last

Mailing Address _____ Birth Date: _____

Citizenship: _____

Country of Permanent Residence:* _____

Telephone No.: _____

*Alien residents of North America attach 8 copies of Alien Registration Card or other evidence of intent to remain in North America.

1. EDUCATIONAL HISTORY

Dates	Degree	Institution	Major Field	Advisor

Doctoral Dissertation Title: (if any)

Postdoctoral Research Topic:

2. OCCUPATIONAL HISTORY

Present Position:

Prior Positions:

Dates	Title	Institution	Department	Supervisor

SPONSORS

#1. Name: _____ #2. Name: _____

Mailing Address: _____ Mailing Address: _____

Telephone No. Zip Code Telephone No. Zip Code

I have read the guidelines for applicants and sponsors and this application and attest that the applicant is qualified for membership.

#1 Signature _____ #2 Signature _____

Each sponsor must submit an original and 7 copies of a confidential letter of recommendation to the Society, under separate cover.

APPLICANT'S LAST NAME _____

3. **DESCRIBE YOUR PHYSIOLOGICAL TEACHING** – What percent of your time/effort is spent in teaching Physiology?_____

Describe in the space provided your teaching of physiology including course descriptions (content, format); supervision of pre-doctoral and post-doctoral students; special contributions (films, textbooks, etc.).

4. **INTEREST IN THE SOCIETY** – List any APS Meetings attended by date and check the appropriate box for any papers.

SPRING (FASEB)			FALL (APS)		
Date	Presented	Coauthor	Date	Presented	Coauthor
_____	☐	☐	_____	☐	☐
_____	☐	☐	_____	☐	☐
_____	☐	☐	_____	☐	☐
_____	☐	☐	_____	☐	☐
_____	☐	☐	_____	☐	☐

List other scientific societies of which candidate is a member:

In the space provided state your interest in wanting to join the Society:

5. **SPECIAL CONSIDERATION** – Include any other contributions (Administrative, university, national service, awards and honors) that may be important to physiology.

6. **DESCRIBE YOUR RESEARCH** – What percent of your time/effort is spent in research?_____

Describe the fundamental physiologic questions in your research and how you have answered these questions. Limit the paragraph to the space provided.

7. **BIBLIOGRAPHY** – Attach a list of your publications under the following categories:
   1. Complete physiological papers, published or accepted for publication.
   2. Physiological abstracts (limit to ½ page).
   3. Other papers not primarily physiological (limit to ½ page).

The entire bibliography should not exceed 2 pages. Give complete titles and journal references with inclusive pagination. Use the bibliographic form found in the Society's journals. List authors in the order in which they appear in the publication.

Robert S. Dow to Hallowell Davis:

I am still at work at Good Samaritan Hospital and Medical Center where I have practiced neurology and EEG for almost 40 years. I am relieved of the duties of head of the department of neurology since January 1978 and as director of the EEG Laboratory since July 1978. I remain a member of the Neurological Sciences Institute of the hospital and I am back-up consultant to the Division of Clinical Neurophysiology as the EEG Laboratory is now called. I have had an advisory role in the Epilepsy Center of Oregon, one of five established throughout the country under contract from NINDSC, and found that enjoyable along with my practice. While the transition was taking place for my replacement, we were fortunate to obtain the help of outstanding retired neurologists in our training program beginning in September 1976. These included Karl Von Hagen, Russell De Jong, Adie Sahs, Alex Ross, Preston Robb, Earl Walker and Ben Boshes. They all made a great contribution toward the training program.

My wife and I are both well and active. We live in a condominium apartment overlooking the Willamette River in downtown Portland, but commute almost every weekend to central Oregon where we have a home on hole No. 11 of a beautiful golf course at Black Butte Ranch. We even cross country ski on the golf course in winter. I find this gradual relinquishment of responsibilities to younger colleagues just fine, but hope to keep up some clinical work for some years to come.

Hugh Montgomery to Hal:

I remember you when I was a student in Harvard Medical School, and attended your lectures on neurophysiology. Your knowledge and understanding of the complex relationships of phenomena in the field was very impressive. My only claim at that time to being a physiologist was that I was doing some research of my own, leading into a happy association with Alfred Redfield in purifying some of the hemocyanins, beautiful blue proteins of blood, and helping learn their combining powers with oxygen and their minimal molecular weights. Most of the last year in medical school was spent in James Gamble's and Alan Butler's laboratories at Children's Hospital. I did not then plan to practice medicine and returned to Philadelphia on invitation of Alfred N. Richards where I was allowed to play a part in investigations of the physiology of the kidney. After several years, it become apparent that I was unlikely to succeed as a pure physiologist; the compromise was medicine, with clinical investigations in combinations with physiology and pharmacology, in the relatively new branch of peripheral vascular disease, under influences of Isaac Starr, Gene Landis and Cuthbert Bazett. Dr. Bazett asked me to become a member of the Circulation Group of the Society, a fascinating opportunity for a young man in that day.

As Emeritus Professor of Medicine, I am no longer at the Hospital of the University of Pennsylvania, no longer making investigations or writing papers. I am full time in medical consultations in clinical peripheral vascular disease with an office in Bryn Mawr Hospital. I am well and happy and satisfied with consultive and advisory activities in medicine. I am still honored by having the company of Isaac Starr in trout fishing. I might remind younger colleagues, that while they are crowded by their complex problems, they should continue to keep time clear for their most promising research and for their families and friends. What I fear is the diverting influences of too many organizations.

Ragnar Granit to Hal:

I have published a book on the MIT Press titled "The Purposive Brain," have given talks to a number of Symposia on Motor Control and to one on Vision, and written a historical introduction to the volume of Motor Control, to be published by the American Physiological Society under the editorship of Vernon Brooks. For the Bicentenary of Linnaeus, the Swedish naturalist, I have edited a collection of essays, contributed the Preface and an article on Banks and Solander in the London of the 18th Century. I have been at the Fogarty International Center, NIH in 1971-72 and again in 1975. I have represented the Italian Consiglio Nazionale delle Ricerche in the Council of a very fine Research Institute at Pisa.

I am in good health owing to my belief in the last words of Voltaire's Candide: "I1 faut cutiver son jardin." I spend some five months annually in my island home working in the garden, doing any reading and writing that may catch my fancy. This place in the archipelago is surrounded by a family colony of several households providing company for both young and old.

Sid Harris to Edward Adolph:

My scientific activities consist of attendance and occasional comment at the weekly grand rounds meetings of the excellent medical staff of the Community Hospital of the Monterey Peninsula, occasional review of manuscripts, attendance at one or more national or international meetings each year, and reading hospital library publications and my own basic science journals.

Nancy and I continue to enjoy living in Carmel and we both are in good health. We subscribe to a variety of musical and cultural organizations. Travel is a grest pleasure, and history, the arts and travel have been lifelong interests of ours. All of them enrich our lives in retirement.

Carl Pfaffmann to Edward:

I have not retired as Professor but have retired as Vice President. This has relieved me of some administrative concerns and has given me more time to get back into the laboratory. I am still doing business at the same old stand (Rockefeller University). I had the pleasure of visiting with Horace Davenport in Ann Arbor when I participated in a symposium organized by the Dental School of the University of Michigan. He and I were fellow students at Oxford reading for the B.A. in Physiology from 1935 to 1937. We manage to get together every three or four years. Sorry our own paths haven't crossed much lately.

Thomas R. Noonan to Hy Mayerson:

I retired from the Comparative Animal Research Laboratory in Oak Ridge in April 1977. Since moving from the Unviersity of Rochester in 1967, my primary duties have been administrative, as Scientific Assistant to the Director. At present my scientific activities are negligible and I am surprised to find that the situation doesn't bother me. The interest of the Society in its older members is appreciated.

Clara Torda to Hy:

I am trying to publish the results of my past yet unpublished experimental work. Also, I have some very interesting new observations in the field of memory forming and retrieval and I am in the midst of writing my fourth book related to this field.

Earl H. Wood to Hy:

On January 1, 1977, on my 65th birthday, chairmanship of our Biodynamics Research Unit was transferred to the very able shoulders of my younger colleague of ten years, Dr. Erik L. Ritman. However, I seem to be as busy as ever, majorly at my desk working on manuscripts, grant requests, etc. Our laboratory group has been heavily preoccupied during the last six years with the development of a new generation computerized tomographic system for non-invasive studies of the dynamic relationships of the anatomic geometry to the functions of moving organ systems particularly the heart and lungs and the vascular system in any region of the body. The components of the machine which include 28 x-ray television imaging chains and a total weight of over 15 tons are scheduled to be delivered to our laboratory in May. Now that the struggle to get this system designed, funded and built is near completion I am looking forward to spending a major portion of my time in the laboratory once again, hopefully at least until my 70th birthday.

I am the current Chairman of the APS Centennial (1987) Celebration Committee. One of the projects that may evolve from this activity is the solicitation and eventual publication of historical vignettes of the circumstances surrounding the initiation of various important advances in biology and medicine in which physiology played an important role and if possible written by an individual directly concerned with the advance in question. Any suggestions you or any of your senior colleagues, or junior for that matter may have in this regard would be welcome.

Georges Masson to Bruce Dill:

When I retired a few years ago to the Niagara Penunsula, I planned to continue investigations at a nearby university, but when I realized that I would have to commute seventy miles round trip, I considered that life was too short to spend on highways. Instead, I embarked on a subject which has always fascinated me: grapes and winemaking. Now it is almost a full-time project - lecturing on winemaking and on wine appreciation, making wine, and editing a book on these subjects, which should be on the market in July. At least I have the pleasure of drinking the resuts of my investigations and confirming that *bonum vinum laetificat cor hominis!*

Florent Franke to Bruce:

In 1930, two years after our marriage, my wife and I moved from an apartment in the city to the suburb of Webster Groves, MO. According to Clarissa Start's history of Webster Groves, it got its name from the towering oaks, the flaming maples and full-skirted elms. In recent years elm disease has taken its toll. Other trees have been planted and it is said that the area can be distinguished from a plane by its abundance of trees.

Richard Whitehead to Bruce:

I am a consultant for the Medical Care and Research Foundation of Denver. They do a considerable amount of research on new drugs. I also attend many seminars at the Colorado Medical School. I am still interested in medical history. I became interested in the lives of the Irish figures that we know so well, when I was in Dublin during 1964-65 when I served as Visiting Professor at Trinity College Medical School. My favorites are Stokes and Graves. I served as member of a Committee of the Colorado Medical Society which published its report in a book "A Century of Colorado Medicine 1871-1971." My interest in history continues. It has been several years since I have been on the summit of Pike's Peak but I live near a park which gives me a view of the whole front range from Pike's to Long's. I go there frequently for a long look at the many places where I lived, worked and played.

John D. Thomson to Horace Davenport:

I retired on June 30, 1978 but I still have an office and secretarial help in the Department of Physiology and Biophysics at the University of Iowa. I am engaged in writing a brief history of the Department and also in compiling as complete a record as possible of the Department's history to serve as a source of material that might be useful in 1987, the APS Centennial year. We intend to stay in Iowa City as long as we can stand the rigors of midwest winters. As a major hobby, I plan to concentrate on an old interest of mine - print making.

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HIRAM E. ESSEX

1893-1978

With the death of Dr. Hiram E. Essex in December 1978 the American Physiological Society lost one of its most active and colorful members. A scientist, philosopher, painter and farmer, Doctor Essex was one of a dwindling generation of investigators whose interests were in almost every aspect of mammalian physiology. He was a member and past president (1954-55) of the American Physiological Society, the Society for Pharmacology and Experimental Therapeutics, the Society for Experimental Biology and Medicine, the American Society for the Advancement of Science, the American Association of University of Professors and the Minnesota Academy of Science. He served on the Board of the Hormel Institute as an active and an emeritus member.

Doctor Essex was born in Illinois, a state for which he retained great affection, and received his scientific training and degrees from the University of that state. He joined the Institute of Experimental Medicine at the Mayo Foundation in 1928 and from 1952 until his retirement in 1958 he was co-chairman of the Section of Physiology at the Mayo Clinic and Mayo Foundation. Author or co-author of more than 200 scientific publications, Doctor Essex also supervised the research and preparation of theses of some twenty-seven candidates for university degrees. His research activity covered a wide range of subjects in biology, experimental physiology, pharmacology and experimental surgery. Representative titles range from "The Physiologic Action of the Venon to the Honey-bee" (Am. J. Physiol. 1930) to "The Mechanism of Regulation of Blood Sugar by the Liver" (Am. J. Physiol. 1938) and "Studies on Chronic Effects of Ligation of the Canine Right Coronary Artery" (Am. J. Physiol. 1954). He is best known for his work on the physiology of the circulation, an area in which he was a recognized authority.

Doctor Essex's energy and enthusiasm led him to engage in many interests other than those of his profession. He was a painter and collector of works of art, a founder of the Rochester Art Center and a member of its Board of Directors. A long-time member of Olmsted County Historical Society he served as Vice-President and as an active member of the Board of Directors. His interest in music was considerable and he acted as President of the Rochester Music club. A noted breeder of Holstein cattle he was engaged in Holstein husbandry at county and state levels. Philanthropy was an integral part of his way of life as evidenced by his gift of an extensive area of woodlands to the City Parks System shortly before his death.

These statistics speak of a man eminent in his profession, respected by his peers and active in cultural and civic matters. They cannot portray, however, the man himself, his great enthusiasm for life, his generosity of spirit and his sincere and genuine concern for others. This writer recalls, as do many others, a long and happy association with Doctor Essex, first as a pupil, later as a colleague and friend. A particular episode illustrates one of his most endearing qualities, a wonderful sense of humor. During a particularly detailed dissection he kept moving an old-fashioned operating light closer and closer to better define the area of interest. I asked a question regarding the technic, and in answering he suddenly raised his head and made contact between a near bald area on his crown and the extremely hot surface of the lamp. The reaction was instantaneous but Christian training triumphed and no offending work was spoken. On regaining his composure he ordered the light to be banished forever with the injunction to Art Meeker, his technician, that "the torch of science should illuminate - not incinerate."

Dr. Essex was active until shortly before his death. His passing is mourned by the wide circle to whom he was affectionately known as "Uncle Hi."

David Donald, Ph.D.
Mayo Foundation

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*GENICHI KATO**

1890-1979

Professor Genichi Kato, who was a member of the IUPS Council (1959-1971) and the Japan Academy, and an honorary member of the IBRO, the American Physiological Society and the Argentine Medical Association, died May 1, 1979, at the age of 89. He was born February 11, 1890, in Niimi, Okayama, Japan. He received his M.D. in 1916 from Kyoto Imperial University, along with an Imperial gift watch in honor of his being first in the class of 1916. He received his Dr. Med. Sci. in 1920 from the same institution which is presently called Kyoto University. For two years after receiving his M.D. he stayed in the Department of Physiology of his Alma Mater where he majored in neurophysiology. In 1918 at his age of only 28, he was invited to Keio University as Professor of Physiology of its Medical School, which was founded one year earlier (1917) by Shibasaburo Kitasato, a bacteriologist best known for his success, during work in Germany with R. Koch, in achieving a pure culture of tetanus bacillus and in serotherapy of tetanus. After a chairmanship of 42 years, Kato became Professor Emeritus in 1960 but held his office in the same Department and continued to teach medical students until very recently. The number of students who attended his lectures totaled about 6,000.

Kato became internationally known by his theory of nondecremental conduction of nerve. In the early part of the 20th century, M. Verworn and his school's theory of decremental conduction prevailed in the physiological world: According to this old theory the impulse, which is conducted without decrement and follows the all-or-none principle in the *normal* nerve, would be so altered in a narcotized *(subnormal)* region that progressive decrement would occur in both the impulse size and conduction velocity in disobedience to the all-or-none principle. This old theory was mainly based, among others, on the observation that the time necessary to suspend nerve conduction depends on the length of the narcotized region. Kato and his colleagues repeated the experiment using the long nerve of the Japanese toad, *Bufo vulgaris,* and demonstrated that the suspension time is the same between longer and shorter narcotized nerves and hence conduction along the narcotized region is also nondecremental and obeys the all-or-none principle.

In 1923 at the 2nd Annual Meeting of the Japanese Physiological Society, Kato proudly reported the above observation and his new theory, but the response of the audience was not as he expected. On the contrary, the response was so unfavorable that he was petrified on the platform for a while. This made him determined to publish the results in monographs (Kato, G. The theory of decrementless conduction, 1924, pp. 1-166, and Kato, G. The further studies on decrementless conduction, 1926, pp. 1-163,both from Nankodo, Tokyo), and also to demonstrate the experiments at the 12th International Physiological Congress in Stockholm, 1926. He attended the Congress with his three associates who carried with them more than 150 Japanese toads all the way via the Siberian Railroad. Their painstaking task was rewarded with great success and prestige. After returning from Stockholm, Kato was recognized by the 1927 Japan Academy Award. In the meantime, the same topic was taken up independently by A. Forbes of Harvard and his colleagues whose results were in full support of Kato's (Davis, H., Forbes, A. et al. Conduction without progressive decrement in nerve under alcohol narcosis. Am. J. Physiol., 72; 177, 1925). This major con-

*Shortened from "A farewell word" given by Prof. Y. Tsukada, Committee Chairman of the Memorial Service for Prof. Kato, at the Kitasato Memorial Hall, Keio University, May 26, 1979.

tribution of Kato was not only well known among neurophysiologists, but also widely popularized in general textbooks of physiology (Fig. 1).

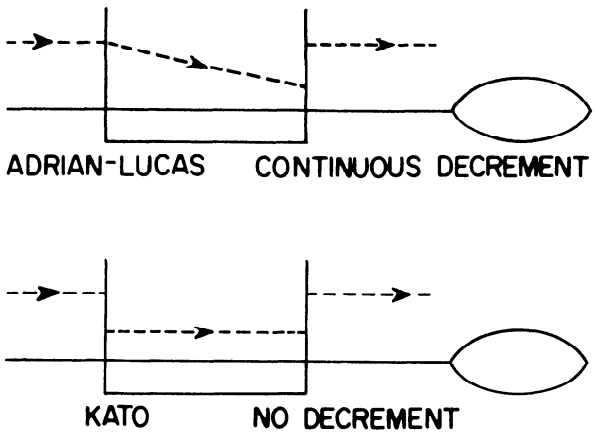

Fig. 1. Illustrating Kato's most important contribution which was to firmly establish the all-or-none principle of nerve conduction by proving that it also applied to the narcotized region. Prior to his work the nerve impulse was thought to decrement in the region of narcotized nerve, according to Verworn, Lucas, Adrian and other neurophysiologists of that period. (From "Physiological basis of medical practice", C.H. Best and N.B. Taylor, 5th Ed., Fig. 385, p. 909, Williams and Wilkins, Baltimore, 1950.)

Kato's next interest was to study the problem of nerve conduction using single fibers dissected out of the nerve trunk. Such attempts by means of a pair of sharply pointed needles were rewarded by the first success in 1930. He reported the technique and some earlier results at the 14th International Physiological Congress in Rome, 1932. This presentation of Kato probably motivated I.P. Pavlov to invite him as a guest of honor to the 15th International Physiological Congress in Leningrad and Moscow, 1935, for demonstration of his experiments on single nerve fibers. Kato again took the Siberian Railroad for the Congress, accompanied by his six associates, who carried with them as many Japanese toads as before for the 1926 Stockholm Congress. Their observations were published as a monograph (Kato, G. Microphysiology of nerve, 1934, pp. 1-138, Maruzen, Tokyo).

Kato was full of enthusiasm, which was manifested in several ways: as utmost devotion to research as mentioned, as enthusiasm in lectures, as patriotism during wartime, and as love of his University. He was an excellent teacher. He often likened him to a sculptor who bows to statues of Buddha carved by himself. In his lectures he often talked with great passion of his own experiences not only in research itself but also of episodes connected with his research activity. This attracted many students (more than 300) to his Department during his whole academic life. Many of them later turned to clinical studies, but over 80 who remained physiologists attained posts as professors in medical colleges and university schools all over the country.

During World War II and for the subsequent several years (1944-1952) he rendered distinguished services for training young doctors as dean of a medical college temporarily established in addition to the traditional Keio Medical School.

He was an idol of all Keio boys for many years (1933-1960) as a beloved leader of their cheering sections during athletic events. It was he who brought up the early disorderly rooters to their present, well-disciplined organization. It was something to see him, half bald-headed, highly excited among thousands of young Keio boys cheering for their baseball team.

When the 23rd International Congress of Physiological Sciences was held in Tokyo in 1965, Kato served as President of the congress where over 3,000 members met from 46 countries. In recognition of his lifelong service, the Japan Medical Association honored him by the Highest Award for 1966.

The above mentioned achievements of Kato demonstrated that he was distinguished in being endowed with an unusual amount of energy, enthusiasm and ability and that he consistently applied these talents to leave lasting marks in the fields of research, education and administration.

NRC PROGRAMS FOR POSTDOCTORAL RESEARCH IN 1980

The National Research Council announces its 1980 Research Associateship Programs which provide postdoctoral opportunities for scientists and engineers in the fields of:atmospheric and earth sciences; chemistry; engineering; environmental sciences; life sciences; mathematics; physics and space sciences.

NRC Research Associates will conduct research on problems largely of their own choice in selected federal research laboratories at various geographic locations in the United States. The programs are open to recent recipients of the doctorate and, in many cases, to senior investigators also. Some programs are open to non-United States nationals.

The basic annual stipend (subject to income tax) will be $18,000 for recent recipients of the doctorate. Higher stipends will be determined for senior awardees. Applications must be postmarked by January 15, 1980. Awards will be announced in April. Requests for information should be directed to: Associateship Office, JH 608-D3, National Research Council, 2101 Constitution Ave., NW, Washington, DC 20418. Tel: (202) 389-6554.

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THE PHYSIOLOGY TEACHER

PHYSEU: A COMPUTERIZED INSTRUCTIONAL AND SELF-EVALUATION PROGRAM FOR LEARNING MEDICAL PHYSIOLOGY

Joseph A. Lipsky, Lawrence L. Gabel, John J. Curry, III, Margaret T. Nishikawara, and Heinz P. Pieper

Dept. of Physiology,
The Ohio State University
Columbus, Ohio 43210

INTRODUCTION

Since 1970, the College of Medicine at The Ohio State University has allowed medical students to complete preclinical requirements by progressing through either an Independent Study Program (ISP) or a Lecture-Discussion Program (LDP). In the latter case, the basic sciences of anatomy, physiological chemistry and physiology have been presented in the first twenty-two weeks of the curriculum.

Throughout this period of time, anatomy has utilized a small group lecture and laboratory approach. Physiological chemistry began with a lecture format, but successfully initiated a modified Keller plan in 1973. Physiology initially depended upon a traditional format of lectures by many faculty members, supplemented either by demonstrations, conferences or quiz sessions. However, it was noted that students tended to behave passively, coming to grips with the subject matter of physiology only when confronted with examinations. It was then that many students recognized their deficiencies; of course, it was much too late for proper remedial action. This set of circumstances resulted in poor understanding of physiological principles, poor performance in examinations, and typically negative attitudes toward physiology. In 1976, it was decided to modify the physiology program utilizing Computer Assisted Instruction (CAI) as a basis for change. The following goals were established: 1) to develop a cohesive format, 2) to actively involve students in a continuous teaching-learning process, 3) to enhance students' achievement in physiology, 4) to improve students' attitudes toward physiology.

This report describes our experiences with the principle innovative change in our program, PHYSEU (Physiology Self Evaluation Units), and peripheral effects as they relate to the achievement of our objectives.

OVERVIEW

Curriculum Framework. Physiology, anatomy and physiological chemistry operate under the direction of a single administrator and committee. This committee formulates a unified, interrelated instructional and examination schedule. Four examination dates are scheduled, at which time internal examinations are given in each discipline. At the conclusion of the sequence, appropriate shelf copies of the National Board Examination* are administered. Students receive a pass/fail grade for the combined program; honors are also awarded.

Physiology Framework. The physiology component of this combined program was originally presented in "dive-bomb" fashion by a relatively large number of faculty. This sometimes resulted in unwarranted repetition, fractionation, and inadvertent loss of content. In order to increase structural cohesiveness, the number of faculty participating in this segment of the curriculum was reduced to four. Each assumed complete responsibility for developing and presenting all physiological concepts which were required prior to each of the four internal examinations. Thus, lectures, handouts, text assignments, self-evaluation and testing became the total responsibility of one individual. In essence, that individual had complete control of the development of a discrete segment of physiology. The unifying instructional themes were 1) development of core handout materials, and 2) the development and use of PHYSEU utilizing a computer format.

PHYSEU STRATEGY

PHYSEU was developed in collaboration with the Division of Computing Services of The Ohio State University College of Medicine utilizing Coursewriter language and an IBM 370/158 computer system. The primary objectives were to develop a CAI program which provided for 1) self-evaluation, 2) immediate remediation, 3) a minimal acceptable level of performance, and 4) a required completion schedule. PHYSEU was introduced primarily to spread the learning process over a period of time, and thus perhaps enhance achievement. Although extensive revisions have occurred since its inception, the basic format of PHYSEU has remained the same.

*Physiology, anatomy and biochemistry portions of previously administered Part I, National Board Medical Examination.

The latest version of PHYSEU consists of fifteen basic self-evaluation units and four review units (Table 1). Each basic unit has two sections, "A" and "B". Each section contains approximately twenty-five multiple choice questions. The flow chart (Figure 1) depicts a student's involvement with the PHYSEU program. Essentially, a unit is made available to students after specific physiological concepts have been presented. A student accesses PHYSEU utilizing an assigned personal ID number. Interaction occurs by means of a computer terminal which provides hard copy print-out.

TABLE 1
PHYSIOLOGY SELF-EVALUATION UNTIS (1978 REVISION)*

DIVISION	PHYSEU UNIT	CONTENT
	1	Cellular and Neuronal
I	2	Muscle
	3	Integrative and Peripheral Sensory
	Review I	
	4	Cardiovascular I
II	5	Cardiovascular II
	6	Cardiovascular III
	7	Cardiovascular IV
	Review II	
	8	Respiration I
	9	Respiration II
III	10	Renal
	11	Digestion
	Review III	
	12	Neuroendocrine; Pituitary Control; Ion Balance
IV	13	Reproductive Endocrinology
	14	Sensory Mechanics and Motor Control
	15	Higher Functions and Special Senses
	Review IV	

*Extensive reorganization was accomplished in 1978; titles and unit numbers do not relate to units in Table 3.

A student must perform at or above the eighty percent level in each unit in order to progress to succeeding units. Failure to achieve this level of performance in Section "A" of a given unit necessitates additional study on the student's part prior to attempting Section "B" of the same unit. As would be expected, Sections "A" and "B" deal with the same concepts. Performance below eighty percent in both Sections "A" and "B" results in automatic computer lock-out and a required conference with a tutor or a faculty member before the next unit is made available to the student. Since the student is forced to seek help before being allowed to advance, areas of weakness are identified and resolved early, either by the student himself or in consultation with members of the staff.

After three or four basic units are completed and immediately prior to an internal examination, the student has an option to enter a special review unit. This unit is a condensed version of the preceding units. It contains only one section and is not scored. In addition, he has an option to review any section of previously completed units.

The present version of PHYSEU provides more than 900 questions covering almost the entire range of basic physiological concepts normally presented to medical students. Each question has five possible responses. The student must make a decision for the

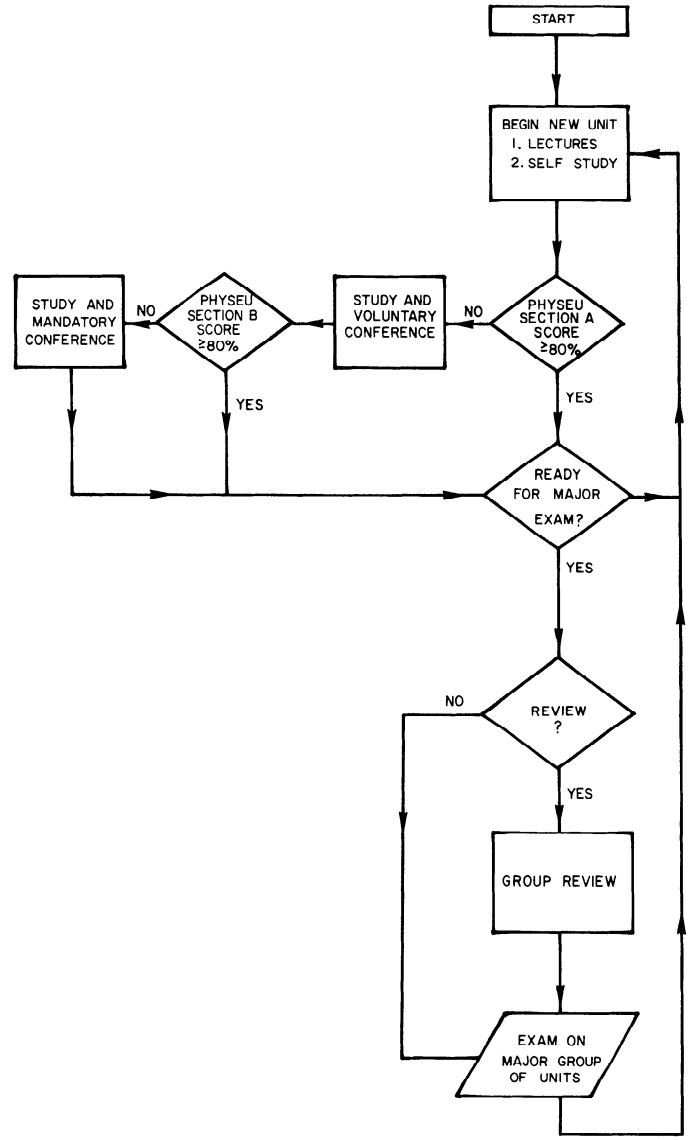

Fig. 1. This flow chart indicates possible progress pathways as a student proceeds through PHYSEU under the Track 1 management option.

record. His decision, right or wrong, results in immediate feedback of information. Sometimes, branching statements are used to develop understanding of the basic concept. In all cases, the student's first answer to the main question stem is used to determine his performance level. However, he is usually given one or two more opportunities to arrive at the correct response to the original question. In the process, the student is presented with additional feedback. The entire program contains almost 5000 immediate feedback responses. Computer scoring and record keeping are maintained only for self-evaluation and informational purposes.

PHYSEU MANAGEMENT OPTIONS

A management and reporting system was designed to allow the instructor flexibility with regard to the following:

1. registering students,
2. correcting errors,
3. following student or class performance on one or more units,
4. releasing students to proceed,
5. making units available at specific times,
6. controlling the progress of students through PHYSEU units,

7. controlling the presentation sequence of PHYSEU units, and
8. receiving on-line reports of student performance and progress in a manner which can be easily utilized by secretarial staff.

PHYSEU management allows an instructor to choose one of four specific track options:

Track 1 (Sequential controlled access). In this track, the student moves from one unit to the next as determined by the instructor. Scores and restart points are kept. If a student scores less than eighty percent on Section "B", he is prevented from progressing until he is released by the instructor.

Track 2 (Sequential controlled access without minimal performance level). This track is similar to Track 1 with one exception; even if the student does not score eighty percent or greater in Section "B", he is still permitted to progress to the next unit. That is, student progress is not stopped as a result of a low score.

Track 3 (Direct access review mode). The student may select any section of PHYSEU in any order. No scores or restart points are kept.

Track 4 (Direct access). The student may select any section of PHYSEU in any order. If the student does not complete a section, his restart point and unit score are kept.

These options permit usage of the PHYSEU program in curricula with differing instructional tehniques. Additionally, the instructor may choose to use PHYSEU as an integral part of the curriculum or simply as an adjunctive learning tool. To date, only Track 1 has been used in the Lecture-Discussion Program at The Ohio State University.

RESULTS

Terminal Time. Table 2 summarizes the logistic evolution of the PHYSEU program. It was initiated in 1976 with sixteen basic units; the following year, four review units were added; in 1978, one basic unit was deleted. Throughout this period of time, the average student spent approximately 23.5 hours at a terminal during a twenty-two week instructional period. This figure for terminal time per student represents combined data, i.e., students taking Section "A" only, students taking Sections "A" and "B", and students using the Review options. Student responses on yearly questionnaires indicate that the large majority are of the opion that both preparation time and terminal time were reasonable (80% Agree; 15% Neutral; 5% Disagree).

TABLE 2

INTERACTIVE HOURS

	1976	1977	1978
Number of Students	173	172	180
Number of Units	16	20	19
Total Questions	762	862	903
Number of Available Terminals	17	19	19
Average Number of Interactive Hours Per Student for the 22 Week Course	23.0	23.6	23.9

PHYSEU Unit Performance. Since the Track 1 management option was used each year, a minimum performance level was required; failure to achieve this level of performance resulted in a required conference. Table 3 presents data collected during 1977 which is directed toward the self-remediation aspect of PHYSEU. Little emphasis needs to be directed toward specific unit results which merely indicate that some physiological concepts are more difficult to understand and manage than others. It is important to point out that the mean of the data for all units indicates that 1) 73% of all students (N = 171) interacted only with with Section "A"; 2) 20% were able to clarify basic knowledge deficiencies and misunderstandings, presumable by self-study; and 3) approximately 7% of the students were required to attend conferences in order to continue advancing through PHYSEU. Thus, a large majority of the students achieved the minimum performance level of eighty percent while receiving immediate remediation in the concepts they failed to grasp; apparently, approximately 20% of the class benefitted sufficiently from the immediate feedback and concept emphasis given by Section "A" of a unit so that they were able to achieve the eighty percent level in Section "B" without additional formal help. Parenthetically, mean class performance on the four written examinations was similar to the required performance level in PHYSEU; i.e., eighty percent.

National Board Examination Performance (Shelf Copy). The twenty-two week curricular presentation of anatomy, physiology and physiological chemistry was begun in 1971; modification of the physiology component was initiated in 1976. An appreciation of the effect of the modified physiology program on student achievement can be gained by an examination of Figure 2. Using the mean class physiology score in 1970 as a basis for comparison, the mean class scores from 1971 - 1975 (pre-modification) increased by 10 standard score points. However, the mean class scores from 1976 - 1978 (post-modification) increased by 50 standard score points.

TABLE 3***

PERFORMANCE ON PHYSEU UNITS(1977; N = 172)

PHYSEU UNIT	Section A*	Section B*	Required Conference**
1	83.1	11.6	5.2
2	80.8	9.9	9.3
3	79.7	15.1	5.2
4	41.3	44.8	14.0
5	75.0	14.0	11.0
6	68.6	16.9	14.5
7	52.3	30.8	16.9
8	91.9	5.8	2.3
9	83.7	14.0	2.3
10	72.7	25.6	1.7
11	76.7	18.0	5.2
12	87.2	11.6	1.2
13	60.5	30.8	8.7
14	80.2	17.4	2.3
15	65.1	33.1	1.7
MEAN	73.3	20.0	6.8

*Percent of class scoring $\geq$ 80%

**Percent of class scoring $<$ 80% in Section B

***Although 16 basic units and 4 review units were available, one basic unit and all review units were intentionally not scored. Unit numbers do not relate to Table 1.

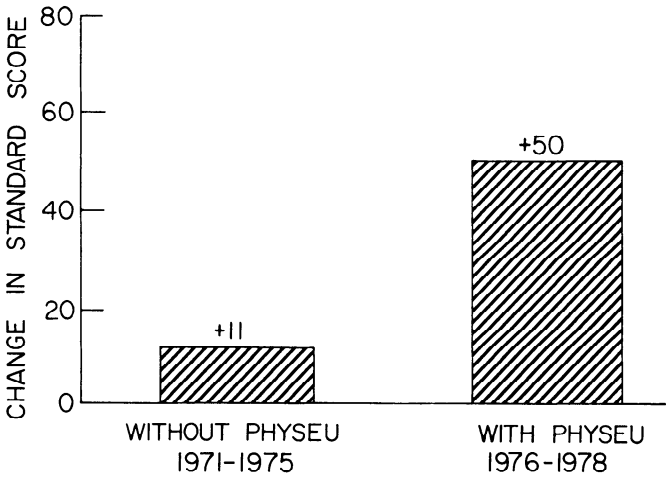

Fig. 2. National Board Examination Performance Relative to 1970 (Shelf copies).

Student Perceptions. Each year, a questionnaire was utilized to elicit student attitudes toward various aspects of the modified program. Responses to selected items are presented in Table 4. Students perceived handouts and PHYSEU to be more influential in their learning physiology than were lectures and assigned texts. It may be inferred that participating faculty members are gradually developing their own "texts in the form of well-constructed handouts, and that PHYSEU, as a means of self-evaluation, helps to clarify concepts emphasized during lectures. More than ninety percent of the students agreed that their knowledge of physiology was enhanced by the use of PHYSEU. A similar percentage saw PHYSEU as being helpful in that it forced the student to study on a continuing basis and to keep up with material presentations (Track 1 option). In addition, ninety percent rated the PHYSEU program as "Excellent" or "Good"; in 1977 and 1978, when asked if the PHYSEU concept should be retained for future classes, 100% said "yes".

DISCUSSION

Computer assisted instruction can be the sole instructional medium for a course. When used in this way in physiology, CAI has been shown to be as effective as the traditional lecture approach (1,2). Moreover, the computer-based approach has been shown to require less time for students to complete assignments, and to be the preferred instructional mode when compared to large group traditional instruction (3).

Those individuals who have developed CAI courses have undoubtedly found that an extensive committment of time and effort is necessary in order to develop effective strategies. For this reason, many individuals do not undertake the task even though they recognize the potential benefits. The alternative is to use the computer as one instructional medium in conjunction with more traditional methods. This approach has also been shown to be effective (4,5,6).

The results from the modified physiology component of the Lecture-Discussion Program at The Ohio State University strongly support this latter approach to computer utilization. Recognizing PHYSEU to be one of several simultaneous changes in the physiology program, the faculty has been encouraged by its remarkably enthusiastic acceptance by the students. It is evident that medical students perceive PHYSEU to be a powerful tool which serves to increase both their knowledge and confidence levels prior to written examinations.

TABLE 4
STUDENT RESPONSES TO SELECTED ITEMS ON END-OF-COURSE QUESTIONNAIRE

*I. On a Scale of 1 - 5, Rate Each Factor in Terms of its Influence on Your Learning Physiology.

(1) Strong Negative Influence (2) (3) Little or No Influence (4) (5) Strong Positive Influence

	1	2	3	4	5
A. Handouts	0.3	0.6	3.3	43.0	53.0
B. PHYSEU Units	1.3	2.0	6.3	44.7	46.0
C. Lectures	0.3	4.7	15.3	57.7	21.7
D. Reading Assignments	1.3	7.7	28.0	50.3	13.0

*II. SD - Strongly Disagree, D - Disagree, N - Neutral, A - Agree, SA - Strongly Agree

	SD	D	N	A	SA
1. My Knowledge of Physiology was Enhanced by the Use of PHYSEU Units.	0.6	1.3	4.0	48.0	46.0
2. The Units Were Helpful in Preparing for the In-Phase Exams.	0.6	6.3	8.0	42.3	43.3
3. Preparation Time Required for PHYSEU was Reasonable	0.3	5.3	14.0	66.7	13.3
4. The Units Were Helpful in That it Forced One to Study and Keep Up.	0.6	4.3	3.0	33.3	58.0
5. It Sould be Helpful to be Able to Use the Units for Review Purposes Before Part I National Board Exam.	2.0	8.3	21.0	36.7	31.7

*III. Overall Evaluation of the PHYSEU Program:

Excellent	Good	Fair	Poor
37.3	52.0	7.0	3.3

*IV. The Overall PHYSEU Concept Should be Retained for Use by Future Classes.

Yes	No
100%	0

*Mean Values: 1976, '77, '78
N = 364
Expressed as Percent of Respondents

**Mean Values: 1977, '78
N = 208
Expressed as Percent of Respondents

Faculty generally feel that a computer-based PHYSEU system is superior to paper and pencil systems. A computer requires that the student make a decision utilizing the available information. Each decision is monitored by the computer, and right or wrong, appropriate feedback of information takes place. The student cannot "turn to the answe page" and delude himself into thinking that he made correct decisions. In the Track 1 option, a standard of performance is required before a student is allowed to proceed to succeeding units.

CONCLUSIONS

The modified physiology instructional program (including traditional lectures, assigned readings, handouts, and PHYSEU) constitutes an effective instructional format. It is a reasonable compromise between the traditional approach and the total independent study approach using CAI. It combines the best of each world, and has several salient features: 1) it results in an evenly paced program of study for most students; 2) the computerized self-assessment feature with immediate confirmation or remediation is supported by respected psychological learning theories; 3) the student is forced to make specific decisions before he can proceed; 4) the program can easily be extended to provide the student with flexibility in breadth and depth of study. Medical students at The Ohio State University have strongly endorsed this approach to learning physiology. Although not directly measureable, student attitudes have changed from negative to highly positive as a result of the modifications in instructional approach. In addition, performance on outside examinations has increased markedly.

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THE ASSOCIATION FOR BIOLOGY LABORATORY EDUCATION (A.B.L.E.)

An international group of biologists involved in teaching undergraduate biology laboratories met recently in Calgary, Canada and formed the Association for Biology Laboratory Education (A.B.L.E.). The organization was inaugurated with a series of workshops presenting specific creative laboratory exercises. One function of the Association will be to publish and disseminate material presented at the annual workshop sessions. The Association plans to publish a newsletter called *Labstracts* and is establishing a clearing house for laboratory teaching materials, exercises, organisms and techniques.

The second annual meeting will be held at the Urbana campus of the University of Illinois, June 2 to 6, 1980. Future meetings are planned at the State University of New York at Stony Brook in 1981 and at Stanford University in 1982. Membership is open to anyone involved or interested in laboratory instruction at the post-secondary level at a cost of $10 U.S. per annum. Persons interested should contact Rosalie Talbert, Treasurer, A.B.L.E., Department of Biology, Nassau Community College, Garden City, New York 11530.

Officers elected at the first meeting were: President - Don Igelsrud, The University of Calgary; Vice President - Joseph Larsen, University of Illinois; Secretary - Anna Wilson, Purdue University; Treasurer - Rosalie Talbert, Nassau Community College; Directors at Large - Marcia Allen, Stanford University, William Elliott, Hagerstown Junior College, Eugene Kaplan, Hofstra University, and Jenny Xanthos, McGill University.

The organization has four main committees and persons interested in specific problems should contact the appropriate committee chairman. The Workshop Committee is chaired by Don Fritsch, Dept. of Biology, Virginia Commonwealth University, Richmond, Virginia 23284. The organization will publish the proceedings of the annual workshop under the editorship of Jon Glase, Section of Neurobiology and Behavior, Division of Biological Sciences, Cornell University, Ithaca, New York 14853. The laboratory Biology Teaching Library is now under the guidance of Daniel Burke, Dept. of Biology, Mercer University, Macon, Georgia 31207. *Labstracts* will be edited by James Waddell, Dept. of Zoology, University of Maine, Orono, Maine 04473. The publication will attempt to facilitate communication among persons trying to solve similar problems by running ads to exchange ideas, organisms, equipment, etc. To help improve local communication *Labstracts* has five regional editors based on time zones: Eastern - Janet Emerson, Dept. of Biology, Emory University, Atlanta, Georgia 30322; Central - Dennis Brown, Dept. of Biology, University of Winnipeg, Canada R3B 2E9; Mountain - John Gapter, Dept. of Biological Sciences, University of Northern Colorado, Greeley, Colorado 80630; Pacific - Don Mansfield, 2509 Whittier Drive, Davis, California 95616; European - Jaume Josa, Laboratorio Biologia General, Faculdad de Biologia, Universidad de Barcelona, Avda. Jose Antonio. 585, Barcelona 7, Espana.

GLUCOSE TRANSPORT INTO EVERTED SACKS OF INTESTINE OF MICE: A MODEL FOR THE STUDY OF ACTIVE TRANSPORT

Ingrith Deyrup-Olsen and Alison R. Linder
Department of Zoology and Office of Biology Education
University of Washington, Seattle, 98115

Despite their key role in physiology, many processes resulting in active transport of solutes are not particularly amenable to demonstration in student laboratories. An exception to this generalization is the transport of solutes by sacks of everted intestines of rodent species. These systems, introduced for student use by Wilson and DeCarlo (1965), are simple, easily studied models for sodium-coupled transport of carbohydrates, amino acids, and other substances. We have used them extensively in our teaching laboratories, especially for the study of glucose transport. Ideally, incubation of everted intestinal sacks results in transwall movement of glucose from the external(mucosal) surface, across the internal (serosal) surface, and into the sack. Results with the intestines of hamsters and rabbits are quite predictable, but the expense and difficulty of student use of these animals are limitations on their appropriateness in the teaching laboratory. A natural choice to substitute for these species is the laboratory rat, which is commonly available, inexpensive, and easily handled. Yet problems have arisen in actual use of the preparations of everted intestine of rats. Quite often students have reported that no convincing serosal/mucosal gradients were developed, or that, indeed, gradients did develop but were in the "wrong direction" (i.e., tissue glucose metabolism resulted in serosal concentrations lower than those on the mucosal side). Review of the literature and informal discussions with colleagues have revealed that other workers have been dissatisfied with the *in vitro* performance of the rat intestine. A satisfactory alternative approach, employing the small intestine of the mouse, is described in the present report.

MATERIALS AND EQUIPMENT

Mice. Experiments may be performed with any convenient strain of mice. The proceduce may be varied by prior exposure of the animals to varying diets, temperature regimes, hormonal injections, etc.

Incubating bath which can be controlled at a temperature of 38 to 40°; oxygen supply for tissues. A convenient arrangement is to place the intestinal sacks in a series of beakers (25 to 50 ml), each containing 5 to 10 ml of Krebs-Ringer saline (see below) in a metabolic shaker (such as a Dubnoff unit), and aerate with oxygen. Alternatively, the tissue may be suspended in a test tube containing Krebs-Ringer saline, and aerated with oxygen entering through a plastic tube leading to the bottom of the test tube (Crane and Wilson, 1958). The test tube is then placed in a bath maintained at 38 to 40°.

Krebs-Ringer Saline. This is prepared from stock solutions on each day of experimentation (the solution may deteriorate, even if stored in the refrigerator).

Stock solutions:

Sodium chloride, 0.75 M
Potassium chloride, 0.75 M
Calcium chloride, 0.75 M
Magnesium chloride, 0.75 M
Phosphate buffer: 2 ml 1 N HCl + 1.78 g Na_2HPO_4 (*or* 2.68 g $Na_2HPO_4.7H_2O$) made up to 100 ml with distilled water; this solution to be prepared on the day of the experiment.

Krebs-Ringer saline:

Mix 100 ml NaCl + 4 ml KCl + 3 ml $CaCl_2$ + 2 ml $MgCl_2$; to 100 ml of the mixture add 21 ml of phosphate buffer, and make up to 500 ml. For experiments on glucose transport, add 1 g glucose (glucose concentration = 200 mg %; other transportable solutes may, of course, be substituted for glucose, but at least 100 mg % glucose should be present even in such cases, to serve as a substrate for the tissue). The pH of this solution is 7.3.

Dissecting instruments, ether, hypodermic needle and 1 ml syringe, fine (ca. 0.5 mm) plastic tubing, short length of glass rod or plastic tubing (diameter about 2 mm) for everting intestine, fine cotton thread.

Reagents and spectrophotometer for quantitative determination of glucose or other solutes. For example, glucose may be measured conveniently with one of the commercially available glucose oxidase kits (e.g., Glucostat, or the kits supplied by Fisher or by the Boehringer, Mannheim Corporation).

PROCEDURE

The animal is anesthetized with ether, and then sacrificed quickly by fracture of the neck or exsanguination by removal of the heart. A loop of thread is placed around the duodenum near the pylorus, and a second loop is placed at the ileocecal junction. It is important to keep track of the polarity of the intestine, sine the transport capabilities vary in different regions of the intestine. Next, the entire intestine is transferred to a flat vessel (for example, a Petri dish) containing Krebs-Ringer saline, and quickly extended to its full length. At this point it may be cut into segments of convenient length, e.g., 6 to 10 cm, before it is everted. A simple procedure for eversion and preparation of an intestinal sack is diagrammed in Figure 1.

The filled sack should look firm and well filled, as in the example shown in Figure 2. It is incubated for a suitable period (e.g., 1/2, 1, or 2 hours) at 38 to 40°, with a good supply of oxygen. The sack or its surroundings should be gently agitated throughout the incubation period to insure an adequate supply of transportable molecules and oxygen, and to prevent accumlation of mucus and metabolic wastes at the transporting surface.

At the end of the incubation period, the sack is removed from the incubation bath, blotted gently with laboratory tissue, and one end is cut off in order to allow drainage of the sack contents into the collecting vessel. The sack contents and incubation medium are sampled for quantitative measurement of the concentrations of transportable solute, permitting calculation of the gradient: *serosal concentration* (= sack contents concentration) divided by *mucosal concentration* (= incubation medium concentration). Representative results of 4 experiments are shown in Figure 3. These data indicate how the capacity to develop gradients varies in different regions of the intestine. Different solutes show differing patterns of transport across the intestinal wall. For example, vitamin B_{12} differs from glucose in that its transport occurs almost entirely in the ileum (Wilson and DeCarlo, 1965).

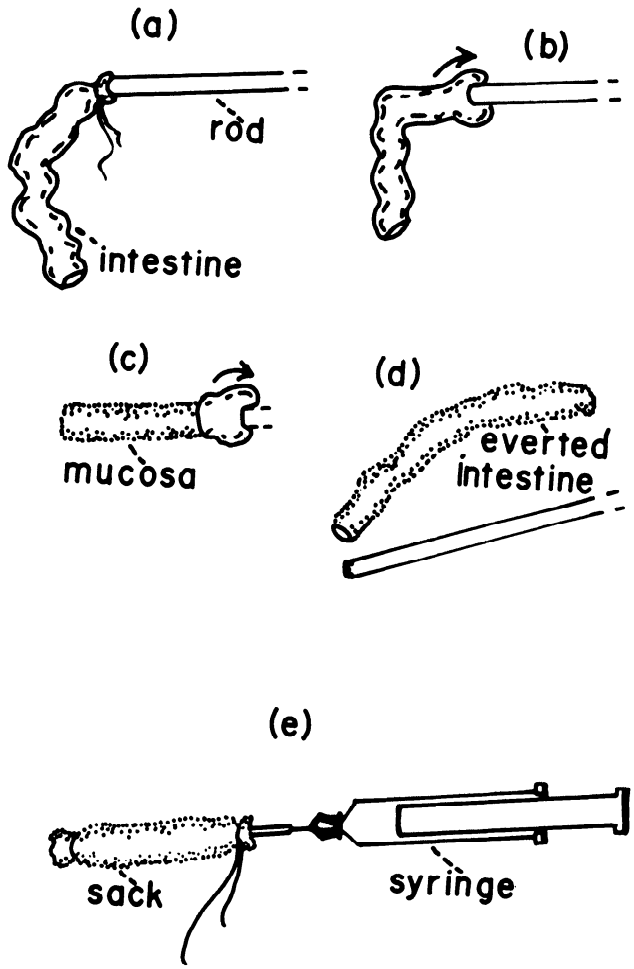

Fig. 1 (a) A loop of thread is placed close to one end of the intestinal segment, and tied firmly to close off the lumen. A fine, fairly rgid rod (plastic tube or glass rod) is inserted into the short, tied-off end of the segment. (The figure is not drawn to scale).

(b) The wall of the intestine just beyond the tie is gently worked over the rod so that the wall doubles over itself.

(c) The procedure of (b) is continued until the rod projects --- it is now covered with a closed sleeve of intestine with the mucosal surface outwards. The eversion process is continued until ...

(d) ... the entire intestinal segment has been turned inside out. Next the rod is pulled out, and the outside (mucosal surface of the everted intestine is rinsed with Ringer's solution (caution! the mucosa is delicate and easily damaged).

(e) A segment about 2 to 3 cm is cut out from the everted intestine, and tied off at one end. A fine plastic tube attached to a hypodermic needle is slipped into the opposite end of the segment, and fixed in place with a string tied with a single knot. Through this tube the sack may be filled with any desired solution. For a sack 2 to 3 cm long, a volume of 0.3 ml may be injected. The filling tube is pulled out quickly while the loop of thread is drawn tight to seal off the sack. The knot is secured with a second tie; from now on the sack can be moved about by handling the thread without touching the mucosal surface.

The procedure outlined above may be modified by taking account of water movements across the intestinal wall, occurring simultaneously with solute transport. This is done most easily by weighing the filled sack just before, and at the termination of incubation. Solute gradients may then be corrected for uptake or loss of water from the filled sack. It may be noted, however, that the Krebs-Ringer saline formula given above was chosen in order to minimize water transfer as well as glucose utilization by the intestinal tissue. Water transfer may be much greater in other incubation media, especially if bicarbonate is used in place of phosphate buffer. An interesting area for student manipulation of variables is systematic change in the concentration in the medium of ions (especially sodium; and also calcium, magnesium, phosphate, and pH).

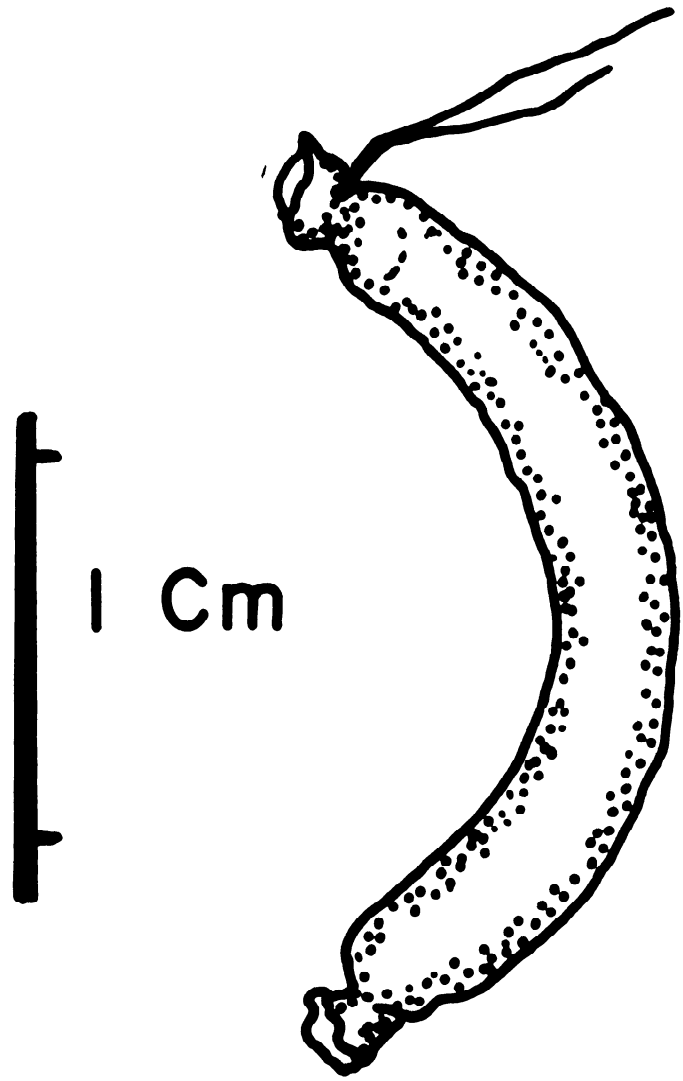

Fig. 2. An intestinal sack, filled and ready for incubation.

The relative ease of use of the mouse intestine as a transport model results in part from the fact that the wall of the viscus is very thin, minimizing problems with slow diffusion inherent in non-perfused *in vitro* systmes. Because students tend to work slowly, especially when they are first becoming acquained with the technique, we have tested the stability of the preparation. The use of light surgical anesthesia with ether greatly facilitates the student's task of obtaining the intestine and does not seem to impair subsequent transport ability of the intestinal mucosa. Everted, washed intestinal segments of mouse intestine, immersed in Krebs-Ringer saline, can be retained prior to incubation for at least 45 minutes at room temperature without apparent loss of their ability to transport glucose. Some diminution of this ability was noted, however, if the preparation was cooled to 0 to 4° in an iced bath prior to incubation at 38°. The relative stability of the system makes it possible to encourage students to work carefully and without a sense of hurry as they make their preparations.

Needless to say, the intestinal transport model is not fail-safe. The single most common source of difficulty experienced by students is inadequate filling of the intestinal sack. Unless the preparation has a slightly distended, sausage-like appearance, showing the fuzzy surface texture of the barely visible intestinal villi, as indicated in Figure 2, it is unlikely that transwall gradients will be detected. Adequate oxygenation, and accurate preparation of incubation solutions, are nearly equal in importance for the success of this experiment.

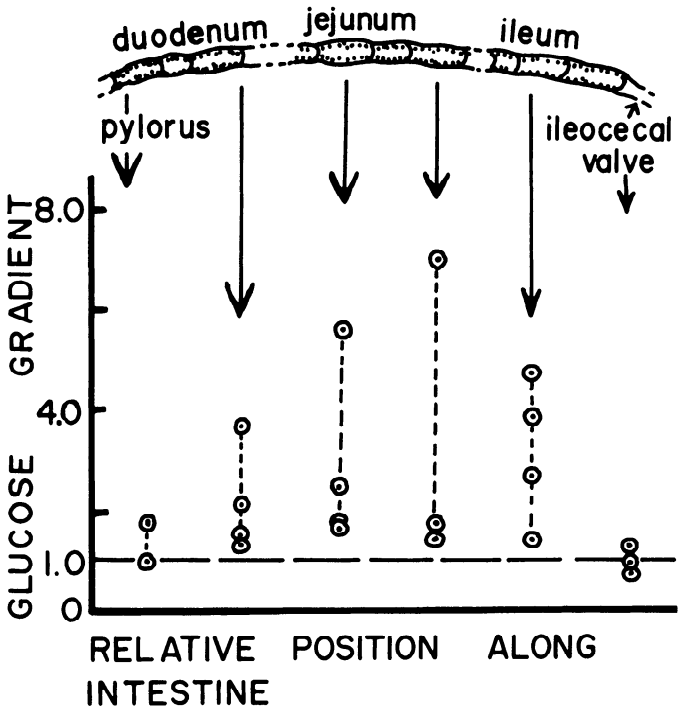

Fig. 3. Results of 4 experiments with everted intestine of mouse. The diagram at the top of the figure represents the positions along the intestine from which the tissue for each sack was removed (not drawn to scale). Abscissa: relative position along the intestine. Ordinate: Glucose gradient = (concentration in sack) ÷ (concentration in incubation medium). Incubation period was one hour.

CONCLUSION

The small intestines of laboratory mice can serve as useful models for student experiments on transport of glucose and other solutes. They can be used in simple class demonstrations of active transport in elementary classes; and more advanced students can use them as tools to investigate various aspects of transport, manipulating the experimental conditions in search of answers to questions that the students themselves formulate. Such questions might include evidence for sodium coupling; comparisons among a variety of solutes; effects of temperature, osmotic, or other environmental variables imposed on the viscus; or the action in the intact animal (intestinal donor) of dietary, endocrine, or pharmacological agents.

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HUMAN SIMULATED DIVING EXPERIMENTS

David S. Bruce and Dexter F. Speck
Wheaton College
Wheaton, Illinois 60187

As reported earlier (1), simulated diving experiments can be performed on many animals commonly used in the physiology teaching laboratory, with excellent results illustrating the diving reflex. The present report details several simulated diving experiments on the human, suitable for the undergraduate or graduate teaching laboratory in human or environmental physiology.

In our studies, a Narco Bio-Systems Physiograph was used to record EKG, impedance pneumogram, indirect blood pressure by electrosphygmomanometry, and peripheral pulse.

To record EKG and impedance pneumogram, place self-adhering surface electrodes (with electrolyte paste in the well) two inches lateral to the nipple on either side of the chest. Place the electrosphygmograph cuff on the left arm, with the Korotkov sounds microphone just over the antecubital fossa. Place the photoelectric pulse transducer on a finger of the left hand. Connect each transducer to its appropriate coupler/amplifier on the physiograph.

Part 1. Obtaining Control Data and Recording the Effect of Apnea.

1. To begin, test each subject while at rest (normal heart rate, blood pressure, respiratory rate), while lying in the prone position.
2. To demonstrate the effect of anoxia on heart rate, instruct the subject to hold his breath about 1 min. Readings should be made during the last 15 sec.
3. After the subject's heart rate returns to near the original resting level, instruct him to immerse his face in water (at room temp.).
4. The readings are taken again during the last part of breath-holding while under water. The subject should *not* breathe out as is usually done by a swimmer while his face is submerged.

NOTE: THIS IS *NOT* AN ENDURANCE TEST! The subject should try to hold his breath only as long as he can do so without any discomfort. *A few trial runs should be used* to determine the approximate length of time the subject can comfortably hold his breath. Record heart rate and blood pressure.

5. Average data from several successful experiments on a given subject. After data from the entire experimental group have been obtained, determine average for the group, and enter in Table 1. Construct histograms of heart rate and mean arterial pressure (M.A.P. = diastolic pressure + 1/3 pulse pressure) for pre-dive period (normal control), anoxia in air, diving (try to record after 30 sec. of immersion), and recovery following removal of the face from water (record at 15 sec. following removal).

Table 1. Control and Apneic Heart Rate and Mean Arterial Pressure (M.A.P.). (N=4)

	$\bar{X}$ heart rate (bpm)	M.A.P. (mm Hg)
Rest	70.5	83.0
Apnea	60.5	98.0
Face Immersion	56.0	111.0

Table 1 shows representative results from a recent experiment conducted in our undergraduate physiology lab. Means are plotted in Fig. 1. Heart rate falls during breath-holding and during apneic diving. M.A.P. *rises* during breath-holding and apneic diving. The bradycardia and increased peripheral blood pressure (due to peripheral vasoconstriction) seen during the dive are the so-called "diving reflex."

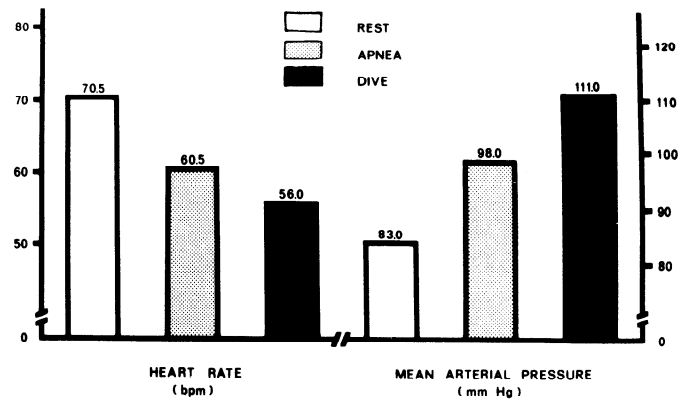

FIG. 1 AVERAGE HEART RATE AND M.A.P. DURING APNEA AND FACE IMMERSION

Part 2. Effects of a Snorkel and/or Face Mask on the Diving Reflex.

In this series of experiments, the effects of a snorkel and/or face mask on the diving reflex are examined. In the protocol that follows, the relative effects of facial wetting/cooling and apnea can be compared. The student should, on the basis of results, assess the importance of each to the onset and depth of cardiovascular responses.

1. Using the same approach as above, make the same measurements with the subject breathing through a snorkel (no immersion). Compare to control above.
2. Next, fit the subject with a diving mask and snorkel, and ask him to immerse his face as before. Record data after 30 sec. of *non-apneic immersion without facial wetting.*
3. Remove the snorkel and repeat the immersion with the face mask in place. Record data after 30 sec. of *apneic immersion without facial wetting.*
4. Give the subject a snorkel, but remove the diving mask. After 30 sec. of immersion record the effects of *non-apneic immersion with facial wetting.* (A nose clamp may be used by students who experience difficulty breathing only through their mouths).
5. Repeat, without mask *or* snorkel, recording effects of *apneic immersion with facial wetting.*
6. After collecting the data, determine mean heart rate and M.A.P. values for each phase for the experimental group. Enter in Table 2. Graph mean heart rate for each phase of the experiment as a histogram, with apneic and nonapneic immersions indicated on the same histogram by using hatching or color.

Table 2. Effects of Snorkel and/or Face Mask on the Diving Reflex. (N=33)

	Snorkel Control	Non-Apneic Imm. w/Mask	Apneic Imm. w/Mask	Non-Apneic Imm. (No Mask)	Apneic Imm. (No Mask)
$\bar{X}$ H.R.	73.1	70.7	63.1	67.6	60.1
M.A.P.	80.6	83.8	89.3	82.4	92.2

7. Can you assess the relative effects of facial wetting and apnea to the development of the reflex?

This experiment allows the student/investigator to assess the relative contributions of facial wetting and apnea to the onset and deepening of the reflex. Typical results from our lab are recorded in Table 2.

Part 3. Effects of Water Temperature on the Diving Reflex.

Use the same basic approach and recording technique as above. Record effects of immersion temperature on heart rate and peripheral blood pressure.

1. Record data during control and apneic periods.
2. Have the subject immerse his face in a water bath at 25°C. Record the effect after 30 sec. of immersion.
3. Repeat #2 with water at 35°C. At 15°C. At 5°C. At 0°C. Mix crushed ice with the water for the colder temperatures. Wait until the temperature stabilizes before instructing the subject to immerse his face. Allow several minutes between immersions at different temperatures.
4. Again calculate mean heart rate and M.A.P. values for each temperature from the experimental group. Graph heart rate vs. immersion temperature.

Here we examine how the temperature of the immersing fluid affects the development of the diving reflex. Data from our lab suggest that both temperature and apnea play an important role in establishment of the reflex. Table 3 shows results from an experiment in environmental physiology lab last Spring. In general, the colder the water, the deeper the bradycardia and the more profound the M.A.P., with some divergence, possibly due to the low N. In an earlier study (2), with 16 student subjects, the results were quite linear (Table 4). A nociceptive stimulating effect of the very cold water (0°C) may offset the diving reflex slowing of the heart and vascular bed constriction (see Table 3).

Table 3. Heart Rates and M.A.P.'s During Face Immersion in Water at Different Temperatures. (N=3)

		Immersion At					
	Cont.	APNEA	35°C	25°C	15°C	5°C	0°C
H.R. (bpm)	78	61.3	67	58	62	49	51.3
M.A.P. (mm Hg)	83.6	91.8	90	97.6	87.7	91.7	97

Table 4. Heart Rates and M.A.P.'s During Simulated Dives at Different Water Temperatures. (N=16)

	Cont.	APNEA	35°C	25°C	15°C	5°C	0°C
H.R. (bpm)	73.2	63.9	64.8	62.4	55.3	49.9	-
M.A.P. (mm Hg)	95.8	100.7	100.7	102.8	106.1	116.4	-

These experiments can illustrate several principles of adaptation to the hypoxic underwater environment: 1) that the "diving reflex" is precipitated by both facial cooling and apea (but probably not by any direct effect of water contact except cooling); 2) the combination of bradycardia and peripheral vasoconstriction, as evidenced by increased M.A.P.'s during diving, is adaptive to an air-breathing animal by decreasing the aerobic energy-expending activity of the heart by depressing its rate of beating as well as redistributing blood flow *away* from the periphery and *to* central (*i.e.*, heart-brain axis) viscera; and 3) that such effects are actively, reflexly regulated and predictable.

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REGULAR COURSES IN CHRONOBIOLOGY AT THE UNIVERSTIY OF L'AQUILA, ITALY AND THE UNIVERSITE RENE DESCARTES, PARIS

The first introductory course in chronobiology held March 4-10, 1979 in L'Aquila, Italy at the Albert-Farma plant consisted of four lectures each day. The next course of this twice-yearly event planned for the end of November 1979 is to include laboratory sessions in the Chronobiology Laboratory now nearing competion of construction at the hospital on the Collemaggio in L'Aquila. It also will amplify concerning details of "autorhythmometry--procedures for physiologic self-measurements and their analysis" (1). Under the latter title the *Physiology Teacher* in 1972, the first year of its publication, had introduced the field of chronophysiology by reference to method. Today, automatic measurement of at least some variables by miniaturized instrumentation stored in solid-state recorders has become available for human ambulatory monitoring in a form which complements the analysis of physiologic self measures.

Some of the instructors of the course have been active in both automatic- and self-measurement and are long-term investigators of time-dependent phenomena. Table 1 provides with lecture titles the names of instructors, individuals involved with basic experimental work and/or clinical applications as well as some focusing primarily on data analysis. With a review of bioperiodic aspects of body defense--chronoimmunology (2)--including the demonstration of an apparently partly endogenous 7-day periodic component in the spectrum of physiologic rhythms, discussion included clinical physiology, namely rhythm alterations in disease, notably a change in about-yearly rhythms (3,4) not only in fibrocystic mastopathy but also more broadly with increased risk of breast cancer. For the clinical laboratory, physiologic rhythms constituted the basis of time-qualified reference intervals (5).

The inclusion of mathematical procedures was fortunate and was the highlight for "students" who were physicians or other biomedical scientists, from diverse fields such as general biology, anatomy, physiology, diabetology, geriatrics or psychiatry.

Table 2 shows the program of a second course held February 7-May 16, 1979, at the University Rene Descartes of Paris. This course also was intended to be a regular event and, although the sequence was different from that visualized on the program, the lecturers were the same. Some overlap among lectures between the courses in L'Aquila and Paris is apparent. In comparing the two courses, a first point meriting consideration is whether the very broad interdisciplinary scope of the Italian endeavor constitutes a plus or a minus. It may be an indispensable step toward overcoming the lack of communication so often encountered in the specialized world of today, by fostering healthy interactions across disciplines.

Several students were outstanding in terms of actual research productivity. For example, one had already completed the study of a circadian rhythm in nerve-conduction velocity. It was a pleasure to discuss with him the merits of his work and of its analysis. He became acquainted with the concept of imputation, i.e., of intermediate steps in the summary of results on a group when, for instance, a 24-hour cosine is fitted to data from each member of the group and the results from a number of such fits are used irrespective of whether a given fit is statistically significant or not, so long as the use of such results is restricted to a fur-

TABLE I

COURSE IN CHRONOBIOLOGY
March 4-10, 1979
at the Center for Chronobiologic Research, L'Aquila
under sponsorship of the Italian Society for Chronobiology

PROGRAM

F. Ceresa - Introduction to the course
F. Halberg - Historical outline

1. BASIC CONSIDERATIONS
   F. Carandente - (Session No. 1 and practice A)
   -definitions
   -parameters and characteristics of biological rhythms
   -temporal structure of the organism; spectra of rhythms
   -synchronizers, schedule shifts
   -ubiquity of biological rhythms

2. BIOLOGIC CHARACTERISTICS OF THE RHYTHMS
   J. Aschoff - (Session No. 2)
   -freerunning circadian rhythms: their dependence of present and past conditions
   A. Reinberg - (Session No. 3)
   -human heritability
   F. Halberg - (Session No. 4)
   -collateral hierarchies of rhythms
   -coordination in chronobiology with regulation in classical physiology
   T. Vanden Driessche - (Session No. 5)
   -cellular chronobiology
   E. Wagner - (Session No. 6)
   -chronobiology of cell metabolism

3. METHODIOLOGY
   E. Batschelet - (Session No. 7 and practice B)
   -mathematical and statistical analysis of the rhythms
   E. Halberg - (Session No. 8 and practice C)
   -experimental planning for chronobiologic studies:
   in the laboratory
   in the clinic; protocols
   J. Aschoff - (Session No. 9)
   -circadian principles to be considered in shiftwork research

4. APPLIED CHRONOBIOLOGY
   F. Carandente - (Session No. 10)
   -autorhythmometry and preventive medicine
   -short notes on immunological themes
   A. Angeli - (Session No. 11)
   -chronoendocrinology
   M. Cagnoni - (Session No. 12)
   -chronopathology
   A. Reinberg - (Session No. 13)
   -chronopharmacology and toxicology
   F. Halberg - (Session No. 14)
   -chronobiology and depressive illness
   M. Apfelbaum - (Session No. 15)
   -a) chronobiology and nutrition
   S. Sensi -
   -b) chronobiology and intermediate metabolism
   N. Montalbetti - (Session No. 16)
   -chronobiology and the clinical laboratory
   D.K. Hayes - (Session No. 17)
   -chronobiology in experimental animals
   J. Fondeville - (Session No. 18)
   -chronobiology of plants
   F. Halberg - Perspectives

The President
Professor F. Ceresa

ther summary. In this case, the imputations (i.e., the first-order statistics of the original time series) are followed by the computation of a mean cosinor. Another student documented a case in which the application of a cosinor without a trend was inappropriate, yet demonstrated by original work with other methods a circadian rhythm in blood insulin during human starvation.

TABLE 2

Rene Descartes University of Paris, Faculty of Medicine
of Saints Peres
University Year 1978 - 1979

INSTRUCTION IN CHRONOBIOLOGY

Instruction in chronobiology will take place under the patronage of Florian Delbarre, President of the Rene Descartes University of Paris, Professor and Director of the Institute of Rheumatology Paris-Cochin, INSERM Unit 5. It is organized with the collaboration of Franz Halberg, President of the International Society for Chronobiology, Professor of Laboratory Medicine and Physiology and Director of the Chronobiology Laboratories at the University of Minnesota (U.S.A.), and Alain Reinberg, Clinical Professor at the University of Minnesota, Chief of Research and Head of the research team in human chronobiology, CNRS Unit 105.

PROGRAM (Wednesdays in 1979, at 17^{30}):

February 7: A. Reinberg, Notions of chronobiology; definitions
February 21: R. Mornex, Professor and Chief of Endocrine Service L'Antiquaille Hospital, Lyon: Endocrine rhythms in human health and disease
February 28: P. Gervais, Professor of Toxicology, University of Paris VII: Chronobiology and pathology due to the environment
March 14: F. Halberg: Why chronobiology?
March 21: M. Apfelbaum, Professor, Department of Physiology and Functional Exploration, Bichat Hospital, Paris: Chrononutrition
March 28: J. de Prins, Professor of Physics, Free University of Brussels: Chronobiologic data analysis
April 4: A. Reinberg: Chronopharmacology
April 25: J. Ghata, Associate Professor, University of Geneva: Synchronizers in human chronobiology
May 2: F. Delbarre and C. Job, Institute of Rheumatology, Paris Chronobiology in rheumatology
May 9: P. Fraisse, Professor of Experimental Psychology, Rene Descartes University, Paris: Behavioral circadian rhythms (sleep-wakefulness, activation, time estimation)
May 16: I. Assenmacher, Professor of Physiology, University of Montpellier II: Neuroendocrine circadian rhythms.

University President — F. DELBARRE
Director, U.E.R. — A. DELMAS

It has been a slow process to realize that confidence intervals are needed for values used in clinical physiology or medicine (6,7). Moreover, as yet those who worry about confidence intervals do not worry much about their time qualification and individualization, the point made in the *Physiology Teacher* seven years ago (1) already with reference to rhythm characteristics. On the occasion of a first encounter, any reference to an individualized confidence interval (calculated for an estimate of some characteristic of a rhythm in a single person) appears to a contemporary physiologist or physician as a contradiction in itself (since so many investigators rely on so few observations or determinations--if not on a single one--of a given kind in a given individual). Hence the great merit of those who early recognized and, what is more important, implemented the need for: 1) the collection of time series rather than of single or very few casual observations; and for 2) the interpretation of single samples against tolerance limits that are time specified as well as individualized.

Both courses, the one in L'Aquila and that in Paris, emphasized the importance of chronophysiology in providing the essential control information for any endeavor in biomedicine, once this endeavor relates to time-varying function. In both courses the interesting problem of time measurement was dealt with by reference to physiologic mechanisms in anatomical locations, namely by reference to a circadian cell cycle involving a sequence of metabolic and morphologic events, to an adrenal pacemaker and to a suprachiasmatic pace-resetter, rather than by reference to physiologically and anatomically unqualified clocks or oscillators.

In both courses autorhythmometry as advocated in the *Physiology Teacher* was included as an essential aspect of bioscience laboratory activity, as noted in combination with automatic rhythmometry facilitated by various solid-state devices that record motor activity and temperature (from the breast surface, the body core and other sites), among other functions such as heart rates, extrasystoles and asystoles, etc., and thus allow insight into the usual range of time-varying physiologic and pathologic parameters. Automatic monitoring, however, is not generally available as yet. Where it is available, it remains a mixed blessing because of occasional vexing failures, notably data losses. There is as yet no satisfactory cheap, large-scale substitute for implementing by autorhythmometry the universal acquisition of chronobiologic literacy (starting preferably in the context of secondary, rather than only college education).

It is dangerous to draw analogies and even more dangerous when these analogies are drawn with psychoanalysis. A chronobiologically-based inquiry involving the monitoring of many psychophysiologic functions is decidedly distinct--in approach, assessment and interpretation--from a conventional psychoanalytical inquiry. There is, however, one point in which chronobiology and psychoanalysis overlap. In each case it seems desirable, if not indispensable, that the analyst do a self-study and evaluate data thus obtained--doing unto others only what he has done to himself.

New facts constitute the best stimulant to a student body witnessing a science in progress--the experience of being taught by some teachers with material that as yet is not in the published literature. Let us hope that the field of chronobiology continues to develop rapidly enough to ensure that new courses can bring new materials for new and old students. Only then will the scope of chronobiology be fully realized. Chronobiology complements reliance on concepts of health or normality in medicine or biology that are based only on the absence of disease or the absence of abnormality, respectively. As opposed to group approaches, chronobiologists try to bring an individualized, positive time-qualified approach to health (via rhythm assessment). In this fashion chronobiology complements group statistics of morbidity and mortality (which also have temporal aspects). The lack of reference to individualization and time-qualification in discussions of confidence intervals (for instance, 6,7) eventually may be overcome by added courses teaching the use of individualized and time-qualified confidence and tolerance intervals attainable, e.g., as chronodesms anywhere (3-5) for treatment self-monitoring (8) as well as for health and risk assessment (3,4). Let us hope that the cost-effectiveness of chronodesms (5) and of chronopsies (9) as time-qualified and individualized measures will soon bring about the use of such procedures as a *physiologic* complement (or substitute for) spatial morphologic changes in a biopsy.

Students of L'Aquila and Paris may now reject the assumption that physiologic changes in body functions are minimal in extent, random in occurrence and trivial in mechanism. They know that the same drug, poison or other agent may or may not harm the organism--depending solely upon the time of exposure to the insult (1,10,11). This has been the reason prompting a chronotherapy endeavoring to decrease side effects in certain systems while achieving desired effects in others (10). In order to survive and adjust to its ecosystem, a living system--prokaryote (12,13) or human being (11)--must be first internally integrated in time. The same condition for survival might eventually apply to future courses in physiology.

Franz Halberg*
Chronobiology Laboratories
Department of Laboratory
Medicine and Pathology
University of Minnesota
Minneapolis, Minnesota 55455

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Dear Sir:

One of the problems facing physiologists teaching or doing research in underdeveloped countries is lack of adequate equipment and funds, so that many times one has to improvise.

I am collecting information on details on "how to" build simple apparatus and on simple techniques which can be used in physiology practicals for medical students. In this context I would appreciate it if any of your readers could send me circuits, schematics, or details of equipment they have designed or improvised (like thermostat baths, stimulators, transducers, telemetry systems, etc.). After collecting, assembling and evaluating, I would be glad to share this information with my other colleagues.

Sincerely,
Carlos Peres da Costa, M.D., Ph.D.
Professor of Physiology
Dept. de Fisiologia e Farmacologia
Universidade Federal de Pernambuco
Recife. PE 50.000 Brazil

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RESPONSE OF THE COLLECTING DUCT TO THE DEMANDS OF HOMEOSTASIS*

James A. Schafer
Nephrology Research and Training Center,
Departments of Physiology and Biophysics,
and Medicine, University of Alabama in
Birmingham, Birmingham, Alabama 35294

INTRODUCTION

Renal physiologists have long considered the collecting duct to be the final regulator of urine composition and volume. Although about 90% of the filtered loads of salts and water are absorbed by earlier portions of the nephron, the collecting duct can develop the greatest concentration differences of most solutes between the tubular fluid and plasma. The collecting duct has been shown to be the primary target for the two most important hormones known to regulate renal salt and water excretion, i.e., aldosterone and vasopressin, or as the latter is otherwise known, antidiuretic hormone. Furthermore, the collecting duct may well be the target for other, as yet unidentified, hormones which regulate salt and water excretion.

In spite of the importance of the collecting duct to the homeostasis of body fluid composition and volume, until recently, most studies of the collecting duct have been indirect. That is, the function of the collecting duct has been inferred from comparisons of distal tubular fluid to the final urine. In addition, much of our understanding of the biochemical mechanisms for the actions of aldosterone and antidiuretic hormone have come from studies using anuran epithelia which respond to these hormones, such as the toad bladder and the frog skin. It has been widely assumed that these mechanisms are at least similar in the mammalian collecting duct.

More recently, methodological developments for both functional and morphologic examination of the collecting duct have provided a considerable amount of new information concerning this region of the nephron, and in particular on how the collecting duct may change its functional and morphologic characteristics under various physiologic circumstances. This paper focuses primarily on these new investigations in which the collecting duct has been examined directly.

The general location of the collecting duct is depicted diagramatically in Figure 1 below. The most proximal (i.e., closest to the glomerulus) portion of the collecting duct is in the cortex where the *initial collecting duct* or collecting segment begins as a transition from the distal convoluted tubule. In general, 4 to 8 connecting segments merge to form the *cortical collecting duct* or tuble. This portion of the collecting duct then runs unbranched through the outer zone of the medulla to the inner zone of the medulla and papilla. In the latter two regions collecting ducts merge to form larger and larger tubules which eventually empty at the tip of the papilla as the *ducts of Bellini.* The collecting systems of nephrons having their glomerulus of origin in the superficial cortex and those having their glomerulus of origin in the juxtamedullary cortex are very similar, with the exception that in juxtamedullary nephrons the initial connecting segment forms an arch from the deep cortex where the distal convoluted tubule is located to the outer cortex where the cortical collecting duct begins.

There are two cell types which form the epithelial cell layer of all segments of the collecting duct. These are referred to as light and dark cells. The distinction between these cell types is based on the dense packing of mitochondria in the dark cells. The proportion of light to dark cells increases along the length of the collecting duct until almost all of the epithelial cells are light cells in the inner medulla. Functional differences between these two types of cells have not been described, although, in analogy with the toad bladder, it is likely that these cells may have different transport properties and they may have different responses to the hormones affecting the collecting system. Stokes et al. (1) have recently shown that there is a correlation between the magnitude of the lumen negative potential developed in isolated perfused collecting duct segments and the relative proportion of dark cells, but the significance of this observation to the function of the dark cells remains unknown.

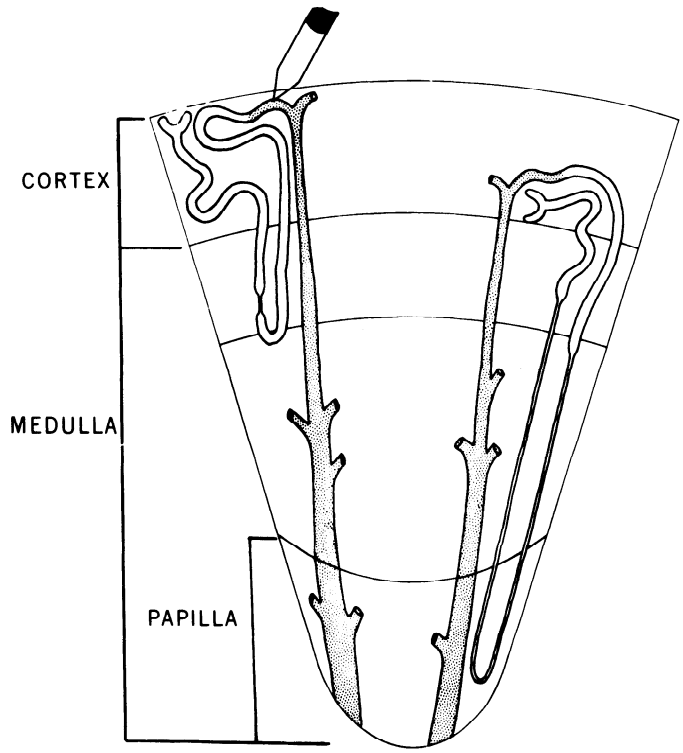

Fig. 1. Comparison of distal tubule micropuncture samples with final urine. The rate of delivery of solutes and water to the late portions of the distal convoluted tubule can be assessed by micropuncture sampling and compared to the rates of excretion in the final urine.

METHODS OF STUDY

The collecting duct is one of the more difficult regions of the nephron to study because most of the tubule segment is located deep within the renal parenchyma. As illustrated in Figure 1, one method of investigation has been to infer the function of the collecting tubule by comparing the composition of tubular fluid in the late distal convoluted tubule with the composition of the final urine. The problem with this technique is that distal tubular fluid samples can be obtained by micropuncture only from superficial nephrons, whereas the urine derives from both superficial and

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juxtamedullary nephrons. Consequently, any difference in the distal tubular fluid composition between these two types of nephrons may cause misinterpretation of the function of the collecting duct.

Alternatively, the function of the papillary collecting duct may be inferred by direct fluid sampling from this region of the nephron. In the rat and hamster it is possible to expose the papilla for most of its length and to obtain these fluid samples by micropuncture (Figure 2). The primary difficulty with this method is in finding a segment which is unbranched for a sufficient length to allow comparison of solute and water delivery to a proximal and distal micropuncture site and thus to calculate the net transport occurring between the micropuncture sites. Much of the medullary collecting duct may also be examined by the method of microcatheterization (Figure 2). In this method, a polyethylene tube, which has been pulled to a very fine outside diameter, can be advanced into the lumen of a duct of Bellini from its orifice at the tip of the papilla. The microcatheter can then be advanced as high as the corticomedullary junction and fluid samples can be taken and compared to the final urine composition. However, this method involves some of the same difficulties as comparison of distal tubular micropuncture samples with the final urine. The confluence of several collecting ducts in the inner zone and papilla of the medulla may cause changes in the urine composition between the sampling site and the effluent urine which have nothing to do with the transport of solutes and water occurring along this region of the nephron.

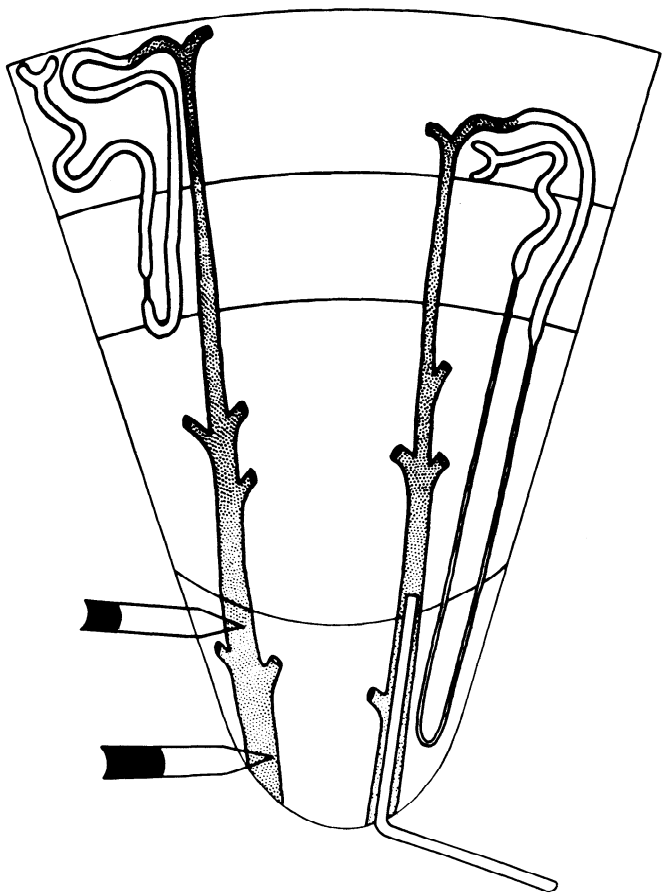


Fig. 2. Fluid sampling from the papillary collecting duct. In the rat and hamster a significant portion of the renal papilla can be exposed and micropuncture techniques can be used to obtain fluid samples at varying points along the length of the collecting duct, or short segments can be microperfused. Alternatively, as shown on the right hand side of the diagram, fluid samples can be obtained by passing fine polyethylene catheters up the papillary collecting duct from their orifice at the tip of the papilla.

Finally, the technique of perfusing isolated collecting duct segments in vitro has been of considerable use in the investigation of transport processes occurring across the collecting duct epithelium. Using this method, segments of cortical collecting duct, outer medullary collecting duct and papillary collecting duct have been dissected from untreated rabbit kidneys and perfused in vitro using glass micropipettes. Most studies employing this technique for evaluating collecting duct function have involved the cortical collecting tubule, since it is difficult to obtain long enough segments of unbranched tubules from the medulla for such in vitro study. The primary advantages of this technique are that the location of the tubular segment can be positively identified, the composition of the bathing and perfusing solutions can be easily manipulated as experimental variables, and the segment can be isolated from humoral factors which are not under the control of the investigator. On the other hand, the absence of such factors may alter some of the basal transport characteristics of the epithelium.

Fortunately, these varying methodologies of studying the collecting duct have in most cases provided a consistent set of observations on this segment of the nephron from which many important aspects of its function have been deduced.

OVERALL FUNCTION OF THE COLLECTING DUCT IN REGULATING WATER, NA^+ AND K^+ EXCRETION.

In this paper I will restrict my consideration of the functions of the collecting duct exclusively to its role in regulating the urine volume flow rate and osmolality, and the rate of Na^+ and K^+ excretion. Limiting the discussion to these topics certainly ignores one of the most important functions of the collecting duct, that is its role in producing an acid urine and generating new bicarbonate which is returned to the systemic circulation as a result of the acidification process. However, there are relatively few studies in which this process has been examined directly in the collecting duct either in vivo or in vitro.

The overal function of the collecting duct in regulating water and salt excretion has been assessed classically by comparisons of the volume flow rate and composition of the urine in the late distal tubule with that of the final urine. From such comparisons, the rates of absorption or secretion of water or solutes by the collecting duct have been approximated. However, as stated above, it must be recognized that if there are significant differences in the volume flow rates and composition of distal tubular fluid between superficial and juxtamedullary nephrons, this means of assessing collecting duct function may be considerably in error. Nevertheless, much of the data obtained from direct examination of the collecting duct supports the general conclusions which have been made previously on the basis of this more gross assessment of function.

Table I shows a quantitative comparison of volume flow rates and Na^+ and K^+ filtration rates, delivery rates in the late distal tubule, and excretion rates in the final urine. These data have been extrapolated from clearance experiments in man together with data on distal tubular fluid composition which have derived largely from micropuncture experiments in the rat. In man the glomerular filtration rate is on the order of 120 ml/min, and the glomerular ultrafiltrate is isosmotic with plasma at 290 mOsm/kg H_2O. By the time the tubular fluid has reached the distal nephron the volume flow rate has been reduced to approximately 15% of the glomerular filtration rate, and the osmolality has been reduced to approximately 150 mOsm/kg H_2O by absorption of NaCl in the thick ascending loop of Henle without accompanying water absorption. In states of maximal water diuresis, such as occurs

after the ingestion of large quantities of water in normal man or in the presence of diabetes insipidus, urine volume flow rates may exceed 15 ml/min, which is greater than 10% of the glomerular filtration rate. Under such conditions of maximal diuresis, the urine reaches a minimal osmolality of 35 mOsm/1 or less. During maximal water conservation, as occurs after severe dehydration or hemorrhage, the urine volume flow rate may be reduced to 0.5 ml/min or less, with a maximal osmolality of 1200 mOsm/1 or more. This range of urine volume flow rate and osmolality can be achieved, at least in the rat and other experimental animals, without significant changes in distal tubular volume flow rate or osmolality. Therefore, the response of the kidney to the state of hydration, which is mediated by changes in plasma levels of antidiuretic hormone (ADH), has been attributed to the effect of this hormone on the water transport properties of the collecting duct. In the normally hydrated state, the collecting duct absorbs over 90% of the fluid delivered from the distal convoluted tubule. Under conditions of maximal diuresis, the collecting duct absorbs less than one-third of the volume flow rate presented by the distal nephron, whereas with maximal water conservation more than 96% of the volume flow rate entering the collecting duct is absorbed.

Table 1. Modification of Urine Volume Flow Rate and Composition by the Collecting Duct as Assessed by Comparison of Distal Tubular Fluid and Final Urine.†

	Glomerular Ultrafiltrate	Distal Tubular Fluid	Final Urine	
			Maximum	Minimum
Volume Flow (ml/min)	120	20	>15	<0.5
Osmolality (mosmoles/kg H_2O)	290	150	>1200	<35
Na^+ Delivery (meq/min)	17	1.5	>0.7	~0
K^+ Delivery (meq/min)	0.6	0.06	>0.3	<0.01

†Values are approximated for a 70 kg male. Distal tubular fluid composition and flow rate were extrapolated from rat in vivo micropuncture data.

Considering Na^+ next, in man approximately 17 meq/min are filtered at the glomerulus. Less than 10% of this amount is delivered to the distal tubule and of this amount 50% or more is absorbed along the collecting duct under all circumstances. When the rate of salt ingestion is high, with a consequent expansion of the extracellular fluid volume, rates of sodium excretion are maximal. But even under these conditions almost 50% of the sodium entering the collecting duct is absorbed. With salt restriction and a decrease in extracellular fluid volume, or with dehydration and consequent decrease in extracellular fluid volume, there is maximal absorption of sodium in the collecting duct such that the rate of excretion may approach zero. The control of sodium absorption in the range of 50 to 100% of the load presented to the collecting duct appears to be largely under the control of the hormone *aldosterone* which increases the rate of Na^+ absorption and K^+ secretion in the distal regions of the nephron.

As in the case of Na^+, on the order of 10% of the filtered load of K^+ is delivered to the distal tubule. Under most circumstances, however, the rate of K^+ excretion in the final urine exceeds the amount of K^+ delivered to the distal tubule. Over 20 years ago, Berliner (2) proposed that the collecting duct was responsible for secreting most of the potassium which appeared in the final urine, and for absorbing sodium under most physiological circumstances. This model was based on comparisons of distal tubular fluid and the final urine such as those presented here. However, it appears that K^+ may also be absorbed along the collecting duct under conditions of K^+ deficiency or under conditions of maximal volume contraction. In these settings, the K^+excreted in the final urine may be less than 0.01 meq/min. If the distal tubular delivery rate is truly representative of the average for all nephrons, this would mean that approximately 85% of the K^+ presented to the collecting duct could be absorbed.

The next section presents a more detailed account of recent experimental observations concerning Na^+ and K^+ transport in the collecting duct. The final section of this paper will consider new information bearing on the mechanism by which ADH brings about changes in the water permeability of the collecting duct.

NA^+ AND K^+ TRANSPORT BY THE COLLECTING DUCT.

The general picture of Na^+ absorption and K^+ secretion in the collecting duct, which had been deduced from data such as that in Table 1, was confirmed in the in vitro microperfusion studies of Grantham et al. (3), the results of which are shown in Figure 3. In these experiments, isolated segments of rabbit cortical collecting tubule were perfused at very slow rates with a solution containing Na^+ and K^+ concentrations equivalent to those found in plasma, and equal to those in the artificial solution bathing the isolated tubule segment. Under these slow flow conditions, it was found that the fluid collected from 2-3.5 mm tubules exhibited a markedly decreased Na^+ concentration and a markedly increased K^+ concentration. The authors calculated that in order for Na^+ to be passively distributed at electrochemical equilibrium, given the concentration gradient observed, the transepithelial voltage would have had to be on the order of +60 mV (lumen with respect to bathing solution). On the other hand, in order for K^+ to be at equilibrium, the transepithelial voltage would have had to be -82 mV. Since the observed transepithelial potential was -46 mV, the authors concluded that K^+ had to be secreted and Na^+ absorbed against their respective electrochemical potential qradients; i.e., both processes were active.

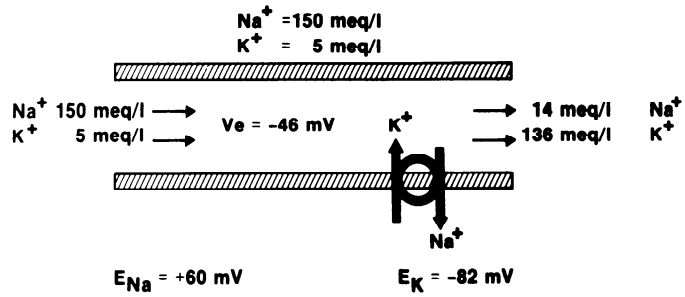


Fig. 3. Na^+ absorption and K^+ secretion by the isoloated rabbit cortical collecting tubule. The isolated perfused tubule segment is shown schematically. It is bathed in a solution containing Na^+ and K^+ concentrations of 150 and 5 meq/1, respectively. The perfusate Na^+ and K^+ composition, shown at the left, is the same. At very slow perfusion rates, the Na^+ concentration is greatly reduced while the K^+ concentration is increased in the fluid collected, as shown on the right hand side of the diagram. E_{Na} and E_K represent respectively, the Na^+ and K^+ equilibrium potentials for the ion distribution between the collected fluid and the bathing solution. The actual transepithelial voltage, V_e, was -46 mV. Data of Grantham et al. (3).

Na^+ and K^+ transport have also been examined directly in the in vivo *papillary* collecting duct in various micropuncture studies. As an example of some of the conclusions reached from such experiments, I have chosen the data of Diezi et al. (4) as shown in Table 2. In these experiments rats were maintained either on a normal diet, a low Na^+ diet, a low K^+ diet or a high K^+ diet prior to experimentation. In another protocol the animals were given an acute infusion of isotonic NaCl solution during the course of the experiment. Under all of these various protocols, all animals exhibited net Na^+ absorption in the papillary collecting duct. In contrast, animals on the control diet exhibited quite variable K^+ transport in the collecting duct, which ranged from net absorption to net secretion. However, animals pretreated by either a low

Na^+ diet or a low K^+ diet exhibited net K^+ absorption with none of the animals in these protocols exhibiting net secretion. With a high K^+ diet, the rate of K^+ delivery to the papillary collecting duct was greatly increased such that very high rates of absorption or secretion were observed. Similarly, in the case of acute isotonic NaCl infusion, the rate of Na^+ delivery to the papillary collecting duct was greatly increased, resulting in an increase in the absolute amount absorbed in the papillary collecting duct even though the amount of sodium excreted in the final urine was greatly increased.

Table 2. Papillary Collecting Duct: Micropuncture Analysis of Na^+ and K^+ Transport in the Rat.

Treatment	% Filtered Amount Transported per mm		
	Na^+ Absorbed	K^+ Absorbed	K^+ Secreted
Control	0.47	4.4 (5)	4.4 (4)
Low Na^+ Diet	0.89	6.5 (5)	0
Low K^+ Diet	2.06	0.7 (5)	0
High K^+ Diet	1.16	31 (5)	19 (8)
Acute Isotonic NaCl Infusion	2.51	7.4 (4)	0.7 (1)

Data from Diezi et al. (4). Numbers in parentheses represent the number of animals in each group exhibiting net K^+ secretion or absorption in the micropunctured papillary collecting duct.

Changes in Na^+ and K^+ transport in the distal nephron have been attributed largely to changes in plasma *aldosterone* levels. Uhlich and his collaborators (5) have shown, for example, that Na^+ absorption in the papillary collecting duct as assessed by in vivo microperfusion, is decreased by prior adrenalectomy. More recently, Schwartz and Burg (6) have shown that such effects of in vivo aldosterone levels may persist even when the collecting duct is examined in vitro. The results of their studies are shown in Table 3. These investigators used three groups of rabbits, one of which was maintained on a control diet and exhibited plasma aldosterone levels in the normal range. The second group was maintained on a low Na^+ diet and was given the diuretic furosemide which resulted in significant volume depletion with a consequent increase in plasma aldosterone to maximal levels. The third group of rabbits was maintained on a high Na^+, low K^+ diet and exhibited maximal suppression of aldosterone secretion with nondetectable plasma levels. The rates of Na^+ and K^+ transport observed in vitro are indicated in the last two columns.

Table 3. Effect of Diet on Plasma Aldosterone and In Vitro Na^+ Absorption and K^+ Secretion.

Diet	Plasma Aldosterone	V_e	J_{Na}	J_K
	ng/dl	mV	peq cm^{-1}	sec^{-1}
Control	12	-16	7.1	-2.3
Low Na^+ + Furosemide	215	-49	11.6	-5.0
High Na^+ - Low K^+	0	-15	3.5	-0.6

Data from Schwartz and Burg (6). V_e is the transepithelial voltage, lumen with respect to bathing solution. J_{Na} and J_K are the rates of net Na^+ and K^+ transepithelial transport. Positive numbers denote absorption, negative secretion.

A positive number indicates net absorption and a negative number indicates net secretion. The perfusing and bathing solutions used in these experiments were artificial, and therefore contained no aldosterone. The control group of animals exhibited net Na^+ absorption and net K^+ secretion, both of which were increased in the volume depleted group which had high plasma aldosterone levels. The high plasma aldosterone levels were also associated with a significant increase in the lumen negative transepithelial voltage. In contrast, the group of animals on the high Na^+-low K^+ diet exhibited significantly lower rates of Na^+ absorption and K^+ secretion. I wish to emphasize that the important observations are not only the changes in transport rates for these two cations, but also the fact that these tubules retained the hormonal influence in vitro.

O'Neil and Helman (7) have also examined the effects of long term administration of the mineralocorticoid, deoxycorticosterone acetate (DOCA). When this aldosterone analogue is administered acutely to animals on a normal Na^+ diet, it is observed that the rate of Na^+ excretion diminishes and K^+ excretion increases. However, when the administration of DOCA is continued over a period of 3-7 days, a phenomenon of so-called *DOCA-escape* is exhibited whereby Na^+ and K^+ excretion rates return to normal and become equal to the rates of ingestion. In their experiments, O'Neil and Helman examined the rate of Na^+ absorption and K^+ secretion in isolated cortical collecting tubules from rabbits treated with DOCA for varying periods of time up to 4-1/2 weeks.(See Table 4) As in the case of the previous experiments, the perfusing and bathing solutions used for the in vitro transport measurements were artificial and contained neither aldosterone nor DOCA. Even in cortical collecting tubules isolated from animals treated with DOCA for 3 to 6 days, there were significant increases in the lumen negative transepithelial voltage, the rate of Na^+ absorption and the rate of K^+ secretion compared to controls. With continued administration of the mineralocorticoid (beyond the period in which DOCA escape should have occurred) there was a further significant increase in Na^+ absorption and K^+ secretion, as well as the transepithelial voltage, and maximal effects on all of these parameters were observed after 11-18 days of treatment. These observations have recently been correlated with morphological changes occurring in this tubule segment. In these experiments, Wade et al. (8) isolated cortical collecting tubules from rabbits treated for two weeks with either DOCA or with the glucocorticoid *dexamethasone*. These tubules were fixed and sectioned, and electron micrographs were made. Then, using morphometric techniques, the authors obtained the surface areas of the basolateral membranes and the cell volume for both light and dark cells.

Table 4. Effect of In Vivo DOCA Administration on In Vitro Na^+ Absorption and K^+ Secretion.

No. of Days DOCA Given at 5 mg/day	V_e	J_{Na}	J_K
	mV	peq cm^{-1}	sec^{-1}
0	-8	2.7	-0.5
3-6	-12	3.9	-1.1
11-18	-58	6.3	-3.1
23-31	-29	4.9	-3.9

Data of O'Neil and Helman (7). Abbreviations are the same as in Table 3.

From a summary of their data presented in Table 5, it can be seen that both hormones produced a dramatic increase in the ratio of the basolateral membrane area to the cell volume in light but not dark cells. It's at least tempting to speculate that this increased basolateral membrane surface area is also correlated with an increased Na-K pumping capacity associated with these membranes.

Since animals treated this long with DOCA and normal dietary salt levels exhibit DOCA escape in vivo, the persistence of the DOCA effect on both in vitro collecting duct transport and on the basolateral membrane surface area might suggest that there is another unknown regulator which is present in vivo and serves to reduce Na^+ absorption by the collecting duct during DOCA escape but which is absent in the in vitro situation. However,

Hass et al. (9) recently demonstrated that net Na^+ absorption by the cortical and/or outer medullary collecting duct was enhanced in DOCA-treated rats, but the delivery of Na^+ to the late distal tubule was increased by more than 2-fold compared to normal or salt-loaded control animals. They concluded that the DOCA escape phenomenon was due to the increased Na^+ delivery to the collecting duct which exceeded the enhanced Na^+ absorptive capacity produced by DOCA.

Table 5. Effect of Long Term Steroid Treatment on Basolateral Membrane Area of Rabbit Cortical Collecting Tubules.

Treatment	Surface-to-Volume Ratio ($\mu m^2/\mu m^3$)	
	Light Cells	Dark Cells
Control	3.1	2.2
DOCA (11-18 days; 2 mg/kg/day)	5.9	2.5
Dexamethasone (11-18 days; 2 mg/kg/day)	5.1	2.1

Data of Wade et al. (8).

However, it is still possible that factors other than aldosterone may modulate Na^+ absorption and/or K^+ secretion in the collecting duct. Investigation of this possibility is of considerable importance in trying to resolve the mechanisms by which Na^+ excretion is acutely altered by maneuvers such as extracellular volume expansion or depletion. These mechanisms remain one of the most important unsolved problems in renal physiology. The suggestion that hormonal regulators other than aldosterone might alter collecting duct Na^+ absorption was made by Stein et al. (10) in interpreting their experiments in which distal tubular micropuncture was used to assess collecting tubule function in the rat during natriuresis produced either by isotonic Ringer's solution expansion, or by a hyperoncotic albumin solution. Figure 4 relates the sodium excretion observed to the tubular Na^+ delivery rate observed in micropunctured superficial distal tubules. With either type of volume expansion, distal Na^+ delivery was observed to increase. However, at any given distal Na^+ delivery rate it was observed that there was significantly less natriuresis with hyperoncotic albumin expansion than with the Ringer's solution. It should be noted that whereas both types of volume expansion increased blood volume, the hyperoncotic albumin solution should have reduced interstitial fluid volume whereas the saline infusion should have increased interstitial fluid volume. These observations were initially interpreted to indicate that the collecting duct received some signal of increased interstitial volume which led to a decrease in Na^+ absorption when volume was expanded with the isotonic Ringer's solution.

Also, Sonnenberg (11) has examined the effect of blood volume expansion on medullary collecting duct Na^+ absorption using the microcatheterization in the in vivo rat. (See Table 6) One group of animals was sham-operated and the other group of animals was adrenalectomized three days prior to the experiment. Under control, hydropenic conditions both the normal and adrenalectomized animals exhibited approximately equal Na^+ absorption. However, during blood volume expansion equivalent to 2.3% of the body weight, both the sham-operated animals and adrenalectomized animals exhibited a significant decrease in sodium absorbed in the medullary collecting duct. The lesser change observed with the adrenalectomized animals was attributed to the superimposed volume contraction which was present in these animals. These results were taken to indicate that changes in collecting duct Na^+ absorption could be brought about by changes in extracellular fluid volume status independent of changes in plasma aldosterone levels.

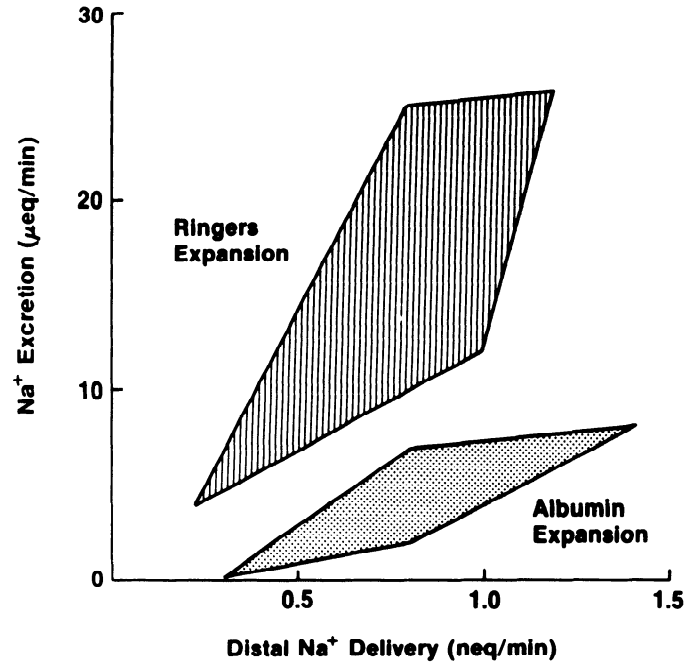


Fig. 4. The effect of volume expansion with Ringer's solution or hyperoncotic albumin solution. Data of Stein et al. (10).

However, the interpretation of these results remains controversial. The main problem is that, as discussed above, with either the microcatheterization or distal micropuncture method of assessing collecting duct function, it is difficult to exclude the effects of differential Na^+ delivery rates to superficial and juxtamedullary distal nephrons. In a more recent work, Osgood et al. (12) re-examined the effect of Ringer volume expansion on collecting duct Na^+ absorption. Based on the results of these studies, they concluded that the proximal juxtamedullary nephron absorbs less sodium than the same portion of the superficial nephron. Increased Na^+ excretion observed with volume expansion could result primarily from an increase in Na^+ delivered to the collecting duct of juxtamedullary nephrons rather than a decrease in Na^+ absorption by the collecting duct. However, the importance of this issue certainly warrants close attention to the possibility of hormonal influences other than aldosterone on collecting duct Na^+ absorption.

Table 6. Effect of Blood Volume Expansion on Medullary Collecting Duct Na^+ Absorption.

Group	% Filtered Na^+ Absorbed by Medullary Collecting Duct.	
	Control	Blood Expansion (2.3% BW)
Sham-operated	1.4	0
Adrenalectomized	1.2	0.8

Data of Sonnenberg (11).

In summary, the results of studies which have examined the collecting duct directly have shown that Na^+ is actively absorbed and K^+ actively secreted in the collecting duct. In addition, under certain circumstances such as K^+ depletion or volume depletion, net K^+ absorption may also occur. Aldosterone and DOCA-treatment in vivo enhance Na^+ absorption and K^+ secretion even in vitro, and these changes in the transport characteristics are correlated with morphological changes in the light cells of the collecting duct. Finally, the possibility may still exist that there are

other hormonal influences on collecting duct Na^+ absorption, although in these studies it becomes imperative to take into account the heterogeneity of Na^+ handling in more proximal segments of juxtamedullary as compared to superficial nephrons.

THE EFFECT OF ADH ON WATER PERMEABILITY IN THE COLLECTING DUCT

Changes in the volume flow rate and osmolality of the urine are brought about by changes in the circulating plasma levels of antidiuretic hormone (ADH). The primary biochemical events occurring in the collecting duct in the presence of antidiuretic hormone were described originally in the toad bladder (13, 14) although the primary aspects of the scheme proposed have been confirmed in the isolated cortical collecting tubule (15,16). ADH binds to receptors located on the basolateral membranes of collecting duct cells. This binding activates adenyl cyclase resulting in an acceleration of conversion of ATP to cyclic-3', 5'-AMP (c-AMP). Both in the toad bladder and in the isolated collecting duct, the primary barrier to the transepithelial transport of both water, salt and small hydrophilic solutes has been shown to be the luminal (or apical) plasma membrane. By as yet unknown intermediate mechanisms, c-AMP results in an increase in the water permeability of this membrane. In the presence of maximal plasma ADH levels, the luminal membrane water permeability is maximal, which allows osmotic equilibrium between the tubular fluid in the collecting duct and the medullary interstitium, resulting in a low urine volume flow and a maximal osmolality. The action of c-AMP on the apical membrane in the toad bladder is now known to involve protein phosphorylation reactions (17) and is also dependent upon the integrity of microtubules (18) both of which may be associated with the apical membrane.

In this section I will deal exclusively with the final effect of ADH, i.e., its effect in increasing the water permeability of the luminal membrane of the collecting duct. Water permeability in this and other systems has been traditionally assessed in two ways. First, the water permeability may be measured by imposing an osmotic gradient and measuring the volume flow which results. The permeability derived from these studies is referred to as an osmotic or flow water permeability which I will abbreviate P_f. Alternatively, the water permeability may be assessed in the absence of net volume flow by using tritiated water (THO) and measuring the tracer flux. In this case, a diffusional water permeability (P_W) is measured. In almost all cells and tissues as well as artificial membranes the universal observation has been that P_f exceeds P_W. Similar observations were made in the toad bladder and toad skin in the absence of ADH, and it was found that ADH increased P_f to a greater extent than P_W (19,20). In addition to this effect of ADH on water permeability in these anuran epithelia, ADH was observed to increase the rate of active transepithelial Na^+ transport and the permeability to small hydrophilic solutes such as urea. The classical explanation of all of these events was that ADH resulted in enlargement of aqueous pores in the apical membrane which permitted increased diffusional movement of Na^+, small solutes and water (20,21,22). In order to explain the difference between P_W and P_f on the basis of such pores, the pore radius was required to be on the order of 10-15Å. But, if the apical membrane had pores of this size, the epithelium would have been expected to exhibit high permeabilities even for moderate sized molecules, whereas observed permeabilities were low. Consequently, the existence of an outer dense diffusion barrier which limited sloute access to the underlying porous barrier was proposed (20,21,22). The existence of a porous barrier was also suported by the additional observation that water flow could produce an asymmetry of solute fluxes referred to as solvent drag (21,22).

However, more recent reassessments of this pore model have indicated several deficiencies in explaining the total response to ADH (23-27). First, by using various drugs and other treatments of the tissues, it is possible to dissociate the effects of ADH on Na^+, urea and water transport in the toad bladder (24,27,28). Second, Hays and Franki (25,26) have shown that over 80% of the resistance to water diffusion in the toad bladder epithelium is due to the presence of unstirred layers adjacent to the epithelial cell layers. These unstirred layers hinder movement of water by diffusion to a much greater extent than they restrict bulk flow of water. Third, Hays (26) has shown that the solvent drag effect is abolished when unstirred layers are eliminated.

In effect, unstirred layers are regions either adjacent to or within the epithelium in which the movements of water and solutes must occur by diffusion due to the absence of convective mixing. Unstirred layers are generally thought of as regions of the external bathing solutions which cannot be adequately mixed by convection due to experimental limitations. However, the cytoplasm of the epithelial cells themselves, as well as supporting serosal tissue elements in more complex epithelia such as the toad bladder, also serve as unstirred regions. The importance of unstirred layers associated with epithelia and individual membranes is that they serve as barriers or resistances to solute and water diffusion in series with the limiting membrane barrier. In order to understand this effect, it is helpful to think of membranes and unstirred layers as areas of resistance to diffusion. In the same way that an electrical resistor limits electric current flow, diffusion resistances limit the movement of solutes and water. In keeping with the electrical analogy, the permeability of a membrane is equivalent to a conductance, and the diffusion resistance of a membrane to a substance is equivalent to the reciprocal of the permeability to that substance. In an aqueous unstirred layer the diffusion resistance is given by the thickness of the unstirred region divided by the diffusion constant of the given substance in aqueous solution. Because unstirred layers serve as diffusion resistances, it was recognized that, if such unstirred layers were in fact large enough, they would lead to a significant underestimate of the true diffusional permeability of the luminal membrane, whereas they would have little effect on estimates of the water flow permeability because bulk water movement would not be retarded by the unstirred regions. In this way the presence of unstirred layers could account for the observation that P_f exceeded P_W and eliminate the necessity of a porous barrier which allowed hydrodynamic water flow.

Both diffusional and flow water permeabilities have been measured in the presence and absence of ADH in the isolated cortical collecting tubule (15,16,23), and in the isolated outer medullary and papillary collecting duct (23,30). Table 7 shows the measured water permeabilities in the cortical collecting tubule and, for comparison, the urea permeability.

We examined the possibility that the difference between P_f and P_W might be attributed to unstirred layers in the solutions adjacent to the epithelial cell layer in the cortical collecting tubule much as it has been responsible for a considerable portion of the disparity between the two permeabilities in the toad bladder. However, we found that such unstirred layers are prevented almost completely by the geometry and the experimental situation presented by the isolated perfused collecting tubule. First, the luminal diameter is only approximately 25μm, which is too small a solution layer to allow the establishment of significant

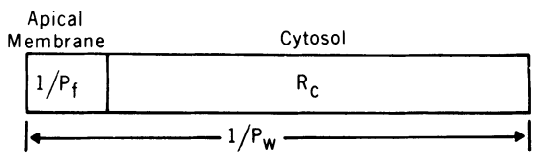
unstirred layers, particularly in the presence of luminal perfusate flow. Second, the tubule in vitro is constantly bubbled with a gas mixture which produces oscillations in the tubule which have been shown to preclude the development of external solution unstirred layers (23).

Table 7. The Effect of ADH on Water and Urea Transport.

Permeability to	-ADH	+ADH
	μm/sec	
Osmotic water flow (P_f)	20	186
THO diffusion (P_w)	5	20
Urea	0.03	0.02

Taken from data of Schafer and Andreoli (23,31) and Burg et al. (15,32).

The remaining possibility was that the difference between P_f and P_W was due to the presence of a significant diffusion resistance in the cytosol of the epithelial cell layer itself. This argument is presented in Figure 5. In this figure the luminal membrane and the cytosol are represented schematically as two series barriers to the movement of water. A resistance to diffusion is equivalent to the reciprocal of the permeability. If the movement of water through the apical membrane involved diffusion rather than flow through large pores, and if the cytosol offered little resistance to bulk flow of water, then the entire resistance to transepithelial water flow would reside in the apical membrane. The resistance to diffusion in this region can be expressed as the reciprocal of the flow permeability ($1/P_f$). Thus for osmotic water flow all of the resistance would reside in the apical membrane and the cytoplasm would offer none of the resistance. However, in the case of tracer diffusion, the cytosol would offer at least as much resistance to diffusion as an unstirred aqueous layer. In this case the resistance to tracer diffusion offered by the apical membrane would still be equivalent to the reciprocal of P_f; however, in order to explain the low value of P_W, the resistance to diffusion in the cytosol would have to be more than eight times as great as that in the apical membrane. In effect, the cytosol would have to offer at least twenty times as much resistance to the diffusion of water as would be expected for an unstirred solution layer having the same thickness (6-7 μm) as the epithelial cell layer (23).



	Diffusion Resistance (sec/cm)		
	Apical Membrane ($1/P_f$)	Cytosol (R_c)	Total
Osmotic water flow	54	0	54 ($= 1/P_f$)
THO diffusion	54	430	484 ($= 1/P_w$)

Fig. 5. The luminal membrane and cytosol of collecting duct epithelial cells as series resistances to water diffusion.

In order to measure the relative diffusion resistance of the cytosol alone, we needed a molecular probe whose transepithelial movement would be expected to be limited only by its rate of diffusion through the cytosol and not at all by the luminal plasma membrane. Highly lipophilic solutes such as butanol, pyridine and 5-hydroxyindole were used for this purpose. Because these molecules are so lipid soluble, they have extremely high permeabilities even across unmodified artificial lipid bilayer membranes (23), and their rate of transepithelial diffusion could be used to assess the diffusion resistance of the cytoplasmic layer alone.

Using these highly lipophilic solutes, we showed that the cytosolic resistance was in fact 10-20 times that of a free aqueous solution layer having the same thickness as the epithelial cell layer. Thus we concluded that the difference between the flow and diffusional water permeabilities was due (at least in part) to the resistance to diffusion afforded by the cytoplasmic resistance in series with the apical plasma membrane.

If this conclusion is correct, and the mechanism of water permeation across the apical membrane of the collecting duct is in fact by diffusion in both osmotic and diffusional water movement, the question then becomes how does ADH change the diffusional water permeability of the luminal membrane.

Pietras and Wright (33) and Levine et al. (34) have argued that the increased water permeability produced by ADH in the toad bladder might reflect a generalized increase in the fluidity, i.e., the extent of disorganization or "looseness" of the apical membrane. They supported this argument by the observation that ADH produced an increase in the permeability of the toad bladder to moderately lipophilic probe molecules whose permeability is limited by the apical membrane. Moderately lipophilic solutes are expected to cross the apical membrane primarily by a solubility-diffusion process through the hydrocarbon matrix. Consequently, an increase in the permeabilities for such solutes could be interpreted to reflect an increased disordering of the hydrocarbon matrix. We (35) also oberved this effect in the cortical collecting tubule as shown in Table 8. It can be seen that ADH approximately doubled the permeabilities of three moderately lipophilic solutes. However, we do not believe this reflects a generalized increase in the membrane fluidity. First, as shown in Table 9, the water permeability of the apical membrane of the cortical collecting tubule is considerably higher than the maximal water permeability observed in any artificial lipid bilayer membrane. This water permeability is higher even than the water permeability which can be computed for a 60Å layer of completely disorganized pure hydrocarbon (29,36). In other words, even maximally disorganized hydrocarbon layers do not have a sufficiently high water permeability to explain the water permeability observed for the apical membrane in the presence of ADH.

Table 8. Effect of ADH on Permeation of Moderately Lipophilic Solutes.

Solute	Permeability Coefficient	
	-ADH	+ADH
	μm/sec	
butyramide	0.12	0.23
Isobutyramide	0.14	0.32
antipyrene	0.25	0.40

Date of Al-Zahid et al. (35).

Another contraindication to a fluidity increase as an explanation for the effect of ADH comes from a comparsion of the activation energies for the permeation of water and moderately lipophilic nonelectrolytes. As shown in Table 10, the activation

energy for water permeation is approximately one-half of that for butyramide permeation. The different activation energies imply different rate limiting barriers in the permeation of water and these solutes. The fact that the activation energy for water permeation remains unchanged upon the addition of antidiuretic hormone implies that the mechanism of permeation is the same in the presence and absence of the hormone.

Table 9. Water Diffusion in Collecting Tubule Luminal Membrane and Lipids.

Membrane		Diffusional Water Permeability
		μm/sec
Cortical collecting tubule, apical membrane	-ADH	20
Cortical collecting tubule, apical membrane	+ADH	186
Lecithin/Decane lipid bilayers		10-40
Pure hydrocarbon, bulk phase of 60 Å thickness		40-50

Adapted from (29).

Table 10. Comparison of Activation Energies for Diffusional Permeation of Water and Moderately Lipophilic Solutes.

Permeability Coefficient	Apparent Activation Energy -ADH	+ADH
Osmotic water flow	9.4	8.9
Moderately lipophilic solutes	19.4	18-20

Data of Al-Zahid et al. (35).

Finally, it has been observed that in bilayer membranes, increased fluidity of the membrane increases the permeability of solutes and water but decreases the activation energy for permeation (37). On the other hand, in the cortical collecting tubule, ADH increases the water permeability with no change in the activation energy. Furthermore, all known artificial lipid systems which exhibit water permeabilities approaching even one-quarter of that seen for the cortical collecting tubule in the presence of antidiretic hormone, also have very high permeabilities for small nonelectrolytes such as urea, acetamide and thiourea (29,35,36). However, in the presence or absence of antidiuretic hormone the cortical collecting tubule exhibits extremely low urea and thiourea permeabilities less than 0.03 μm/sec (31,32). Our conclusion from these results is that ADH increases water permeability by increasing the number of permeation sites, and that these sites represent very narrow channels which permit only diffusional and not bulk flow movement of water molecules (29,35). Finkelstein (38) proposed the same type of mechanism for the water permeability response to ADH in the toad bladder apical membrane. As shown pictorially in Figure 6, ADH would not alter the mode of water movement across the luminal or apical membrane, but would increase the number of water channels in the membrane. The increase in permeability of the moderately lipophilic solutes in the presence of ADH in this model is attributed to separate permeation sites possibly associated with the water permeation channels. For example, as indicated by the stippled areas around the water channels, insertion of these channels in the membrane might disorganize the hydrocarbon region surrounding the channel, thus producing an increased permeability for the moderately lipophilic solutes.

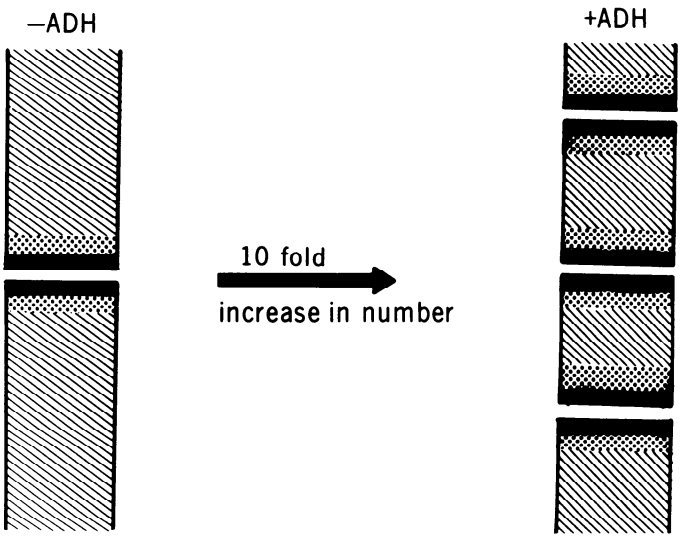


Fig. 6. The effect of ADH on the number of water permeation channels in the luminal plasma membrane of the collecting duct. It is proposed that ADH results in a tenfold increase in the number of water permeation channels in the luminal membrane of the collecting duct. Insertion of these channels into the membrane also results in disorganization of the hydrocarbon matrix of the membrane in the region of the channel.

Channels such as these have not been identified, but at least the water permeability characteristics are very closely approximated by the ionophore gramicidin (39). This ionophore is known to form transmembrane channels with an inside diameter of approximately 4 Å which can span natural and artificial lipid bilayer membranes. Furthermore, Rosenberg and Finkelstein (40) have recently shown that, because water molecules can only pass single-file through gramacidin channels, P_f would be expected to exceed P_w by ~5-fold. If analogous conditions obtain in water channels within the apical membrane of the toad bladder or the luminal membrane of the collecting duct, part of the difference between P_f and P_w could be due to this single-file effect as well as the diffusion resistance imposed by the cytoplasm.

At this point it is interesting to look at some very intriguing morphological observations made by Harmanci et al. (41) on the intramembraneous structure of the rat collecting duct. Figure 7 shows electromicrographs of replicas of freeze-fractured luminal membranes of collecting ducts. This technique exposes the inner part of the lipid bilayer of the membrane and particles embedded in the lipid matrix can be visualized. Figure 7A is a freeze-fracture preparation of the extracellular side of the internal luminal membrane of a collecting duct in the kidney of a Brattleboro rat, which has a congenital absence of antidiuretic hormone. In this preparation few intramembraneous particles are observed. Figure 7B shows the same freeze-fracture plane from the collecting duct of a Brattleboro rat treated with ADH. Numerous clusters of intramembranous particles are seen in this preparation, as indicated by the arrows. These observations suggest that particles of some form (perhaps water channels) have been inserted into the membrane interior and possibly penetrate the membrane after the addition of antidiuretic hormone. Furthermore, Kachadorian et al. (42,43) in their previous observation on the appearance of similar aggregates in the toad bladder apical membrane in the presence of ADH, showed that the number of such aggregates was proportional to the water permeability produced by the hormone, but their appearance was independent of the presence of water flow.

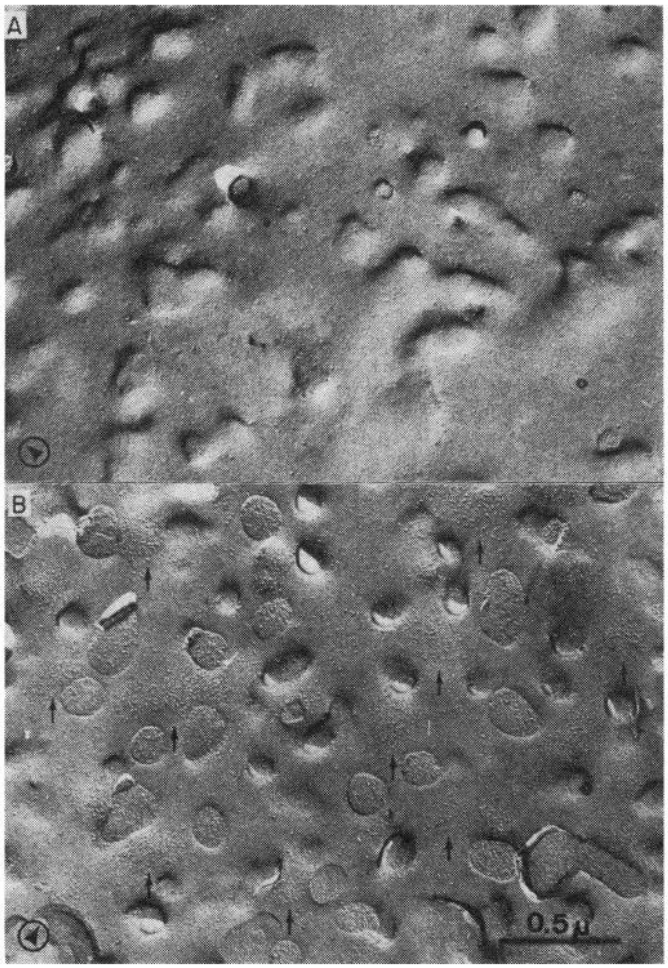


Fig. 7. The effect of ADH on intramembranous particle aggregation in luminal membranes of the collecting duct in Brattleboro rats with hereditary diabetes insipidus. A. The external freeze-fracture face of the membrane from an untreated control rat. B. The same freeze-fracture face from a rat treated with ADH. From Harmanci et al. (41) with permission.

It is very tempting to speculate that these regions of particle aggregation actually represent the water channels which have, by some unknown mechanism, been inserted into the apical plasma membrane.

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BLOOD-GAS EQUILIBRATION OF CO_2 IN PULMONARY GAS EXCHANGE OF MAMMALS AND BIRDS*

Johannes Piiper

Department of Physiology, Max Planck Institute for Experimental Medicine, D-3400 Göttingen, Federal Republic of Germany

Summary

(1) Various laboratories have reported that during rebreathing equilibrium, both in man and dog, P_{CO_2} in arterial or mixed venous blood is lower than in alveolar gas, the difference amounting up to -10 torr. In a study on isolated lung lobes of dogs and on anesthetized dogs in our laboratory this finding could not be reproduced.

(2) During steady state gas exchange in the chicken, end-expired P_{CO_2} has been found to exceed not only arterial, but also mixed venous P_{CO_2}. A detailed experimental and theoretical analysis showed that this was due to a particular action of the Haldane effect on CO_2 transfer efficiency of the cross-current air-blood arrangement in avian lungs.

(3) In dogs, during steady state gas exchange in hypercapnia, arterial P_{CO_2} has been reported to be lower than mixed expired P_{CO_2}. A reinvestigation in our laboratory did not confirm the findings: arterial P_{CO_2} was always found to be distinctly higher than mixed expired P_{CO_2} and higher than, or equal to, end-expired (alveolar) P_{CO_2}.

(4) Several sources of directional errors can be identified that tend to produce fictitious negative blood-gas P_{CO_2} differences. It is thus concluded that such findings can be considered as artifacts and that the classical view of a CO_2 equilibration in lungs leading to P_{CO_2} equalization between lung gas and end-capillary blood should be recognized as fully valid.

I. Introduction: The Problem

In the conventional analysis of pulmonary gas exchange it is assumed that equilibration of CO_2 between alveolar gas and pulmonary capillary blood is nearly complete because Krogh's diffusion constant is high for CO_2 (due to high physical solubility in tissue). Therefore, end-capillary (or arterial) P_{CO_2} should be practically equal to alveolar P_{CO_2} (Fig. 1A):

$$P_{c'CO_2} = P_{ACO_2}.$$

However, the CO_2 transfer between erythrocytes and plasma is a complex process, involving the intrinsically slow dehydration of carbonic acid, accelerated by carbonic anhydrase, and chloride-bicarbonate exchange through the red cell membrane (18). When any of these component processes does not reach equilibrium during the pulmonary capillary transit, P_{CO_2} in arterial blood will rise despite complete equilibration of end-capillary with alveolar P_{CO_2}, and will thus create a positive $(P_a - P_A)_{CO_2}$ difference. The kinetics of red cell/plasma equilibration for CO_2, H^+ and HCO_3^- has recently been reinvestigated particularly with regard to the fact that carbonic anhydrase is absent from blood plasma (17, 18, 26). The resulting overall deficit in CO_2 transfer efficacy, expressed as $(P_a - P_A)_{CO_2}$ difference, however, is extimated to be rather small, about 0.3 to 0.6 torr for normal resting conditions (2, 26). The CO_2 equilibration deficit might be even further reduced by the postulated action of carbonic anhydrase of lung tissue or of pulmonary capillary endothelium on blood plasma (8, 32). Thus it seems safe to assume the end-capillary blood to be close to completely equilibrated with alveolar gas with respect to CO_2.

The deficit in equilibration in terms of $(P_{c'} - P_A)_{CO_2}$, if there were any, should be decreased with decreasing $(P_{\bar{v}} - P_A)_{CO_2}$. With $P_{\bar{v}CO_2} = P_{ACO_2}$, finally, there should be complete equilibrium even when the kinetics of any component of CO_2 equilibration were limiting: this is the condition of primary or preformed equilibrium (Fig. 1B).

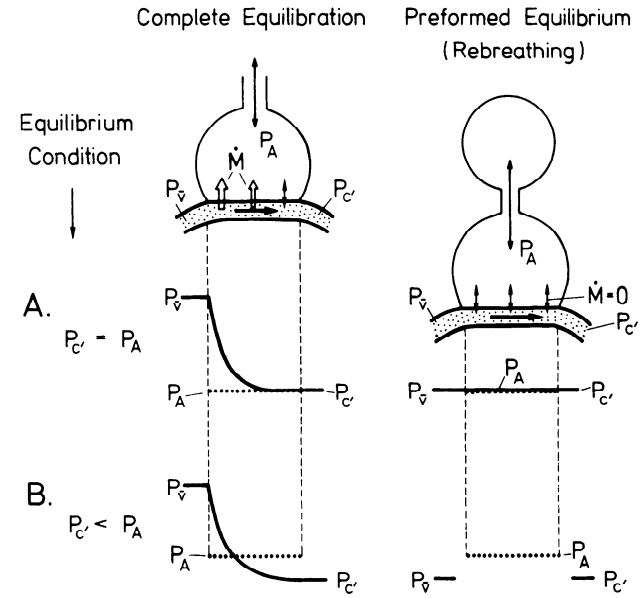

Fig. 1. Blood-gas CO_2 equilibration in lung models. All partial pressures, P, and transfer rates, $\dot{M}$, refer to CO_2. Left: steady state gas exchange, with complete blood-gas equilibration with respect to CO_2. Right: condition of no net gas-blood CO_2 transfer realized during rebreathing. A. Conventional model of equilibration leading to equalization of P_{CO_2} in blood and gas. B. Model in which P_{CO_2} in blod equilibrates to a level lower than alveolar P_{CO_2} (as suggested by some recent experimental findings, see text).

The conditions of preformed equilibrium can be achieved by *rebreathing*, i.e. by ventilation in a closed system, where the attainment of gas/blood equilibrium in terms of zero net transfer rate of CO_2 is recognized by constancy of P_{CO_2} in rebreathing gas. The rebreathing equilibration of CO_2 is the basis of numerous efforts to estimate mixed-venous P_{CO_2} for use in determination of the cardiac output. It was in the course of the development of such techniques that consistent P_{CO_2} differences between alveolar gas (rebreathing system gas) and mixed venous blood or systemic arterial blood were observed, P_{CO_2} in blood being lower than in gas in spite of apparent rebreathing equilibrium (4):

$$P_{\bar{v}CO_2} < P_{ACO_2} \quad \text{or} \quad P_{aCO_2} < P_{ACO_2}$$

Subsequently the phenomenon was observed in several laboratories (see below).

Of the numerous attempts to explain the phenomenon we mention only two:

(1) When CO_2 equilibration in mixed venous blood is not complete as it enters pulmonary capillaries, an apparent negative blood-gas P_{CO_2} difference is expected to arise. However, this

difference is only small, about 0.3 torr at rest and 1.3 torr during exercise (1), much smaller than observed values. (It should be noted that the blood-gas P_{CO_2} differences that are caused by slow kinetics in blood are negative during rebreathing, but positive in steady state with net CO_2 transfer from blood to gas; in both cases, however, they are small.)

(2) An interesting theory was proposed by Gurtner *et al.* (22), according to which a postulated negative charge on the luminal surface of pulmonary capillary endothelial cells produces a disturbance of the buffering and $H^+/HCO_3^-/CO_2$ equilibrium, with increase of P_{CO_2} in the marginal plasma layer which equilibrates with alveolar gas. The theory was criticized on grounds of energy requirement (12) and has subsequently been much disputed (13, 16, 20, 21).

Negative blood-gas P_{CO_2} differences have theoreticaly been postulated for steady state conditions as well, and have indeed been observed experimentally. In this case, the P_{CO_2} in pulmonary capillaries would start from the (high) mixed venous value and cross alveolar P_{CO_2} to approach a level below alveolar P_{CO_2} (see fig. 1B).

II. Consequences For Analysis Of Alveolar Gas Exchange

In the *ideal-alveolar air* approach of Riley and Cournand (40) P_aCO_2 is considered as equal to the effective mean P_ACO_2, and the corresponding effective mean P_AO_2, termed ideal-alveolar P_{O_2}, P_{AiO_2}, is calculated from P_aCO_2, P_IO_2 and the respiratory exchange ratio (R). In Fig. 2 the relationship is visualized in the well-known O_2 - CO_2 Diagram (39). P_{AiO_2} subdivides the alveolar-arterial P_{O_2} difference, $(P_A\text{-}P_a)O_2$, into two components:

(1) $(P_A\text{-}P_{Ai})O_2$, the "alveolar-dead-space-like effect", which is due to ventilation of unperfused or little perfused lung regions, and

(2) $(P_{Ai}\text{-}P_a)O_2$, the "shunt-like effect", which is attributable to true shunt, to perfusion of underventilated lung regions and to diffusion limitation.

It was taken as granted that at equilibrium, blood and gas P_{CO_2} were equal. What is expected to happen in the case that in equilibrium $P_aCO_2 < P_ACO_2$? The situation for this condition is shown in Fig. 2B. Here the blood-gas equilibrium is represented by *two points*, one for gas, one for blood, differing in P_{CO_2}, but not in P_{O_2} (there being no experimental evidence for gas-blood P_{O_2} differences in O_2 equilibrium):

$$P_{AiCO_2}\,(\text{gas}) > P_{AiCO_2}\,(\text{blood}) = P_aCO_2$$
$$P_{AiO_2}\,(\text{gas}) = P_{AiO_2}\,(\text{blood}) > P_aO_2$$

It is evident from comparison of Fig. 2A and B that considerable misinterpretation will arise if the gas-blood P_{CO_2} difference in equilibrium is not taken into account.

(1) The alveolar dead space ventilation, $\dot{V}_{AD}$, is underestimated from $(P_a\text{-}P_A)CO_2$. In the case of a lung without $\dot{V}_{AD}$, $(P_a\text{-}P_A)CO_2$ would not be zero, but negative, equal to the $(P_a\text{-}P_{Ai(gas)})CO_2$.

(2) The underestimation of $\dot{V}_{AD}$ would imply an underestimation of the part of $(P_A\text{-}P_a)O_2$ due to $\dot{V}_{AD}$. Therefore, the part of $(P_A\text{-}P_a)O_2$ attributable to the "shunt-like-effect" would be overestimated, leading to the following misestimations. (a) In hyperoxia and in most cases in normoxia the "shunt-like-effect" is due to the true shunt flow and to perfusion of unventilated or little ventilated lung regions. Therefore, its overestimation would mean overestimation of functional shunting. (b) In deep hypoxia the "shunt-like-effect" is mainly due to diffusion limitation in alveolar-capillary O_2 transfer. Therefore, the pulmonary O_2 diffusing capacity (D_{LO_2}) would be underestimated. (c) Similarly, the CO diffusing capacity (D_{LCO}) would be underestimated when the steady state method using P_{Ai} for CO (15) is applied.

These consequences of negative blood-gas P_{CO_2} difference in CO_2 equilibrium appeared to us important enogh to justify an experimental reinvestigation.

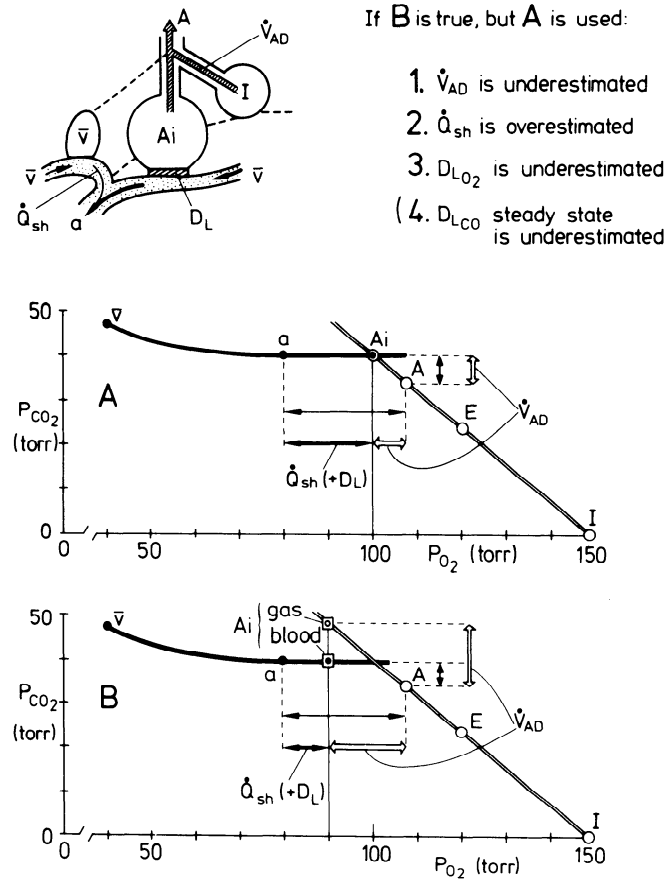

Fig. 2. Ideal alveolar air approach to analysis of alveolar gas exchange. Top left: Three-compartment lung model visualizing shunt blood flow ($\dot{Q}_{sh}$) and alveolar dead space ventilation ($\dot{V}_{AD}$). A. Representation of P_{CO_2} and P_{O_2} values in mixed venous blood ($\bar{v}$), arterial blood (a), ideal-alveolar gas (Ai), end-expired alveolar gas (A), mixed expired gas (E) and inspired gas (I) assuming that equilibration leads to equal P_{CO_2} in blood and gas (Case A in Fig. 1). B. Same as in A, but assuming that equilibration in lungs leads to P_{CO_2} in blood lower than in alveolar gas (Case B in Fig. 1). P_{AiCO_2} for blood is lower than for gas, but P_{AiO_2} for both media is the same. Top right: direction of misestimation of alveolar gas exchange parameters when model B is true, but the conventional model A is assumed. See text.

III. Rebreathing Experiments

A number of studies has been performed in which alveolar P_{CO_2} and mixed venous or arterial P_{CO_2} were simultaneously measured in rebreathing equilibrium of CO_2. Four variants of the rebreathing principle have been applied (Fig. 3).

Method A. In rebreathed isolated lungs (or lung lobes) perfused from a donor animal a long-lasting steady state is achieved. P_{CO_2} is measured in inflowing and outflowing blood and in rebreathing gas. Experiments in dog lungs (34).

Method B. The airways of a lung or a lung lobe are isolated in situ and rebreathed. Rebreathing gas P_{CO_2} is compared with mixed venous P_{CO_2} in long-lasting steady state. Experiments in anesthetized dogs (3, 22, 24, 25, 45).

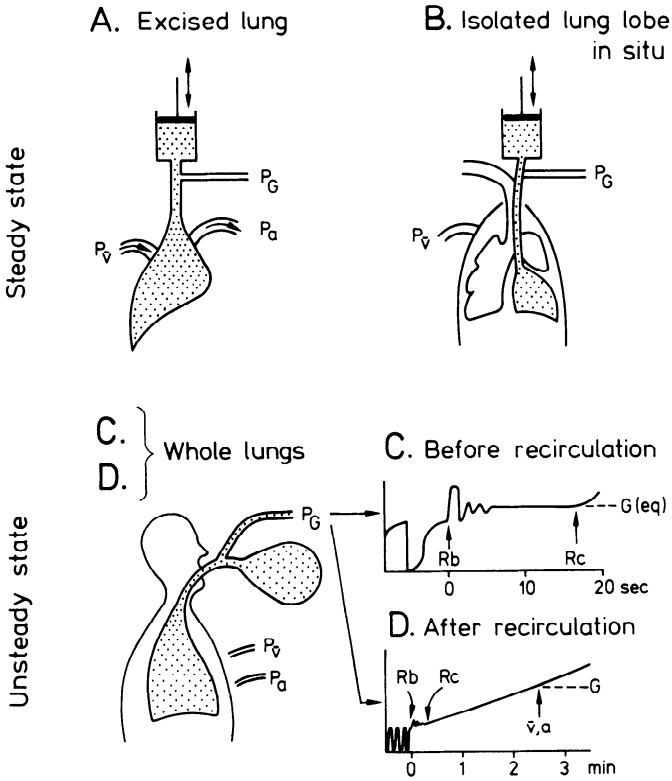

Fig. 3. The various methods (A to D) for measurement of relationships between blood and gas P_{CO_2} in rebreathing equilibrium. All partial pressures, P, refer to CO_2. G, rebreathing gas. G (eq), rebreathing gas in equilibrium with blood. Rb, start of rebreathing. Rc, onset of recirculation. See text.

Method C. A suitable gas mixture (high CO_2, low O_2) is rebreathed for about 20 seconds, gas P_{CO_2} is recorded and compared to mixed venous P_{CO_2} before rebreathing and/or to arterial P_{CO_2} measured during rebreathing. Measurements are completed before onset of recirculation. Applied to anesthetized dogs (22) and to man (normal and patients) (6, 7, 10, 14, 29, 30, 31, 37).

Method D. Longer-lasting rebreathing (several minutes) with slowly rising P_{CO_2}. Comparison of P_{CO_2} in sampled arterial (and mixed venous) blood with simultaneously recorded rebreathing gas P_{CO_2}. Measurements in anesthetized dogs (33) and in man (healthy subjects and pulmonary patients) (5, 11, 14, 19, 29, 35).

In the majority of these studies negative $(P_{\bar{v}} - P_A)_{CO_2}$ or $(P_a - P_A)_{CO_2}$, ranging from a few torr to more than 10 torr, were found in rebreathing conditions (5, 10, 14, 19, 22, 24, 29, 30, 31, 33, 35). In many cases negative blood-gas P_{CO_2} differences were not seen at rest but only in exercise. In some cases, prolonged rebreathing apparently abolished the blood-gas P_{CO_2} difference. In other studies, negative blood-gas P_{CO_2} differences were not observed in any experimental condition (3, 6, 7, 25, 34, 37).

The high degree of overall scatter, but also the consistent differences between the results obtained by different groups of investigators suggest that directional errors are involved. In fact, a number of sources of error leading to overestimation of alveolar gas P_{CO_2} and to underestimation of blood P_{CO_2} can be identified.

1. Loss of CO_2 from sampled blood can easily occur during sampling, during transfer into CO_2 electrode, or inside the electrode by diffusion, particularly when P_{CO_2} is high.

2. In many cases, body temperature has apparently not been measured. Particularly in exercise, rapid increases of deep body (core) temperature may occur, by about 2°C. If P_{CO_2} is then measured at 37°C, the cooling of blood will decrease its P_{CO_2} by several torr. Furthermore, it may easily happen that the effective electrode temperature is lower than the thermostat temperature.

3. When body temperature is underestimated, water vapor saturation pressure in alveolar gas is underestimated and thereby the partial pressures of all gases, including CO_2, are overestimated.

4. End-expired gas is not saturated with water vapor at deep body temperature (36), but gas in the lung alveoli probably is. This implies that during expiration from alveoli to the measuring site all gases, including CO_2, are concentrated in terms of partial pressure, resulting in an overestimation of alveolar P_{CO_2}.

5. Onset of recirculation can occur after 10 seconds in exercise and in many cases is not easily identified in the CO_2 recording. The effect is overestimation of alveolar P_{CO_2} with Method C.

6. When the initial rebreathing bag P_{CO_2} is too high, recirculation may set in before the true equilibrium has been reached. In such a case a "pseudoplateau" of CO_2 is recorded at a higher than equilibrium P_{CO_2} with Method C.

7. Since in Method D, an O_2-rich rebreathing mixture must be used, P_{CO_2} of oxygenated venous blood is measured, which is considerably higher than true mixed venous P_{CO_2} by virtue of the Haldane effect.

8. Another problem with method D is the requirement of correct timing for blood samples relative to the gas record since P_{CO_2} is progressively rising. Circulation time in a cannulated or catheterized vessel can easily be prolonged whereby a fictitious negative blood-gas P_{CO_2} difference would be generated.

Although the effects of each of the above factors may be small, their summation may easily produce large artifacts.

In our laboratory the rebreathing equilibrium of CO_2 was reinvestigated in anesthetized dogs using all the Methods, A to D, with particular care to avoid all the above-mentioned sources of error by appropriate improvements in techniques (42). Moreover, conditions predicted from theory (22) to enhance generation of negative blood-gas P_{CO_2} diferences in equilibrium (high cardiac output, high P_{CO_2}, low pH) were produced. The results are shown in Table 1. No blood-gas P_{CO_2} differences significantly different from zero were found with any method.

This result was interpreted to suggest very strongly that the previously reported negative blood-gas P_{CO_2} differences in rebreathing CO_2 equilibrium were artifacts due to insufficient techniques.

Table 1. Blood-gas P_{CO_2} differences in rebreathing equilibrium in anesthetized dogs (from Scheid et al. (42). P_{CO_2} in torr. Mean values ± SD. n, number of dogs. m, number of measurements.

	Method					
	A	B	C	D	Overall mean	
$(P_{\bar{v}} - P_A)_{CO_2}$	+ 1.1 (± 1.8)	- 0.2 (± 2.6)	+ 0.2 (± 3.2)	+ 0.1 (± 2.8)	+ 0.6 (± 2.4)	
$(P_a - P_A)_{CO_2}$	+ 0.6 (± 1.9)			- 1.1 (± 1.4)		+ 0.1 (± 1.9)
n	9	3	5	3	20	12
m	89	25	22	36	172	125

IV. Blood-Gas CO_2 Equilibrium In Bird Lungs

Davies and Dutton (9) found in chickens during steady state of gas exchange that end-expired P_{CO_2} ($P_{E'CO_2}$) exceeded mixed venous P_{CO_2}, particularly in hypercapnia produced by adding CO_2 to inspired gas. Since this result could not be explained by the existing models for gas exchange in avian lungs (see Scheid, this issue), it was attributed to equilibration of blood to a P_{CO_2} value lower than gas P_{CO_2} (see Figs. 1B and 4B).

The finding was reproduced in our laboratory on chickens (38). However, in rebreathing equilibrium (using Method C, Fig. 4) there was no P_{CO_2} difference between mixed venous blood and rebreathing gas, intimating that also in avian lungs blood-gas CO_2 equilibration led to P_{CO_2} equalization.

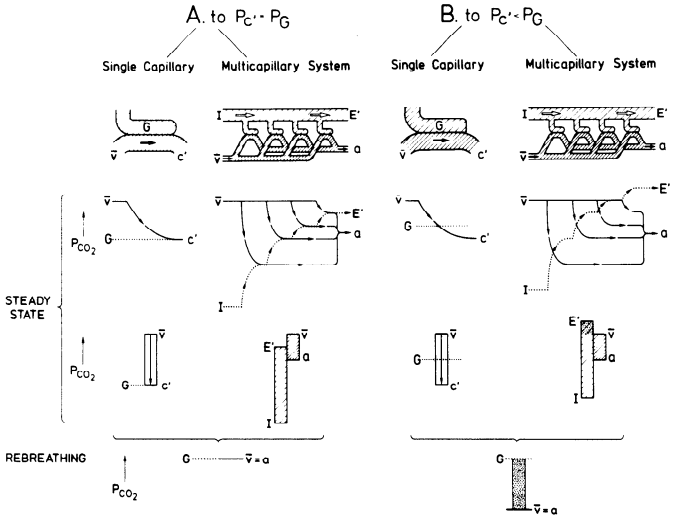

Fig. 4. CO_2 equilibration in bird lung models for steady state gas exchange and for rebreathing equilibrium. A, conventional model of equilibration, leading to $P_{c'} = P_G$. B, equilibration leading to $P_{c'} < P_G$. The parabronchi of avian lungs are represented by the serial multicapillary or cross-current model composed of multiple single capillary units arranged in series with respect to gas flow, but in parallel regarding blood flow. Equilibration model A leads to $P_a < P_{E'}$ due to the fact that $P_{E'}$ represents the gas phase of the downstream end whereas P_a is obtained as an (appropriately weighted) average of $P_{c'}$ of all blood capillaries. In equilibration model B, in which for every capillary $P_{c'}$ is lower than $P_{G'}$ the condition of $P_{\bar{v}} < P_{E'}$ can be achieved provided the difference $P_{c'} - P_G$ is sufficiently negative for the individual capillaries. In rebreathing equilibrium (bottom part of figure), the blood-gas P_{CO_2} difference should be negative for Model B, zero for Model A.

How can the finding of negative $(P_{\bar{v}} - P_{E'})_{CO_2}$ during steady-state gas exchange in avian lungs be explained? The solution of the problem was found in the peculiar action of the Haldane effect (= effect of oxygenation on the position of blood CO_2 dissociation curve) in the serial multicapillary or cross-current gas exchange system that is assumed to be realized in avian lungs.

The mechanism is schematically illustrated in Fig. 5. In each element (I to IV) of the parabronchial lung model complete blood-gas P_{CO_2} equalization is assumed (as in Fig. 4A). The characteristic property of the serial multicapillary model is that the expired gas of an element is functionally the inspired gas of the element following down-stream, whereby a progressive fall of P_{CO_2} and rise of P_{CO_2} along the parabronchus is produced. Towards the down-stream end of the parabronchus P_{CO_2} has come close to $P_{\bar{v}CO_2}$, and little CO_2 is given off by the blood. However, due to the shape of the O_2 dissociation curve, the O_2 uptake is but little affected, and by virtue of the Haldane effect, the O_2 uptake produces an increase of blood P_{CO_2}. At a gas exchange ratio (R) of about 0.3 the loss of CO_2 from blood and the liberation of CO_2 by the Haldane effect are equal, so that CO_2 is released from blood to lung gas without change in blood P_{CO_2}. When the R falls below 0.3, blood P_{CO_2} increases in the gas exchange element (element IV in Fig. 5). Important is now that the gas leaving the last element (IV) is the expired gas of the whole system. It follows that end-expired P_{CO_2} is higher than $P_{\bar{v}CO_2}$ whenever R falls to below 0.3 at the downstream end of the parabronchus. Quantitative model calculations were in good agreement with this explanation (38).

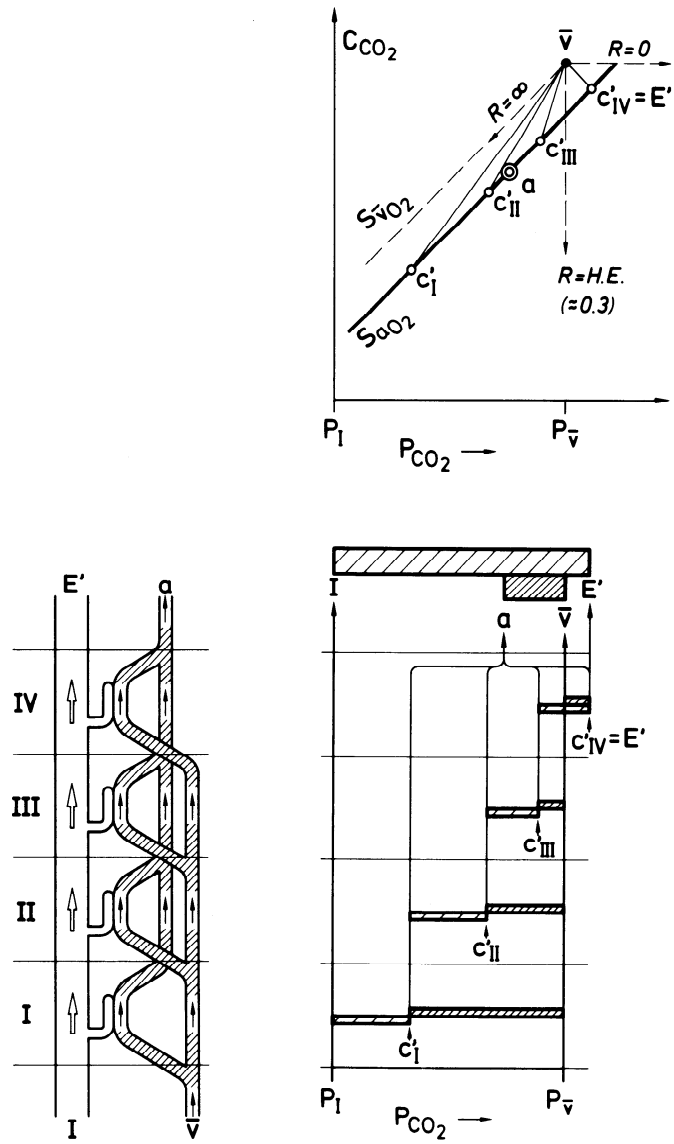

Fig. 5. CO_2 in the multicapillary model with consideration of the Haldane effect. Bottom left: serial multicapillary model. Top right: CO_2 dissociation curve of mixed venous blood (O_2 saturation $S_{\bar{v}O_2}$) and of arterialized blood (S_{aO_2}). The endcapillary blood of the elements I to IV is represented by the points c'_I to c'_{IV}, their mixture yields arterial blood (a). The gas exchange ratio lines, departing from the mixed venous point ($\bar{v}$), are drawn for R = ∞ (no net O_2 transfer), R = 0.3 (CO_2 transfer at constant P_{CO_2}, due to the Haldane effect) and R = 0 (no CO_2 transfer). Bottom right: visualization of P_{CO_2} equilibration in the single elements and in the multicapillary system.

V. Man And Mammals In Steady State Gas Exchange

In man and other mammals usually a positive $(P_a\text{-}P_A)CO_2$ difference is observed and explained as due to alveolar dead space ventilation (see above). Gas-blood P_{CO_2} equilibration to a negative $(P_a\text{-}P_A)CO_2$, if present, could be concealed by effect of alveolar dead space ventilation. That this may be the case, is evidenced by the following experimental findings.

(1) In exercise end-expired P_{CO_2} is frequently observed to exceed arterial P_{CO_2} (28, 44). But this phenomenon is easily explained as due to an averaging error in presence of increased fluctuations of alveolar (and arterial) P_{CO_2} at exercise: mean alveolar P_{CO_2} turns out to be not higher than (mean) arterial P_{CO_2}.

(2) Robertson and Hlastala (41) compared the pulmonary excretion of CO_2 in anesthetized dogs with that of 5 inert gases of differing solubility, infused intravenously. They found the excretion of CO_2 to be higher than predicted from the behavior of the inert gases. The results were best explained by assuming a negative $(P_a\text{-}P_A)CO_2$ of 5 torr.

(3) The most striking experimental results have been contributed by Jennings and Chen (27). They found in resting conscious dogs that the P_{CO_2} difference between arterial blood and mixed expired gas became clearly negative in hypercapnia (Table 2). With 10% inspired CO_2, mixed expired P_{CO_2} was even higher than mixed venous P_{CO_2}. Gurtner *et al.* (23) report qualitatively similar findings in dogs subjected to extreme hypercapnia, P_{CO_2} difference between mean expired gas and blood amounting to 80 torr with 80% CO_2 in inspired gas.

Table 2. P_{CO_2} in awake dogs breathing air and hypercapnic (and hypoxic) gas mixtures (after Jennings and Chen (27), Table 4). P_{CO_2} in torr. Mean values ± 95% confidence limits. n, number of dogs.

F_{ICO_2}	0	0.05		0.10
F_{IO_2}	0.21	0.21	0.10	0.08
P_{aCO_2}	32 (± 4)	39 (± 3)	38 (± 2)	67 (± 7)
$(P_a\text{-}P_{\bar{E}})CO_2$	+ 9 (± 2)	- 4 (± 3)	- 4 (± 3)	- 10 (± 4)
n	6	6	7	4

The occurrence of negative blood-gas P_{CO_2} differences in hypercapnia, but not in normocapnia, may have two reasons. (a) In hypercapnia all P_{CO_2}, differences in lungs are much reduced, in proportion to the difference between inspired and end-expired P_{CO_2}, due to enhanced ventilation. Therefore, all inhomogeneity effects, particularly those due to dead space (both anatomical and alveolar), would be much reduced and the P_{CO_2} difference between expired gas and arterial blood would be predominantly determined by blood-gas equilibration proper. (b) According to the charged membrane hypothesis of Gurtner *et al.* (22) the negative blood-gas P_{CO_2} difference should increase with increasing P_{CO_2}.

On the other hand, also the probability and the extent of artifacts in determination of P_{CO_2} due to inadequate techniques are expected to increase with increasing P_{CO_2}. Of the sources of directional error listed in Section III, the points 1 to 4 pertain also to steady state measurements. In particular the loss of CO_2 and the temperature effects may be of considerable importance.

In our laboratory the experiments of Jennings and Chen (27) were duplicated on anesthetized dogs and particular attention was paid to all the above-listed sources of error (43). The surprising result was that the P_{CO_2} difference between arterial blood and mixed expired gas was always clearly positive. The arterial-to-end-expired P_{CO_2} difference was positive in normocapnia and decreased to practically zero in hypercapnia, but did not become negative to any significant degree (Table 3).

Table 3. P_{CO_2} in anesthetized dogs breathing air and hypercapnic (and hypoxic) gas mixtures (after Scheid *et al.* (43) and unpublished). P_{CO_2} in torr. Mean values ± 2 SE (=95% confidence limits). n, number of dogs. m, number of measurements.

F_{ICO_2}	0	0.05		0.10	
F_{IO_2}	0.21	0.21	0.10	0.21	0.10
P_{aCO_2}	47 (± 3)	46 (± 1)	44 (± 1)	77 (± 1)	76 (± 1)
$(P_a\text{-}P_{E'})CO_2$	+ 5.1 (± 0.8)	+ 0.9 (± 0.2)	+ 2.3 (± 0.4)	+ 0.1 (± 0.2)	+ 0.4 (± 0.2)
$(P_a\text{-}P_{\bar{E}})CO_2$	+ 22.3 (± 6.4)	+ 4.4 (± 0.6)	+ 4.8 (± 0.4)	+ 2.2 (± 0.4)	+ 3.4 (± 0.4)
n	7	7	5	7	2
m	21	30	15	31	6

VI. Conclusion

We conclude that the reported negative blood-gas P_{CO_2} differences in CO_2 equilibration or CO_2 equilibrium are not convincing and may be due to artifacts. Therefore, the classical view of CO_2 equilibration in lungs leading to P_{CO_2} equalization between lung gas and end-capillary blood should be recognized as fully valid.

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RESPIRATION AND CONTROL OF BREATHING IN BIRDS*

Peter Scheid
Abteilung Physiologie, Max-Planck-Institut für experimentelle Medizin,
3400 Göttingen, Federal Republic of Germany

Summary

1. The avian respiratory system comprises two separate structures: the air sacs, mainly for ventilation, and the parabronchial lung, for gas exchange. The parabronchi are long tubes, open at both ends.

2. The direction of air flow through the parabronchi is the same during inspiration and expiration. Aerodynamic mechanisms are partly responsible for this unidirectional flow.

3. The cross-current system appears to be a suitable model for a quantitative evaluation of gas exchange between the air capillaries and blood capillaries in the periparabronchial tissue. Unidirectional air flow appears to be of only little advantage to the effectiveness of gas exchange in this model.

4. Single-unit recordings from vagal afferents have shown the existence of intrapulmonary receptors which increase their discharge rate when lung gas P_{CO_2} is lowered, but are insensitive to stretch. The ventilatory response to CO_2, particularly when carbonic anhydrase is blocked, suggests an important role of intrapulmonary CO_2 receptors (IPC) in the control of breathing. Considering the location of IPC in the parabronchial lung, unidirectional air flow may provide optimal conditions for their operation during normal breathing.

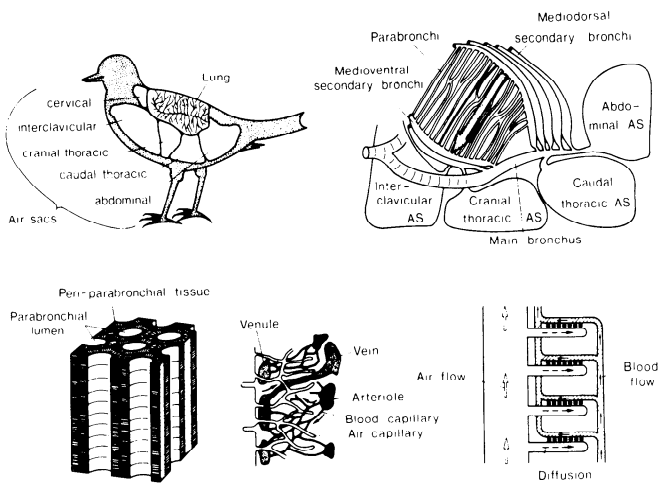

Fig. 1. Schema of the respiratory system in birds. It comprises lungs and air sacs. Gas exchange takes place in the periparabronchial tissue where fine air capillaries meet similarly fine blood capillaries. The serial multicapillary or cross-current system is apt to describe quantitatively gas exchange in the avian lung.

I. Anatomy Of The Respiratory System

The structure of the avian respiratory system is distinctly different from that of other vertebrates, particularly from the well-studied alveolar lung of mammals. Figure 1 is a schema to show that the respiratory tract comprises the *lung,* where gas exchange with the blood takes place, and a number of spacious *air sacs,* which are expanded and contracted with the chest wall by the action of respiratory muscles and provide thus ventilation in the respiratory cycle. The lung constitutes an assembly of long narrow tubes, the *parabronchi,* from which departs in radial direction a meshwork of very fine (some μm) *air capillaries* which entwine equally fine *blood capillaries* in their path from arterioles in the periphery of the periparabronchial tissue towards the collecting venules near the parabronchial lumen. Important progress in the anatomy and histology of the avian respiratory tract is due to work of King and Duncker and their collaborators (1, 9, 10, 11, 15, 16).

II. Ventilation Of The Lung (26a)

1. Direction of air flow through the parabronchial lung

In birds, like in most mammals, ventilatory gas flow is provided by the action of respiratory muscles expanding and compressing the rib cage and the underlying air sac system, which thus constitutes a reciprocating pump for ventilatory air. In mammals, the bronchial tree ends blindly in the gas exchanging alveoli, and the direction of air flow in the bronchi must thus be reciprocating within the respiratory cycle. In birds, however, the parabronchi are open at both ends and thus allow air to flow in either direction. It has long been debated (a) if the parabronchi are ventilated during both respiratory phases, inspiration and expiration; and (b) in which direction gas passes through the parabronchi (22, 35).

All earlier hypotheses on the pattern of air flow were based on indirect experimental approaches and observations, until it became recently possible to implant small flowmeter probes at key sites into the bronchial system of spontaneously breathing birds (3, 5, 29). The results showed that (a) air flows through the lungs during both respiratory phases; (b) the air flow direction is the same during inspiration and expiration, *viz.* from mediodorsal to medioventral secondary bronchi (see fig. 1). This pattern of flow, which is commonly referred to as unidirectional air flow, applies to birds at rest; under heat stress; in anethesia; and even to pump ventilated animals. These results settled the main controversy between the bidirectional flow theory of Zeuthen (36) and the unidirectional hypothesis of Hazelhoff (14) and others. Figure 2 summarizes the pattern of gas flow in the avian respiratory system.

2. Mechanisms responsible for flow rectification

It is tempting to assume valves to control air flow in the lungs and thus to provide unidirectional air flow. But valves have never been demonstrated by anatomists. Scheid and Piiper (29) have shown that air flow remains unidirectional in pump ventilated relaxed animals, and even post mortem. Further experiments (3, 4, 32) suggest that the structure of the respiratory system enables aerodynamic mechanisms to become operative in directing air flow. They would include (a) Bernoulli effect; (b) local jet formation; (c) detachment of boundary layers. This subject is not yet fully understood.

III. Parabronchial Gas Exchange (26a)

1. Significance of unidirectional air flow for gas exchange: the counter-current hypothesis

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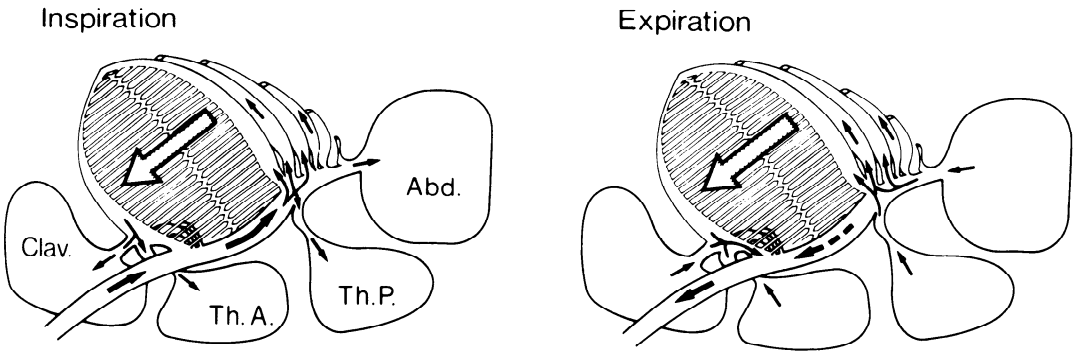

Fig. 2. Air flow pattern in the respiratory system during inspiration and expiration.

Anatomical evidence (9, 10) suggests that unidirectional air flow is a universal phenomenon amongst birds. It is therefore of interest to identify the significance of this complex flow pattern. A tempting assumption is that unidirectional air flow is of advantage to gas exchange.

Schmidt-Nielsen (34) has proposed that a counter-current system is realized for gas exchange in the parabronchial lung. The high efficiency of this system, which has been identified to operate in fish gills, would be of particular advantage to birds flying at high altitude. Reversal of air flow within the respiratory cycle would functionally convert the counter-current into a co-current system which is known to possess a particularly poor gas exchange efficiency. Thus, unidirectional air flow would be of advantage to, if not necessary for, gas exchange in the parabronchial lung provided it operates as a counter-current system.

A counter-current system would require that gas flow and blood flow in the gas exchanging region are arranged in parallel. The anatomical descriptions, however, did apparently support a different model, which Scheid and Piiper (28) had described as a *cross-current system*.

2. The cross-current system

Essential structural parameters for the cross-current model (see fig. 1) are:

(a) Blood capillaries reach contact with air capillaries originating from an only small portion along the parabronchus;

(b) With respect to air flow, the blood (and air) capillaries are arranged in series.

Figure 3 illustrates the arrangement of blood capillaries and air capillaries in the cross-current system in which bulk flow of parabronchial air and blood flow in blood capillaries functionally cross each other. The partial pressure profiles in gas and blood (fig. 3) show that, while arterial blood derives as a mixture from all capillaries, end-parabronchial gas partial pressures reflect those in blood of the last blood capillary, where arterialization is only small. This results in an overlap of the partial pressure ranges in gas and blood (arrows in fig. 3), whereby arterial P_{O_2} can exceed end-parabronchial ($\approx$ end-expired) P_{O_2}, indicating the high gas exchange efficiency of the cross-current system (23).

3. Counter-current *vs.* cross-current system

An important feature of the cross-current system is that its gas exchange performance is independent of the flow direction. In fact, reversal of air flow would simply change the serial order of the blood capillaries without affecting arterial blood, which derives as a mixture from all capillaries. Hence, if this model operates in the avian lung, the significance of unidirectional air flow would not easily relate to parabronchial gas exchange.

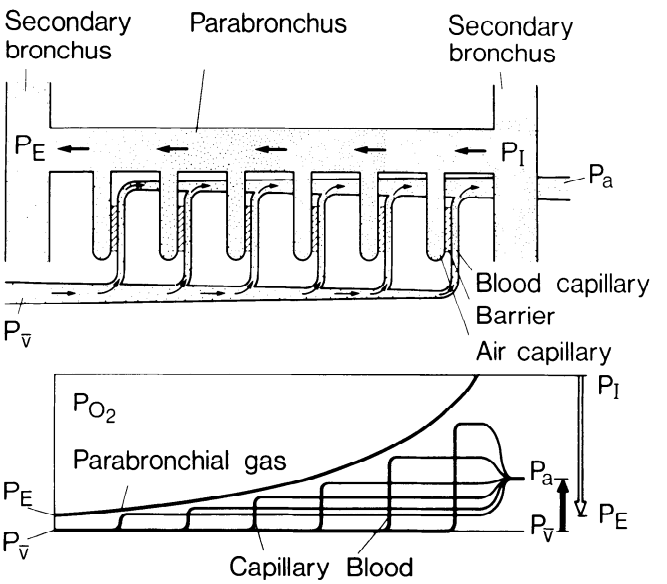

Fig. 3. Model of the parabronchus with air capillaries and blood capillaries. Below, P_{O_2} profiles in parabronchial gas and blood. Arrows to the right show overlap in gas and blood partial pressures as an expression of high gas exchange efficiency (see text).

To test if the counter-current or the cross-current model applies for gas exchange, we have conducted an experiment in the duck (30) which is schematically shown in fig. 4. The schema shows the main bronchus, connected to a caudal air sac, with a mediodorsal and a medioventral secondary bronchus originating from it. The parabronchus is shown to contact blood capillaries in a parallel-current (left) or cross-current arrangement (right). By blocking the main bronchus, as shown in fig. 4, a steady stream of air could be passed through the parabronchial lung in either direction, from caudal to cranial or from cranial to caudal, and partial pressures were measured in gas entering (P_I) or leaving the lung (P_E) and in arterial (P_a) and mixed venous blood ($P_{\bar{v}}$).

The idea of the experiment was to observe the effects of reversal of air flow on gas exchange. If the parallel-current system operates, gas exchange efficiency would be particularly high with flow in caudo-cranial direction, as indicated by the potential overlap in gas and blood partial pressure ranges; but would be seriously reduced when flow is reversed to cranio-caudal direction. In this case, overlap of gas and blood partial pressures would be impossible. On the other hand, existence of the cross-current system would render gas exchange efficiency insensitive to reversal of air flow. In particular, a partial pressure overlap would be possible during both flow directions.

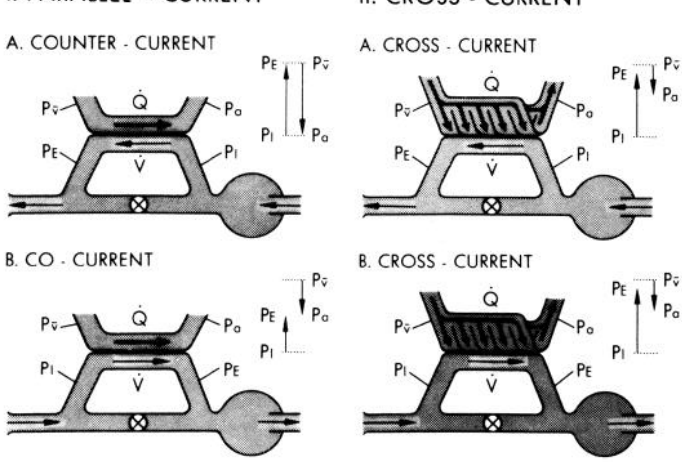

Fig. 4. Schema to show effects on gas exchange of flow reversal in a parallel-current (left) and cross-current (right) system. See text for details.

Results showed (a) no change in blood partial pressures upon flow reversal, indicative of the cross-current system; (b) a partial pressure overlap during both flow directions, which is in conflict with the hypothesis of counter-current gas exchange in avian lungs.

4. Diffusion in air capilaries

The cross-current model was analyzed (23, 28, 30) under the simplifying assumption that the air capillaries offer no diffusion resistance so that there would be no significant gradient of gas partial pressures into the air capillaries. However, it is known for mammalian lungs that such gas concentration gradients may well occur over small distances in peripheral airways, commonly referred to as stratification (21). While both diffusion and convection tend to reduce stratificational effects in alveolar lungs, diffusion is the only mechanism for gas mixing in the air capillaries (fig. 5). This is because the air capillaries end blindly in some bird species, and even in those where neighboring air capillaries communicate (9), there is no pressure difference between adjoining parabronchi to provide convective flow in the air capillaries.

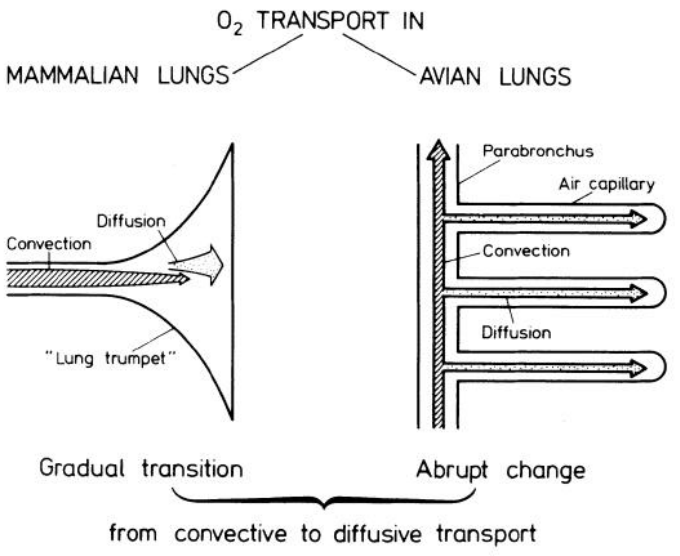

Fig. 5. Gas transport by convection and diffusion in alveolar and in parabronchial lungs.

Zeuthen (36) and Hazelhoff (14) have assessed the diffusional resistance offered by the air capillaries to be insignificant, even when O_2 uptake is enhanced during flight. Scheid (26) has criticized the models underlying their calculations and has theoretically re-assessed the problem using a model which takes account of the anatomical arrangement of air capillaries and blood capillaries. His conclusion was that, while the diffusional resistance imposed by air capillaries could safely be neglected at rest, it may contribute to limiting respiratory gas exchange during flight. Recently, Crank and Gallagher (8) have performed similar calculations with similar conclusions. Experimental support for the insignificance of diffusional resistance in air capillaries at rest was provided by Burger *et al.* (6).

5. Conclusions

It may then be concluded that the cross-current system operates in avian lungs and may be utilized to analyze quantitatively parabronchial gas exchange (6). This system is particularly effective for gas exchange, allowing P_{CO_2} in expired air to exceed not only arterial but also mixed venous levels (18; cf. contribution by Piiper in this issue), and likewise for O_2. However, for the cross-current system, even when considering gas transport in air capillaries, unidirectional air flow has no apparent advantage. It was suggested (22) that the unidirectional air flow pattern would prevent flow reversal and thus prevent functional breath-holding conditions which would be particularly disadvantageous as the parabronchial gas volume is comparatively small. However, recent experimental evidence (33) does not support this view. It must then be concluded that unidirectional air flow has no apparent advantage for parabronchial gas exchange.

IV. Intrapulmonary CO_2 Receptors

It has recently been shown that birds are equipped with a particular lung receptor system sensitive to CO_2. We shall review the evidence for these receptors and their involvement in the control of breathing and shall then investigate if the unidirectional flow parttern in bird lungs may have significance for these receptors.

1. Intrapulmonary CO_2 receptors

King *et al.* (17) recorded single unit activity from fine vagal strands in the chicken and found units that discharged in phase with breathing. The primary stimulus for these afferents (stretch or change in respiratory gas composition) remained unknown, although Peterson and Fedde (20) were able to alter ventilation in the chicken by changing CO_2 in the vascularly isolated chicken lung, suggesting CO_2 sensitive lung receptors. Fedde *et al.* (13) conducted experiments in the duck in an attempt at separating the two potential stimuli for intrapulmonary receptors, stretch and CO_2.

Their results are summarized in fig. 6. In A, the activity of a single unit is shown at five different levels of lung CO_2 (P_{ICO_2}) both at low (left) and high (right) intrapulmonary pressure (P_{ip}). This unit exhibited a distinct sensitivity to CO_2, reducing its activity as the CO_2 level was increased; but it was apparently insensitive to stretch. The dynamics of the response to a step change in lung CO_2 (B) showed a short delay (<1 sec), suggesting an intrapulmonary location. Ventilation of the animal with a respiratory pump produced cyclic variations of the activity of the unit (C).

Fedde *et al.* (13) concluded from similar results in a number of units that these vagal afferents

(a) are sensitive to CO_2 and not to stretch;
(b) are located in the lung.

The terms intrapulmonary CO_2 receptor or intrapulmonary chemoreceptor (IPC; 7) are commonly used.

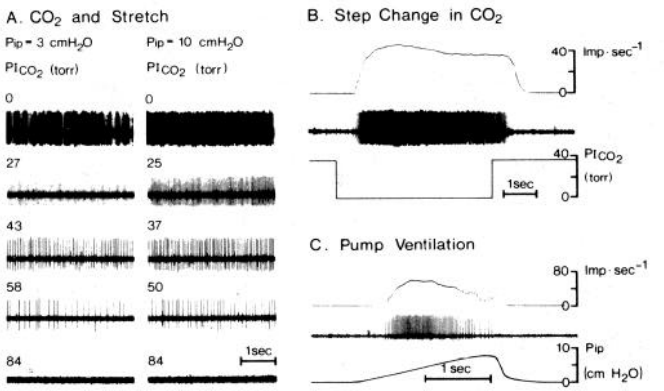

Fig. 6. Summary of observations on an intrapulmonary CO_2 receptor (IPC) in the duck lung.

Scheid *et al.* (31) have attempted to localize IPC by directing flows of pure CO_2 to various parts of the bronchial system. They concluded that IPC are located within the parabonchi, clustering about their caudal ends (close to the mediodorsal secondary bronchi). Although anatomical demonstration of IPC is still lacking, and other authors, using different physiological techniques, have proposed different patterns of distribution of IPC in the lung (7, 19), a potential preferential location of IPC in the lung may be of interest for identifying the significance of unidirectional air flow (see below).

2. Contribution of IPC to the control of breathing

Experimental evidence suggests that IPC are potentially involved in the control of breathing; however, their exact role is not known (2, 12, 25).

In recent experiments, Powell *et al.* (24) have studied the ventilatory response to inhaled CO_2 in awake ducks, before and after blockade of carbonic anhydrase with Diamox. They found (fig. 7A) that (a) ventilation increased with CO_2 (like in mammals); (b) after Diamox, ventilation at room air breathing was suppressed; (c) the ventilatory sensitivity to CO_2 was attenuated. In an additional study on the responses of IPC to CO_2 before and after Diamox (27), receptor discharge at any P_{CO_2} was found to be higher after Diamox than before, and CO_2 sensitivity of the receptor discharge to be attenuated (fig. 7B).

Using the cross-current model for parabronchial gas exchange, and considering that most of the receptors are in caudal regions of the parabronchi (see above), Scheid *et al.* (27) derived a plot of ventilation against receptor discharge (fig. 7C) which showed satisfactory correlation both at control and after Diamox. A similar plot of ventilation against (measured) arterial P_{CO_2} (fig. 7D) was less satisfactory. The authors concluded tentatively that IPC play an important role in the control of breathing, at least under the experimental conditions.

3. Significance of unidirectional air flow for IPC

Could the unidirectional flow pattern be important for the operation of IPC? Figure 8 shows a diagram of the avian respiratory system displaying the flow pattern during inspiraton (closed arrows) and expiration (open arrows). The intrapulmonary CO_2 receptors are shown to be preferentially located in caudal regions of the parabronchus, where they may

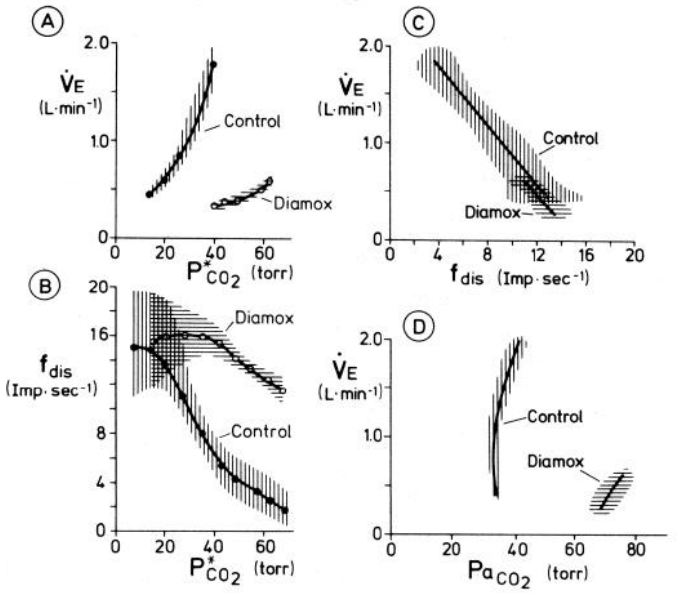

Fig. 7. Sensitivity of ventilation (A) and IPC discharge (B) to lung CO_2. P^*CO_2, calculated P_{CO_2} at the receptor site, assumed to be at the caudal end of the parabronchus. Plots A and B may be used to generate plot C which reveals a good correlation of ventilation with receptor discharge, both during control and after blockade of carbonic anhydrase by Diamox. In contrast, no good correlation is obtained for ventilation with arterial P_{CO_2} (D). In fact, in control, $\dot{V}_E$ appears to increase (with increasing inspired P_{CO_2}) despite decreasing Pa_{CO_2}.

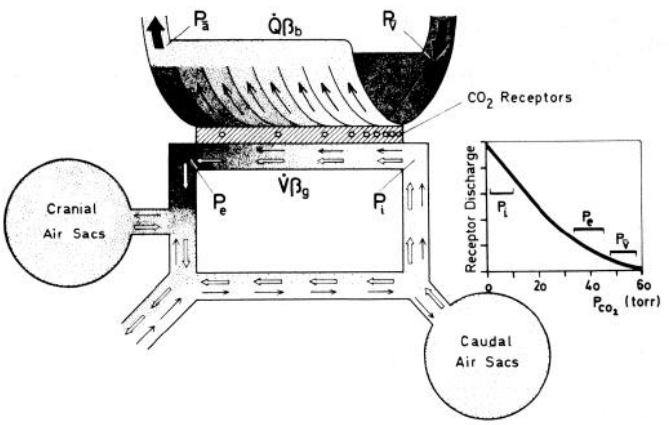

Fig. 8. Schema to show that with unidirectional flow, the CO_2 receptors located at caudal ends may encounter relatively low P_{CO_2} throughout the respiratory cycle. Hence, these receptors are expected to operate in the steep part of their sensitivity curve.

sense the P_{CO_2} of initial-parabronchial gas. During inspiration, this P_{CO_2} would be close to inspired levels (after dead space inhalation); and during expiration, it would be close to caudal air sac P_{CO_2}, which is low, compared *e.g.* with values in cranial air sacs. The following parameters affect P_{CO_2} at the receptor site, P^*CO_2, and may thus be monitored by IPC:

(a) A decrease in parabronchial ventilation, $\dot{V}$, (at unaltered pulmonary flow, $\dot{Q}$) increases P^*CO_2; an increase in $\dot{V}$ decreases P^*CO_2.

(b) An increase in $\dot{Q}$ decreases P^*CO_2; and *vice versa.*

Hence, considering (a) and (b), increasing $\dot{V}/\dot{Q}$ decreases P^*CO_2 and *vice versa.*

(c) An increase in mixed venous or inspired P_{CO_2}, or in both, increases P^*CO_2, and *vice versa.*

Particularly with changes in $\dot{V}/\dot{Q}$, the resulting changes in P^*CO_2 are much more pronounced for receptors close to the inflow end than for those further down in the parabronchus, where parabronchial gas P_{CO_2} has approached mixed venous P_{CO_2}. Furthermore, the diagram (fig. 8) of the average receptor discharge curve (13) shows that IPC are particularly sensitive at low levels of P_{CO_2}, *i.e.* in the expected range of initial-parabronchial P_{CO_2}. Hence, the location at caudal ends of the parabronchus may have distinct advantages for the receptors and their ability to monitor changes in lung gas P_{CO_2}, due particularly to changes in the relative values of $\dot{V}$ and $\dot{Q}$. Reversal of air flow would disrupt this advantage.

V. Conclusions

Experimental studies of recent years have led to the following conclusions:

1. Air flow in the avian parabronchial lung is unidirectional;
2. The cross-current system is suitable for a quantitative analysis of parabronchial gas exchange.
3. Bird lungs contain specialized receptors, which are CO_2 sensitive but not mechanosensitive.
4. These receptors may modify respiration.

On the other hand, a number of questions remain open to date and encourage further experimentation. The following problems relate to the subjects discussed in this paper:

1. Mechanisms underlying rectification of air flow in avian lungs.

2. Significance of unidirectional air flow, the gas exchange efficiency of the parabronchial lung being apparently independent of the air flow direction.

3. Role played by intrapulmonary CO_2 receptors in the adjustment of ventilation under specialized activities and under experimental situations.

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Fellowship Office
National Research Council
2101 Constitution Avenue
Washington, D. C. 20418

FOR
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NATIONAL RESEARCH COUNCIL TO ADMINISTER POSTDOCTORAL FELLOWSHIPS FOR MINORITIES

WASHINGTON, D. C. -- The National Research Council plans to award approximately 25 Postdoctoral Fellowships for Minorities in a new program designed to provide opportunities for continued education and experience in research to Black Americans, Mexican Americans/Chicanos, Puerto Ricans, and Native Americans. Fellowship recipients will be selected from among scientists, engineers, and humanities scholars who show greatest promise of future achievement in academic research and scholarship in higher education.

In this national competition supported by the Ford Foundation, citizens of the United States who are members of one of the designated minority groups, who are engaged in college or university teaching, and who hold doctoral degrees may apply for a fellowship award of one year's duration. New doctorate recipients who intend to pursue careers as college or university faculty members will also be considered.

Awards will be made in the areas of behavioral and social sciences, humanities, engineering sciences, mathematics, physical sciences, life sciences, and for interdisciplinary programs of study. Awards will not be made in professions such as medicine, law, or social work, or in such areas as educational administration, curriculum supervision, or personnel and guidance. Tenure of a fellowship provides postdoctoral research experience at an appropriate nonprofit institution of the Fellow's choice, such as a research university, government laboratory, privately-sponsored nonprofit institute, or a center for advanced study such as the Center for Advanced Study in the Behavioral Sciences, Palo Alto, California; the Institute for Advanced Study, Princeton, New Jersey; the Institute for Research on Poverty of the University of Wisconsin, Madison, Wisconsin; the Newberry Library, Chicago, Illinois; and the Woodrow Wilson Center for Scholars, Washington, D. C.

The deadline date for the submission of applications is February 1, 1980. Further information and application materials may be obtained from the Fellowship Office, National Research Council, 2101 Constitution Avenue, Washington, D. C. 20418.

The Interpretation of Visual Motion. Shimon Ullman. MIT Press, Cambridge, MA, 1979. 229 pp. illus. index, $17.50.

This book represents an attempt on the part of the author to extend the techniques of problem manipulation developed for artificial intelligence to the perception of moving visual elements. The author starts out with the idea that the visual system functions mainly by the manipulation of signals and symbols. He then builds on this with a further assumption that there is a computational theory of visual perception which is independent of the physical (biological) mechanisms underlying it. For example, the different representations of the same figure in space, and its identification by the visual system as the same or different have a correspondence that can be formalized. This general statement of the problem is then made specific for particular situations, such as the Ames illusions and their effects on judgements of size and motion. In particular, the author has carefully analyzed the Ames window. This is a plano-trapozoidal construction resembling a rectangular window in perspective, which often appears in rotation as an oscillation. Many of the illusions connected with motion may be due to differential detection of motion by the peripheral retina as opposed to the macular and foveal regions. Also, in some cases, stereopsis is an important feature of the detection of distance which influences the judgement of motion. These types of motion detection should follow different computational schemes in different parts of the visual system, but there is no indication that this type of localization has even been considered. The author has a tendency to treat the whole visual system as everywhere equal, with non-interacting channels for the detection of the different components of visual perception. The author suggests several ways to test his conclusions. These however, as is appropriate to his theory, are mostly of computational nature. In many ways, the foot notes are the most useful part of the book as they often bring the author's ideas more clearly into the context of the experimental data.

At the present time, from the standpoint of one who works on the neurophysiology of the visual system and attempts to determine both the actual computations and their physiological correlates, this book is not very helpful. However, at some future time, when the visual system is more completely understood, it is certain that we will have to come to grips with the problems Dr. Ullman has formulated. Then his analysis may be more helpful. Those who are committed to the proposition that some day artificial intelligence will converge with real intelligence, will find much of interest in this book.

M. L. Wolbarsht
Duke University Eye Center
Durham, N.C. 27710

Retrospectroscope - Insights into Medical Discovery. Julius Comroe. Von Gehr Press, Menlo Park, CA, 1977. 182 pp. illus. index.

Whenever scientists get together to discuss the adversities of obtaining funds for research, the discussion is likely to develop a statement of regret that the public is not able to see the connection between basic scientific advance and widely appreciated new medical and technical achievements. Usually, the solution is visualized as a well written series of articles tracing the relationship between research in basic science and new advances contributing to the lives of people.

A few science writers have earned international repute for such an historical approach to increasing public appreciation of Science. Paul Dekruif and Ritchie Calder are among the best known of these. Physiology now has its own collection of such mini histories put together by a Past President of the American Physiological Society and a widely respected researcher in his own right, Julius Comroe.

Physiologists will get a great deal out of reading Comroe's "Retrospectroscope - Insights into Medical Discovery," for it is written in entertaining style, contains the origins of some of the most important contributions of physiology to human welfare, and covers a wide spectrum of scientific and practical advances. One chapter "Out of the Mouths of Babes" is a startling list of discoveries made by medical students. Comroe summarizes: "I believe that if, without digging further, we simply accept as the immediate 'pay-off' of medical student research the discovery of carbon dioxide, ether, nitrous oxide, insulin, heparin, mercurial diuretics, and the parathyroid glands; the proof that human emotions can profoundly affect body function; invention of the mercury manometer for measuring blood pressure; the concept that special chemicals specifically combine with special components of cells (basic to most chemotherapy); learning how to go about skin grafting and how to eliminate malaria - research by medical students has paid off handsomely. But we must add a slightly delayed 'pay-off': it converted some hesitant medical school researchers into sure-fire, brilliant investigators."

Although physiologists will be engaged by the reading of this book, it will be much better for the future of physiology if non-physiologists can be induced to absorb it. At the very least, teachers of physiology should be sure that their students are exposed to the view through the Retrospectroscope.

Orr E. Reynolds
Executive Secretary
APS