THE AMERICAN PHYSIOLOGICAL SOCIETY

Founded in 1887 for the purpose of promoting the increase of physiological knowledge and its utilization.

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The Physiologist

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

THE AMERICAN PHYSIOLOGICAL SOCIETY

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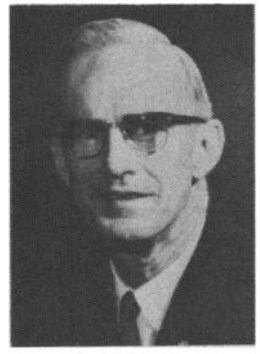

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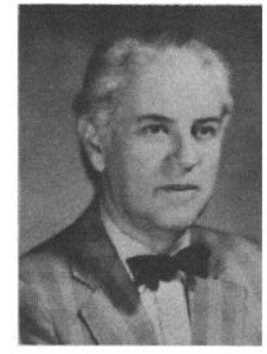

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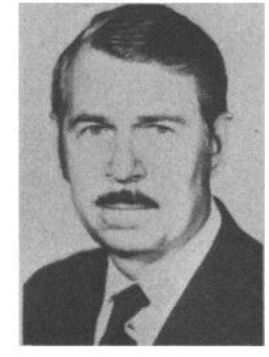
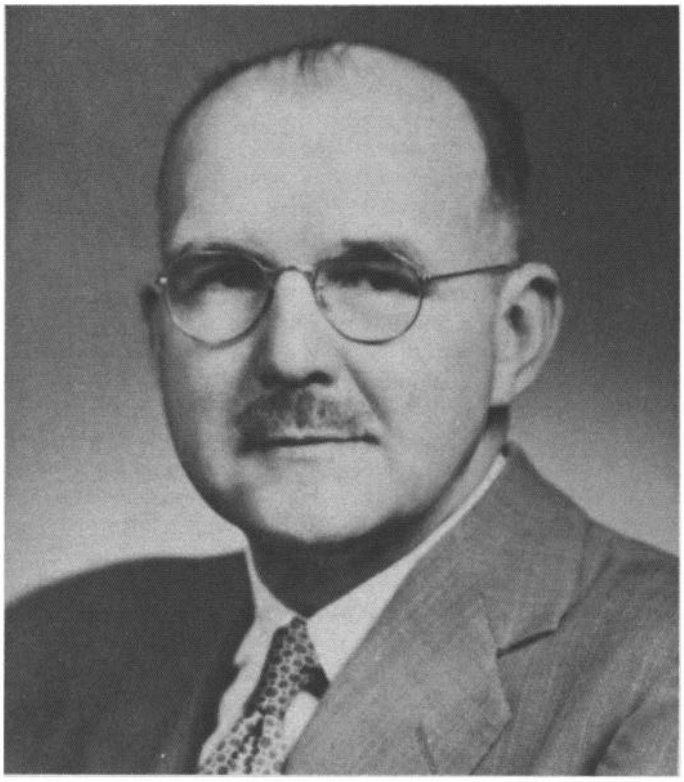


E.E. SELKURT
1976

The fifth composite picture of APS Presidents is now available. Orders may be placed with the Central Office of APS. This composite (11" x 14") shows the last ten Presidents and is a follow-up of the four previous composites. The price for the fifth composite is $12.00.

MAURICE B. VISSCHER

Twentieth President
American Physiological Society



On August 25, 1976, Maurice B. Visscher celebrated his 75th birthday. The American Heart Association recognized him on this occasion with dedication of the October issue of Circulation Research. In this issue, Dr. I.J. Fox presented a beautiful essay on Dr. Visscher's contributions to science and society. On October 29 a Symposium on Cardiovascular Physiology was held in his honor at the University of Minnesota. It is entirely fitting that the organization to which he has probably given more time and effort than to any other should now honor him by having his portrait* appear in THE PHYSIOLOGIST.

Maurice B. Visscher was born in Holland, Michigan. He attended Hope College where he received the B.S. degree in 1922. He entered the University of Minnesota that same year combining graduate study in physiology with medical school work. Minnesota awarded him the M.S. in 1924, the Ph.D. in 1925, and the M.D. in 1931. In 1925-26 he spent a year as a National Research Council Fellow working with Dr. Ernest Starling where his name became inextricably linked with the "Starling Law of the Heart." The following year he worked with Dr. Anton J. Carlson at the University of Chicago. Three degrees from Minnesota and one year each with two of the giants in physiology for an individual with such a fertile mind would be generally considered adequate to launch a productive career in physiology. After appointments as Chairman of the Physiology Departments of the Medical Schools at the University of Tennessee (1927-29), University of Southern California (1929-31), and the University of Illinois (1931-36), he returned to the University of Minnesota in 1936 as Professor and Head of the Department of Physiology. In 1960 he was designated Distinguished Professor, in 1968, Regents Professor, and in 1971, Regents Professor, Emeritus. He voluntarily relinquished the position as Head of the department in 1968. Continuous tenure for 41 years as chairman of a medical school physiology department must be a record.

His scientific contributions cover a wide range of subjects, but certainly his many studies on the heart, beginning with "The Regulation of the Energy Output of the Heart" published in 1927 with Starling, constitute a major part of the total. In the introduction to his presentation at the recent symposium, Earl Wood gave this account of the understanding of Starling's Law of the Heart that was held in Visscher's laboratory in the late thirties and early forties.

> "Anyone who was associated with Dr. Visscher's laboratory in 1935-1945 era could not help but be interested in the relationship of end-diastolic volume to cardiac function; particularly the relationship of the total energy liberated by each contraction to the fraction of this energy which is converted to useful work, i.e., the mechanical efficiency. All of us who were in Maurice's Lab at this time were more or less embroiled in the famous, or infamous as you like, Visscher-Louis Katz polemic as to whether or not heart failure was characterized by a decrease in mechanical efficiency of the contractile apparatus, as Visscher contended, or due to a failure of this apparatus to liberate the energy required to maintain the contractile process, as Katz maintained.
>
> "Gordon Moe's and Visscher's data from heart-lung preparations indicated that if the diastolic volume were kept constant in the spontaneously failing heart-lung heart, its oxygen consumption, i.e., total energy liberation, also remained constant in accord with Starling's Law, but the fraction of this energy converted to useful work decreased progressively with increasing degrees of cardiac failure. Furthermore, they demonstrated that this process, i.e., the decrease in mechanical efficiency, could be reversed by therapeutic doses of cardiac glycosides.
>
> "These findings can be stated in another manner as follows: Under constant conditions of autonomic tone and physical-chemical environment the external work of the heart is a direct function of its diastolic volume. A plot of this function is the classical Starling cardiac function curve. However, if these neural or physical-chemical conditions are changed and then held constant at a new state, the Starling relationship still holds but the curve is shifted upwards or downwards depending on whether the contractility (i.e., the mechanical efficiency) of the contractile apparatus, was increased or decreased by the changed conditions. In other words, for any given heart there is a family of Starling curves depending upon the conditions under which the heart is operating. This was our understanding of Starling's law of the heart as taught and demonstrated to us in Visscher's Lab 40 years ago.

*This issue begins a new format of THE PHYSIOLOGIST, which instead of showing a Past President on the cover, will use the picture, enlarged, along with the lead article.

"Consequently, the more recent reports by Warren, Stead, Rushmer and others that Starling's Law could not be demonstrated in intact animals or patients was to be expected, since in an intact animal or patient the neural, physical-chemical environment of the heart is changing constantly. Consequently, the diastolic volume-external work function is also changing constantly and, hence, cannot be demonstrated in the intact circulation.

"Similarly, and on the same basis, Sarnoff's famous family of Starling curves promulgated in the 1950's and 60's was not unexpected by Visscher's students since the concept was inherent in the Visscher-Starling and Moe-Visscher findings and teachings from the 1930's."

Although his contributions in the field of cardiovascular physiology are numerous and well known, and have continued over an extended period, he considers his most creative contribution to be the pioneering work he did in transport of materials across membranes; particularly the mucosa of the intestine. His background in physical chemistry had prepared him to recognize the unique utility of isotopically labeled water and electrolytes for studying bidirectional movements. Charlie Code puts it this way, "Armed with his isotopes, his optimism, his brains and help from his graduate students, he quickly demonstrated that the movements of water across the mucosa of the bowel were indeed in both directions. There is no area in his multifaceted career in which Visscher's virtuosity is more brilliantly displayed than in his studies of intestinal transport. He really was ploughing new ground—all alone."

Dr. Visscher's first publication was, "A Critical Study of the Nature of the Sugar in Blood." This appeared in the American Journal of Physiology, volume 68, 1924. Fifty-one years and nearly 300 articles later he was still publishing in the same journal on, "Localization of Rapidly Exchangeable Calcium in Mammalian Heart Muscle." There have been contributions since this one and there are undoubtedly more to come. A scientific output of this caliber and degree would represent a full life for most men. This is not the case with M.B. Visscher. His bibliography lists another 180 nonscientific articles. To ignore these contributions and what they represent of the broad interests of this man is to fail to recognize the impact that he has had on our generation. He has emphasized this aspect of his interests and experiences in his introductory article "A Half Century in Science and Society" which appeared in volume 31 of Annual Review of Physiology.

Since the early 1930's he has been in the forefront of the fight to protect the rights of qualified scientists to conduct experiments on living animals—a fight that has continued from the days of Irene Castle to the presidency of the National Society for Medical Research, an office which he still holds. When he was president of our society he recognized the need for comprehensive reviews of the various fields of physiology and, in the years following his term in office, he provided the leadership in establishing the Physiology Handbooks. By almost any standard, this has been one of the very successful ventures of the American Physiological Society.

What was it like to be a graduate student and colleague in the physiology department at Minnesota? On one occasion a graduate student was heard to say that he needed to get away from the department for the summer in order to relax from the pressure. When he was asked if Dr. Visscher or any other senior faculty member had been pressuring him with assignments or deadlines to be met, he answered, "Certainly not. I am speaking of the general atmosphere of this place that puts you under pressure to perform." That it did. It was a busy place. Many different lines of research were being followed. The chief's research did not dominate the department. Any valid idea was examined, criticized, argued and investigated if someone, including graduate students, could make a case for it. If A.J. Carlson's byword was, "What is the evidence?", perhaps M.B. Visscher's was, "Let's see your data." Dr. Visscher had the enviable ability to listen to a discouraged graduate student who had been working on a research problem and, if the neophyte had good data he would leave the chief's office convinced that he was on the trail of a Nobel prize.

What was it like around Dr. Visscher's department? There were always several residents from the clinical departments who were spending a year or more in the department. Many, but not all, were from the Surgery Department. Many of these occupy distinguished positions in academic medicine today. Some, like Francis Haddy, remained to add luster to the discipline of physiology. Those of us who were a part of this close interaction with clinicians soon learned that this was not a one-way street. These very able young men brought talent and ideas to the department. Much of this productive interaction and cooperative effort was fostered by the Tuesday afternoon Conference. This was a joint conference between physiology and surgery, which in those days included anesthesiology. Dr. Visscher and Dr. Wangensteen set the pattern by regular attendance. Faculty, residents, and graduate students followed suit. These were stimulating sessions where many ideas were generated that led to productive research.

Maurice Visscher is a man who gets things done, and done on time. Without this quality he could never have accomplished all of the things he has crowded into 50 years of active professional life. But even a virtue can be overdone. Let Gertrude tell it, "We were married on August 12, 1925. Immediately following the wedding we took the train for New York where we were to board the ship for the trip to England where Maurice was to begin his fellowship year with Dr. Starling. He had insisted that I have my trunk ready to send to New York well ahead of time so that it would be at the dock to be placed aboard our ship. When we arrived at the dock, his trunk was there but mine had been put aboard an earlier vessel and sent ahead. I faced the prospect of living out of an overnight bag for five days. Even with some frantic shopping in New York, I wore the same dress every night for dinner." This experience may account for the fact that Maurice has been constrained to listen when Gertrude speaks. Those who know Gertrude know that she has been a source of strength and a steadying influence through 51 years of married life.

To list and describe all of the honors that have come to Dr. Visscher would require more space than has been allotted to this essay. In 1973, he received the Distinguished Teaching Award from the Association of Chairmen of Departments of Physiology. Two years later our Society honored him with the Ray G. Daggs Award for services to the Society as well as the science of Physiology.

Dr. Visscher, for more than 50 years of unstinting service to physiology and to society, we, the members of the American Physiological Society, salute you! May your contributions continue for many years to come.

E. B. Brown, Jr.
Earl H. Wood

PROPOSED BYLAW AMENDMENTS TO BE VOTED ON AT SPRING BUSINESS MEETING

A number of amendments will be presented for consideration by the membership at the Spring Meeting in Chicago, as recommended by Council. Current Society Bylaws were published in their entirety in the November 1976 issue of The Physiologist. Among the proposed amendments to the Bylaws, one provides for the establishment of a new category of membership to be known as "Student Members." A matching amendment is designed to redefine "Associate Members" by deleting any reference to students in this category of members.

Another substantive Bylaw amendment to be voted on at the Spring Meeting provides for a full appointive term to the Chairman of standing committees who, because of an existing Bylaw technicality, may not currently be permitted to serve a full three years in that capacity following service as a member on the same committee.

An important amendment to be considered by the membership will identify the Chairman of the Publications Committee as an ex officio member of the Finance Committee.

In addition to four substantive Bylaw amendments, eight technical amendments will also be voted on. These amendments are necessary to fully implement Bylaw changes previously adopted and those to be considered at the Spring Meeting by incorporating appropriate similar language in related Bylaws.

The proposed Bylaw amendments concerning student members were developed by the Membership Committee and reviewed by an ad hoc committee of Council. Following that review and further discussion at the Council meeting, the amendments were unanimously approved. Dr. Beverly Bishop, Chairman of the Membership Committee stated that in preparing the amendments her committee had attempted to create a category of Associate Membership for those scientists who were not primarily physiologists but in their day-to-day work were involved with physiology. It was felt that these scientists should be a part of the Society but not a part of the governing body of the Society. The present Associate Membership category serves student members who have just passed their preliminary examinations. Unfortunately, this category of membership has, therefore, been looked down on by established professionals. The Committee recommended a new category of membership for students which was intended to have a transient membership with the right to attend meetings, learn about the Society, purchase journals at member rates and, when ready, be proposed for Associate or Regular Membership. Dues for Student members would be very low.

The substantive Bylaw amendments to be considered at the Spring Business Meeting of the Society are as follows:

Article III "Membership," Section 5 "Associate Members" is amended to read:

"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."

Article III "Membership" is amended by adding a new Section 7, to read:

"Student members. Graduate students in physiology who have completed their preliminary examinations for the doctoral degree provided they are residents of North America. No individual may remain in this category for more than five years."

Article V "Standing Committees" is amended by adding a Section 6, to read:

"Term of Office of Chairman. Chairman of a standing Committee may serve one full term in that capacity in addition to any consecutive term as a committee member limited by other provisions of these Bylaws."

Article V "Standing Committees," Section 2 "Finance Committee," the last sentence is amended to read:

"The President-Elect, Executive Secretary-Treasurer, the Chairman of the Publications Committee, and the Business Manager shall be ex officio members of the Finance Committee, without vote."

The following Bylaw amendments to be voted on, are necessary to fully implement the provisions of the new Sections 5 and 7 of Article III, that redefines "Associate Members" and establishes "Student Members" as well as previously adopted Bylaw amendments. These technical amendments to the Bylaws are: (Additions or changes are underscored.)

Article III "Membership," Section 1, is amended to read:

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

Article III "Membership," Section 7 "Sustaining Associates" is renumbered as Section 8.

Article III "Membership," Section 8 "Nominations for Membership" is renumbered as Section 9 and amended to read:

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

Article III, "Membership," Section 9 "Election of Members" is renumbered as Section 10 and amended to read:

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

Article III "Membership," Section 10 is renumbered as Section 11.

Article IV "Officers," Section 4 "Election of Officers" is amended to read:

First paragraph, first sentence to read, "Nominations for President-Elect and for members of Council will be made by mail ballot, on forms provided by the Executive Secretary-Treasurer, before February 1 of each year."

Second paragraph, second sentence, to read, "Election of the President-Elect and members of Council will be made by

mail ballot, on forms provided by the Executive Secretary-Treasurer, prior to April 1 of each year."

Article VI, "Dues," Section 1, "Annual Dues" is amended to read:

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

Article VI "Dues," Section 2 "Non-payment of Dues," is amended to read:

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

Article VI "Dues," Section 3 "Retirement" is amended to read:

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

1977 FEDERATION MEETING, CHICAGO, ILLINOIS

APS and its guest societies, the Microcirculatory and Biomedical Engineering Societies, will begin the Spring Meeting sessions on Saturday, April 2 and conclude on Wednesday, April 6. Other Federation societies will have sessions during the period, Monday, April 4 through noon on Friday, April 8.

This Spring, we will have programmed a record number of 1460 abstracts, 1428 of which were received from APS members. For the Spring 1976 meeting, we programmed a total of 1217 abstracts from all sources. Since all sessions were not completely programmed at the time this was written, information on the schedule for contributed papers was not available. However, the schedule for invited symposia sessions had been developed and is provided for your information.

April 3 Sunday A.M. 9:30-12 Noon	Round Table: Future Directions in Biomedical Engineering (BMES)
	Renal Handling of Calcium Organizer: John H. Dirks
	Biochemistry of Spermatogenesis Organizer: David W. Bishop
	Neural Functions in Temperature Regulation Organizer: Dennis A. Poulos
April 3 Sunday P.M. 1:30-4:30	Refresher Course on Control Mechanisms (BMES)
4:30-5:30	ALZA Distinguished Lecturer (BMES)
Sunday P.M.	Parathyroid Hormone, Calcitonin and Vitamin D Organizer: Claud Arnaud
	Integration of Information at the Single Neural Level Organizer: Barbara Gordon
	The Microcirculation of Tumors (MCS) Organizers: Marcus Intaglietta and Joseph Gross
	Workshop on Thermogenesis Organizer: C. C. Gale
Sunday P.M. 8:00	Biochemistry of Spermatogenesis (continued)
April 4 Monday A.M.	Cellular Pacemakers Organizer: David O. Carpenter
	Nonrespiratory Aspects of Lung Physiology: Session I – Fetal Development of the Lung Chairman: Claude Lenfant
	Symposium: The Physiology of Lipids and Lipoproteins in Health and Disease, Session I Chairman: John M. Dietschy
Monday P.M.	Functional and Structural Determinants of Glomerular Filtration Organizer: Barry M. Brenner
	Synaptogenesis Organizer: Philip G. Nelson
	Models for GI Transport Organizer: George Sachs
April 5 Tuesday A.M.	Neural Control of Renal Function Organizer: Gerald DiBona
	Symposium: The Physiology of Lipids and Lipoproteins in Health and Disease, Session II Chairman: J. Denis McGarry
	Nonrespiratory Aspects of Lung Physiology: Session II – Lung Cell Functions Chairman: Claude Lenfant
Tuesday P.M.	Auditory Processing and Animal Sound Communication Organizer: Robert R. Capranica
	Circulation Symposium: Alterations in Activity of Vascular Smooth Muscle by Local Modulation of Adrenergic Transmitters Release Organizer: John T. Shepherd
Tuesday Evening	Auditory Workshop: Do Pure Tone Stimuli Lead to Artifactual Interpretation of Auditory Function Organizer: Robert R. Capranica
April 6 Wednesday A.M.	Symposium: The Physiology of Lipids and Lipoproteins in Health and Disease, Session III Chairman: Antonio M. Gotto

At the time of this writing the following related events had been scheduled.

April 3 Sunday	BMES Business Meeting BMES Mixer BMES Banquet Perinatal Dinner
April 4 Monday	Respiration Dinner Neuroendocrine Dinner Neurophysiology Cash Bar Temperature Regulation Dinner Epithelial Transport Workers Dinner Cardiac Muscle Dinner
Tuesday April 5	Circulation Group Dinner and Lecture GI Section Dinner and Hoffman La-Roche Award Lecture President's Cocktails and Dinner 6:30 P.M. APS Business Meeting 4:30 p.m. Renal Dinner

For further information please refer to the published Program.

GI SECTION
STATEMENT OF ORGANIZATION AND PROCEDURES

The following statement, accepted by the APS Council on April 15, 1976 is printed for the information of APS members. This is the first formally accepted document giving recognition to the establishment of a Section within APS. For further information on the GI Section see "Report of the GI Section" printed elsewhere in this issue of The Physiologist.

The Gastrointestinal Section of the American Physiological Society

ARTICLE I. Name

The name of this organization is THE GASTROINTESTINAL SECTION of the AMERICAN PHYSIOLOGICAL SOCIETY.

ARTICLE II. Purpose

The purpose of this organization is: (1) to advise the American Physiological Society on matters of interest to gastrointestinal physiologists, and (2) to assist the American Physiological Society in organizing, and presenting scientific sessions, symposia, and other programs of interest to gastrointestinal physiologists. These activities include sponsoring an annual dinner and organizing an annual symposium for the spring meeting of the Federation of American Societies for Experimental Biology.

ARTICLE III. Membership

Regular Membership is open to any member of the American Physiological Society who signs a statement declaring the wish to be a member. To accomplish this, the entire membership of the American Physiological Society will be polled during the first year that this Statement is in effect. Thereafter, only new members of the organization will be polled to ascertain their interest.

Intersociety Membership is open to those with an interest in gastrointestinal physiology but who are not members of the American Physiological Society. Intersociety Members share all of the rights and responsibilities of Regular Members.

Candidates for Intersociety Membership are nominated by 2 Regular Members who send their written nomination and the candidate's curriculum vitae to the Secretary-Treasurer. If approved by the Steering Committee, membership is granted. If disapproved, letters are sent to the nominators telling of the disapproval and the reasons.

ARTICLE IV. Officers

Section 1. Steering Committee. The responsibility for management and supervision of the affairs of the Gastrointestinal Section shall be vested in the Steering Committee. The members of the Steering Committee shall be the Chairman, the Secretary-Treasurer, two Councillors, and the representative of the Gastrointestinal Section to the Program Committee of the American Physiological Society.

A quorum for conducting official business of the Gastrointestinal Section shall be three of the five members of the Steering Committee.

Section 2. Councillors. There shall be three Councillors elected to the Steering Committee, each for a term of three years, but with only one being selected in any one year, and each such Councillor to serve as chairman of the Steering Committee during his/her third year.

Section 3. Secretary-Treasurer. There shall be one Secretary-Treasurer who shall be elected for a term of three years.

Section 4. Program Committee Representative. There shall be one Program Committee Representative who shall be elected for a term of three years.

Section 5. Election of Officers. One Councillor shall be elected each year, and the Secretary-Treasurer and Program Committee Representative shall each be elected every three years with the Secretary-Treasurer being elected in the year preceding the election of the Program Committee Representative.

Two nominations shall be made annually, as appropriate, to forthcoming vacancies by the Nominating Committee, and the name of the nominees shall be announced by mail to the members two months in advance of the annual meeting. Additional nominations may be made by three or more members submitting the name of a candidate who has agreed in writing to serve if elected. Nominations must be submitted by February 1 of the election year.

Election of officers shall be by mail ballot sent to all members concurrently with the announcement of the annual meeting.

ARTICLE V. Standing Committees

Section 1. Nominating Committee. The Chairman, in consultation with the other 4 members of the Steering Committee, will appoint annually two members to serve with a Councillor (serving as Chairman) as the Nominating Committee. The Committee nominates two members as candidates for the election of the new Councillor.

Section 2. The Chairman may appoint additional committees that are necessary for the proper conduct of the affairs of the Section.

ARTICLE VI. Duties of Officers

Section 1. The Program Committee Representative is responsible for obtaining appropriate chairmen for the scientific sessions in gastrointestinal physiology.

Section 2. The Chairman, in consultation with the other 4 members of the Steering Committee will annually choose a topic to be presented at the annual meeting of the Federation of American Societies for Experimental Biology. They will also choose a person who will organize the symposium and be responsible for its presentation.

ARTICLE VII. Dues

Dues may be assessed annually in an amount established by the Steering Committee.

ARTICLE VIII. Meetings

The Gastrointestinal Section will meet at the time of the annual dinner and at other times determined by the Steering Committee. Members must be notified in writing at least one month before the meeting. Meetings are for transacting the business of the Gastrointestinal Section and are governed by Roberts Rules of Order Newly Revised.

ARTICLE IX. General

Section 1. Amendments. Amendments to these procedures must be proposed in writing to the Steering Committee by five members at least two months before the annual meeting. The proposal must then be sent to the members at the time of the announcement of the annual meeting. An amendment requires the approval of two-thirds of the entire membership for adoption.

Section 2. Quorum. The quorum required for all membership business meetings is no less than 30 percent of the total members of the Section.

ARTICLE X.

Nothing in this Statement of Organizational Procedures shall be construed as contradictory to the Constitution and Bylaws or Operational Guidelines of the American Physiological Society.

* * * * *

SPECIALTY GROUPS TO BE REPRESENTED ON NEW PROGRAM COMMITTEES

APS program development activities have been reorganized to include special interest group representation.

At its April 1976 meeting, the Council appointed an Ad Hoc Committee on Programming to study the annual meeting programming process and make specific recommendations for revising programming procedures. The Committee, which met on July 1, 1976 was chaired by Alfred Fishman and included as members, H. Maurice Goodman, Jere Mead, George Somjen, with ex officio members Bodil Schmidt-Nielsen and Orr E. Reynolds.

The stimulus for the study was the awareness by the Council of the overriding importance of the annual meetings to the members, the difficulties that recent Program Committees have experienced in achieving adequate representation of the diverse subspecialties in the annual programs, and the needs of emerging APS specialty groups for appropriate access to the programming activities of the Society.

The Ad Hoc Committee report was presented to the Council at its August 1976 meeting in Philadelphia. It provided for a two tier structure with a three member Program Executive Committee reporting to the Council and a subordinate Program Advisory Committee composed of representatives of various special groups. The Program Advisory Committee of at least ten members would be very flexible in number so that any current or future APS section could be invited to have a representative. This latter committee would get input from the constituent specialties that would shape the programs, with the final decision to be made by the Program Executive Committee before it goes to Council.

H.M. Goodman, Chairman of the current Program Committee supported the reorganization plan since it promised to provide a better way to reach out to the membership at large for better input into the development of annual programs. His Committee felt that a better means of communication and liaison with the specialty groups was required and the Task Force report achieved that goal in principle.

The Council accepted the recommendation of the Task Force with the thought that the new Program Executive Committee and Program Advisory Committee would be responsible for all regular meetings beginning with the 1978 meetings. Francis J. Haddy, Chairman of the Committee on Committees was authorized to have his Committee make recommendations to the Council for the three members of the Program Executive Committee. Following receipt of the Committee's recommendations, Ewald E. Selkurt, the APS President, named H. Maurice Goodman as the Program Executive Committee Chairman along with Franklyn G. Knox and Melvin J. Fregly as members.

The current Program Committee, at its meeting on October 20, 1976, recommended the following eleven specialty areas be represented on the Program Advisory Committee: Cardiovascular Physiology; Comparative Physiology; Environmental and Exercise Physiology; Gastrointestinal and Hepatic Physiology; Membrane and Transport Physiology; Metabolism and Hormone Action; Muscle Physiology; Neuroendocrinology; Neurophysiology; Renal, Fluid and Electrolyte Physiology; Respiratory Physiology.

Dr. Goodman assigned specific specialty areas to members of the current Program Committee with the request that they arrange to contact each existing, formally organized, specialty group, to obtain the nomination of two candidates for their representative on the new Program Advisory Committee. Where no appropriate group exists, the editorial board of the related Society journal will be asked to name the representative. In addition to the naming of their candidates, each specialty group will be asked to suggest liaison mechanisms that could be implemented between the groups and the Program Advisory Committee.

The initial terms for members of the Program Executive Committee will be staggered so that each may serve a maximum of three years with eligibility for reappointment for one additional three-year term. The term of office for specialty group designees on the Program Advisory Committee will be as specified by the specialty group. All others will be for a maximum of three years.

REPORT OF THE GI SECTION OF APS

At the 25th Annual Meeting of the Gastrointestinal Section of the American Physiological Society held during the Federation Meetings in 1975, Dr. Charles F. Code presented the annual lecture which was titled, "After 25 Years—What Does the Future Hold." He challenged the group to make the Section more responsive to the needs and goals of those interested in the physiology of the gastrointestinal tract. His lecture was published in the Physiologist, Vol. 18, No. 4, 1975.

The G.I. Section of the American Physiological Society has met in conjunction with the Federation Meetings since 1950. The meeting served as a focal point for established investigators, students and clinicians whose research interests were primarily in gastrointestinal physiology. Over the years, the activities of the section were run rather informally by a steering committee which included a Chairman, a Secretary-Treasurer who served for three years and two additional members. The membership was comprised of persons stating a desire to be placed on the G.I. Section mailing list. The section was put on a sound financial basis through the efforts of Dr. David Brody who obtained contributions primarily from the pharmaceutical industry. This enabled them to support invited speakers from the United States and from foreign countries. The section remains financially sound.

Since the challenge offered by Dr. Code at the 1975 meeting, several positive steps have been taken by the steering committee to make the section more responsive to those interested in G.I. Physiology. It asked that the Federation schedule the G.I. papers for presentation within two or three consecutive days. Dr. Leonard Johnson, a steering committee member, accomplished this at the 1976 Federation meeting through his participation on the American Physiological Society Program Committee. In addition a G.I. symposium, organized and chaired by Dr. Johnson, was presented during the Federation Meeting of 1976. The section plans to present an annual symposium on some topic of high interest.

Finally the GI Section established a more formal structure within the American Physiological Society. Dr. Kenneth Hubel, steering committee chairman during 1975-76, prepared a "Statement of Organization and Procedures," which defines the purpose of the section and specifies procedures concerning membership and election of officers. That statement was formally accepted by the APS Council on April 15, 1976 and is printed elsewhere in this issue of The Physiologist. The views of the Gastrointestinal Section will be reflected in the activities of APS chiefly by its Program Advisory Committee representative (see "Specialty Groups to be Represented on New Program Committees" in this issue of The Physiologist) an officer elected by the membership for a term of three years.

A Regular Membership in the Section is open to any member of the American Physiological Society who signs a statement declaring the wish to be a member. An Intersociety Membership is open to those who have an interest in gastrointestinal physiology but who are not members of the American Physiological Society. The GI Section hopes to make the organization responsive to the wishes of its members in order to provide scientific programs of high quality and broad interest.

The activities of the Section are underway for the 1977 annual meeting. The ten-minute papers and the poster sessions have been scheduled to fall within a three-day period (April 3, 4, and 5) at the Federation Meetings to be held in Chicago. A symposium has been organized and is scheduled for Monday, April 4, 1977. The annual dinner meeting will take place on Tuesday evening, April 5, 1977 at 6:00 PM in the Beverly Room of the Conrad Hilton Hotel, when the first annual Hoffman LaRoche Prize in Gastrointestinal Physiology will be presented to the speaker.

The GI Section of the American Physiological Society has been in existence for a long time. The recently introduced procedures should insure a continued life for the section and increase the participation in the American Physiological Society of those interested in gastrointestinal physiology.

The 1976-1977 Officers of the GI Section are:

Paul D. Webster, Chairman
Leonard R. Johnson, Chairman-Elect
James F. Long, Secretary-Treasurer
Henry Binder, Councillor

APPOINTMENTS

Dr. Ewald E. Selkurt, President of APS, and chairman of the Department of Physiology at Indiana University School of Medicine, has been named Distinguished Professor of Physiology. The Distinguished Professorship is the highest honor the University can bestow.

Dr. Daniel C. Tosteson, President of APS in 1973, has been appointed dean of the Harvard Medical School, effective next July. Dr. Tosteson is now vice president for the medical center and dean of the Division of Biological Sciences and the Pritzker School of Medicine, University of Chicago. He received his M.D. degree from the Harvard Medical School in 1949 and was chairman of the Department of Physiology and Pharmacology at Duke University School of Medicine from 1961 to 1975. Dr. Tosteson will succeed Dr. Robert H. Ebert who is retiring after 12 years as dean.

Dr. Francis J. Haddy, a member of the Council of APS, recently left Michigan State University to take up duties as the chairman of the Physiology Department of the new Uniformed Services University of the Health Sciences in Bethesda, Maryland. The University, whose aim is to generate physicians for the Armed Forces and the Public Health Service started its first class of 32 students on November 15, 1976. Dr. and Mrs. Haddy have taken up residence in Chevy Chase, Maryland.

COURSE IN DESIGN AND ANALYSIS OF SCIENTIFIC EXPERIMENTS

Massachusetts Institute of Technology will offer a two-week elementary course in Design and Analysis of Scientific Experiments, June 20-July 1, 1977. Applications will be made to the physical, chemical, biological, medical, engineering, industrial and social sciences. The course will be taught by Professors Harold Freeman and Paul Berger. Further particulars may be obtained by writing to the Director of the Summer Session, Room E19-356, Massachusetts Institute of Technology, Cambridge, Massachusetts 02139.

NEW HANDBOOK OF PHYSIOLOGY, REACTIONS TO ENVIRONMENTAL AGENTS

In the newest volume of the Handbook of Physiology, Reactions to Environmental Agents, the emphasis is on well-known environmental perturbations, particularly physical and chemical agents introduced by man, and the physiological responses evoked by these agents. The volume is divided into six main topics:

Response to Physical Agents, such as sound, heat microwaves, and ionizing radiation.

Nature, Origin, and Distribution of Chemical Agents, including those in the air and those from occupational sources, food additives, medicines and drugs, and cigarette smoke.

Reactions and Determinants at Portal of Entry that affect the respiratory system, the skin, and the alimentary system.

Transportation and Transformation of Chemical Agents within the body.

Distribution and Excretion of Chemical Agents and Derivatives, including storage and release in bone and adipose tissue as well as excretion by the kidney, alimentary tract, and lungs.

Mechanism of Cellular Injury, including effects on permeability of cell membrane, covalent binding to cellular constituents, lipid peroxidation, intracellular digestion, nucleic acids, and protein synthesis.

The Editor, Douglas H.K. Lee, and the Associate Editors, Hans L. Falk and Sheldon D. Murphy, brought with them the varied training and experience in physiology, biochemistry, toxicology, and pharmacology that was necessary for such a volume. The subject index was prepared by Constantine J. Gillespie of the National Institutes of Health Library, Bethesda, Maryland.

The American Physiological Society's interest in environmental physiology as a topic for a Handbook of Physiology is not new. The Society published Adaptation to the Environment, edited by D.B. Dill, E.F. Adolph, and C.C. Wilber, in 1964. At that time the emphasis was on the physiological processes that allow for adaptation in a wide range of animal forms to relatively normal environmental stressors. That volume and this new publication present two aspects of environmental physiology in a way that reflects the broad concerns of this field and the change in emphasis from the 1960s to the 1970s. They are essential additions to the library of every one seeking a broad understanding of physiological reactions to changes in the environment.

The newest volume in the series (667 pages) will be available in March. It and the previously published volume on environmental physiology may be purchased by members of APS at reduced prices from the Subscription Office, American Physiological Society, 9650 Rockville Pike, Bethesda, Maryland 20014.

Adaptation to the Environment, Section 4
Non-member price $32.00
Member price $26.00

Reactions to Environmental Agents, Section 9
Non-member price $80.00
Member price $64.00

NEW CUMULATIVE INDEXES TO APS JOURNALS

Recently completed cumulative indexes to the American Journal of Physiology (1952-1975) and Journal of Applied Physiology (1948-1975) have been distributed to 1976 subscribers to each journal (see The Physiologist, 19(2):71, May 1976). They may also be purchased separately. The indexes now available to Society publications are:

American Journal of Physiology, Volumes 121-167, 1938-1951, 325 pages. Price postpaid, $5.00
American Journal of Physiology, Volumes 168-229, 1952-1975, 490 pages. Price postpaid, $15.00
Journal of Applied Physiology, Volumes 1-39, 1948-1975, 260 pages. Price postpaid, $8.00
Physiological Reviews, Volumes 32-46, 1952-1966, 204 pages. Price postpaid, $5.00

One or more of these indexes may be ordered from the Subscription Office, American Physiological Society, 9650 Rockville Pike, Bethesda, Maryland 20014.

IUPS CHARTER FLIGHTS TO LONDON AND PARIS

Group air charters have been arranged for travel to London and Paris to provide extremely low cost travel to the IUPS meeting. Minimum prices for these charters are $353.00 to $379.00 with the maximums $424.00 to $455.00 depending on the flight selected and the final number of participants.

It should be noted that one need not be a member of APS to participate in these charter flights. To be eligible, a passenger must only be included on the list of original participants or become the assignee of an original participant. This eligibility is established by making a $100.00 deposit to Chevy Chase Travel 65 days prior to departure.

The following charters have been arranged:

Charter #1: New York to London June 29, Deposit required by April 26 — Paris to New York July 24
Charter #2: Washington to Paris July 14, Deposit required by May 10 — London to Washington August 2
Charter #3: New York to Paris July 7, Deposit required by May 3 — London to New York August 3

For further information and applications write to:

Chevy Chase Travel Inc.
4715 Cordell Avenue
Bethesda, Maryland 20014
Telephone: (301) 656-2021

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

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

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

PHYSIOLOGY TEACHER – BOUND COLLECTION AVAILABLE

Beginning with this issue of The Physiologist, members and subscribers will also receive The Physiology Teacher as an insert. The Physiology Teacher, now in its sixth volume, is published under the supervision of the Education Committee of the American Physiological Society. Substantive papers, including laboratory experiment descriptions are refereed by members of the Education Materials Review Board (constituted of slightly over 100 members distributed throughout the specialties of physiology).

The Education Committee has decided to eliminate its inventory of back issues of Volumes I through V of The Physiology Teacher by producing a limited number of complete collections bound in spiral binder for convenient use in the laboratory. This 285 page volume is offered at the extremely low price of $10.00 on a first come first served basis as long as the limited supply lasts.

Please use the order form on page 13 of the attached Physiology Teacher if you wish to obtain this volume. The forthcoming inserts in The Physiologist will then provide you with a complete set of this publication.

NATIONAL SCIENCE FOUNDATION "ROTATOR PROGRAM"

The following is the text of a December 30, 1976 letter from Herbert Harrington, Jr., Director of Equal Employment Opportunity at NSF. The letter, addressed to Ewald Selkurt as President of APS, is printed in its entirety for the information of APS members and other readers of The Physiologist.

Dear Dr. Selkurt:

I want to win your interest and active support in our efforts to increase the representation of minorities, women and the handicapped in the National Science Foundation's Rotator Program. This program has certain features which offer positive benefits to all involved, the Foundation, the individual participant and the educational institution.

Under this program NSF augments its permanent staff of scientists and other professional employees with qualified individuals from the faculties of colleges and universities across the country who serve in non-career positions for periods of one or two years. In obtaining such personnel we secure a continuing source of current knowledge of academic affairs, new ideas and diverse talents. Those selected gain a rich developmental experience and additional insight into Federal support of scientific research, the improvement of science education and the dissemination of science information.

We are most reluctant to add to the staffing problems of colleges and universities. A primary mission of the Foundation is to strengthen science education in the United States. The Rotator Program, however, makes sound human resource investment sense. A one or two year association with the Foundation in administering on-going national programs will prove most valuable to educational institutions on return of the rotators to their regular assignments.

Now—what can you do to help? Please bring the NSF Rotator Program to the attention of minorities, women and the handicapped who in your judgment best qualify for the multiple purposes of the program. Particularly welcome are scientists with a Ph.D. plus 6 years of successful scientific research experience. A broad general knowledge of the applicable field of science and some administrative experience are also desirable. Applicants selected will be offered an excepted appointment under the NSF Act of 1950, as amended. Salary is negotiable based on qualifications and experience. Health, life insurance, and leave benefits are available depending upon the length of assignment.

Interested individuals should send their vitae and statements of interest to me at 1800 G Street, NW, Room 536, Washington, D.C. 20550 (202-632-9178). I will then personally take the necessary steps to insure that qualified candidates receive full and careful consideration in the competition for the limited number of rotator positions (approximately 30 per year).

Although not the primary subject of this letter mention should be made of other service opportunities at NSF. From time to time permanent positions as science program managers become available. The qualifications, pay and fringe benefits are similar to those described above for rotators. We also would be happy to receive applications for these positions from women, members of minority groups and handicapped individuals.

In closing, it should be emphasized that this matter as discussed has the full endorsement of the Foundation's Director and his top management staff.

Thank you in advance for your cooperation and assistance in a program which I am sure will prove to be mutually rewarding.

INTERNATIONAL COURSE IN ADVANCED NEURORADIOLOGY

An International Course in Advanced Neuroradiology will take place in Strasbourg-Bischenberg, March 10-11, 1978. The topics to be discussed are: The narrow lumbar canal and recent advances in computer tomography. For further information please contact: Professeur A. Wackenheim, Service de Neuroradiologie, 1, place de l'Hopital, 67005 Strasbourg Cedex: France.

TWENTY-FIRST BOWDITCH LECTURE

The Epithelial Junction: Bridge, Gate, and Fence

By Jared M. Diamond
Physiology Department, UCLA Medical Center
Los Angeles, California 90024

The hallmarks of epithelial physiology are two phenomena that emerge from the organization of the whole epithelium, and that cannot be explained by any one cell membrane acting alone. These phenomena are net active transport across the epithelial cell layer, and coupling between transepithelial fluxes of actively and passively transported solutes. In the 1950's physiologists tried to explain these phenomena as arising entirely from the properties of two different cell membranes in series. The junctions between the cells were tacitly assumed to be simply pieces of cement. We now know, mainly from work of the past 15 years, that the junctions are as important a key to epithelial physiology as are the cell membranes. The junctions act simultaneously as a bridge, a gate, and a fence. For each of these three junctional roles I shall recount how it was discovered by physiologists, and what are its physiological function and morphological basis. At the end I shall point out what I see as the experimental usefulness of epithelia for nonepithelial physiologists.

The Beer-can Model of Epithelia

Modern understanding of epithelial junctions began with the first detailed electron microscopic study, that of Farquhar and Palade (1963), who showed that junctions include three distinct types of morphological elements: so-called tight junctions, gap junctions, and desmosomes. This organization can best be visualized by referring to the traditional modern epithelial model, a six-pack of beer (Fig. 1). In this model each beer can corresponds to a barrel-shaped epithelial cell; the pop-top end of the can, to the so-called apical cell membrane, which faces the lumen of the epithelium-lined cavity in vivo; the walls of the can, to the lateral cell membranes; the bottom of the can, to the so-called basal cell membrane, which faces the bloodstream in vivo; the spaces between the cans, to the lateral intercellular spaces; and the plastic of the six-pack, to the tight junctions, which constitute hoops encircling the apical end of each epithelial cell and separating the luminal solution from the lateral intercellular spaces. The six-pack model fails to illustrate gap junctions and desmosomes, which are very small contact areas between lateral surfaces of adjacent cells. Whereas the absence of a desmosome analogue lets one flex the six-pack's beer cans apart at their bottoms, the function of the desmosomes is to make this impossible for the epithelium's cells. As bridges, the gap junctions regulate solute movement from inside one cell to inside another cell; as gates, the tight junctions regulate solute movement from the luminal solution directly into the lateral intercellular spaces, by-passing the cells; and, as fences, the tight junctions or associated structures presumably also regulate the movement of membrane constituents from the apical cell membrane to the lateral cell membrane.

The bridge. Of the triple junctional roles as bridge, gate, and fence, the first to be unraveled was that as bridge, in 1965. The discovery of the bridge role was a complete surprise, a by-product of experiments performed for a quite different purpose. Werner Loewenstein and his colleagues wanted to measure the electrical resistance of nuclear membranes, taking advantage of the favorable opportunity provided by the giant epithelial cells of insect salivary glands. To assess this resistance, they inserted several microelectrodes into the same cell, advanced one of these electrodes into the nucleus, passed a current, and measured the resulting voltage step. As a control, they repeated the measurement with one of the voltage-sensing microelectrodes removed to a different cell, expecting to validate their procedure by observing no voltage step (because everyone then assumed the resistance between different epithelial cells to be infinite). Instead, they found to their astonishment that the voltage step was nearly as large as when both microelectrodes were in the same cell!. Evidently, there were some bridge-like structures permitting current flow (i.e., passage of ions) from cell to cell.

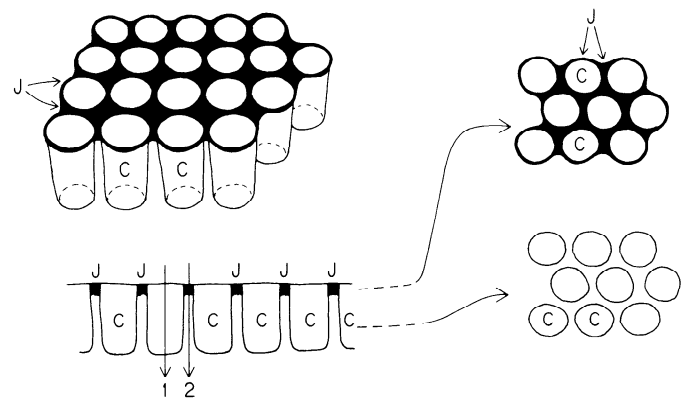


Fig. 1. Schematized conception of epithelial organization. An epithelium consists of cells (C) encircled and held together at one surface by junctions (J), and resembles a six-pack of beer extended indefinitely in two dimensions (upper left). Lower left is a section perpendicular to the epithelial sheet; upper right and lower right, sections in the plane of the sheet at the level of the junctions and lateral intercellular spaces, respectively. Alternative routes across the epithelium are via the cells or via the junctions (routes 1 and 2, lower left). The so-called apical membrane of each epithelia faces the top in the sketches of lower and upper right, while the basolateral membrane faces the sides and bottom.

Much evidence indicates that the junctional element playing this bridge role in vertebrate epithelia is the gap junction. Since the experiments on insect salivary gland in 1965, similar experiments have revealed cell-to-cell current flow under normal conditions within virtually all epithelia examined. Changes in this cell coupling during embryological differentiation and in certain cancers have attracted much interest. Yet the function of the bridges remains unknown. Structures that can transmit ions could be expected to transmit other small solutes, and this has been confirmed by dye microinjection studies. Which solutes are the ones whose exchange via the bridges is physiologically significant? Are they substances that regulate growth and differentiation? Or are they metabolites, ATP, and other high-energy compounds?

The gate. The next junctional role to be clarified was that as gate. Whereas the possible existence of bridges had not even been imagined until their accidental discovery, the question of gates did arise prior to their discovery. However, we assumed that we knew the answer to the question, and our assumption

proved wrong: we assumed the gates to be closed. That is, the tight junctions were believed to prevent transepithelial solute fluxes from by-passing the cells in all epithelia under physiological conditions. The reasons for this erroneous assumption were various: the power of suggestion of the name "tight junction" coined by 19th-century anatomists; demonstrations that junctions actually are tight to proteins and large colloidal tracers, although we now see with the wisdom of hindsight that this need not imply tightness to small ions; and the successes of Ussing and his colleagues in the 1950's in attributing transepithelial ion flow to mechanisms already demonstrated in erythrocyte, nerve, and muscle membranes. As epithelialogists short-circuited tissue after tissue in the 1950's, epithelia were found to exhibit enormous diversity in the identity of the actively transported solute(s), direction of transport, open-circuit voltage, transepithelial resistance, water permeability, and steepness of gradient built up by active transport. A book by Ussing and colleagues (1960) attempted to show that much of this epithelial diversity could in principle arise in cell membranes by different arrangements and quantitative properties of K-Na exchange pumps, K-selective membranes, and Na-selective membranes (Ussing, 1960). As late as 1969, Keynes (1969) exhaustively reviewed the facts of epithelial diversity without seeking the solution in junctional diversity.

During the 1960's, however, several observations began to hint that the junctional gates were normally open to ions in certain epithelia. Shiba (1971), Boulpaep (1971), and Sachs and colleagues (1971) pioneered in applying the technique of cable analysis to epithelia, in attempts to assess the gate question directly. The principle of these experiments was simple: measure the transepithelial resistance, use an intracellular microelectrode to measure the resistance of the apical and basolateral cell membranes, and examine whether the sum of the two cell membrane resistances in series exceeded the transepithelial resistance. A "yes" answer would imply a transepithelial shunt by-passing the cell membranes, such as an open junctional gate. However, the execution of this conceptually simple experiment was greatly complicated by the previously discovered bridge role of junctions, since current injected into one cell to determine its membrane resistances spread to adjacent cells. The bridges were no longer a fascinating surprise but a nuisance that made cable analysis necessary to calculate membrane resistances.

The first full cable analyses of epithelia were performed on renal proximal tubule and gastric mucosa, where tubular geometry or presence of multiple cell types introduced further experimental problems. To circumvent these problems, Eberhard Frömter and I turned in 1971 to *Necturus* gallbladder, a simple flat epithelial sheet with a single cell type (Frömter and Diamond, 1972; Frömter, 1972). The result of cable analysis was that the resistance of the cell membranes exceeded the transepithelial resistance by a factor of 23, meaning that a paracellular shunt accounted for 22/23 of the transepithelial ion conductance. A voltage scanning experiment, in which these shunts were detected by an extracellular microelectrode as local current sinks during transepithelial current passage, confirmed that the shunts were located at the junctions. Thus, the junctional gates of *Necturus* gallbladder, far from being tight, furnish the main pathway for passive ion permeation across the epithelium. From a survey of epithelial properties, Frömter and I concluded that the junctions are similarly "leaky" in small intestine, choroid plexus, and renal proximal tubule, but are relatively tight in frog skin, urinary bladder, salivary and sweat duct, and probably renal distal tubule and stomach. The opposite extremes in this spectrum are rat proximal tubule and rabbit urinary bladder, with junctional resistances of 4 Ω-cm^2 and over 300,000 Ω-cm^2, respectively.

With the recognition that epithelia vary widely in junctional tightness, much of the previously observed diversity in epithelial physiology fell into place. The epithelia with low open-circuit voltages, low transepithelial resistances, and only modest solute gradients maintained by active transport proved to be the epithelia with leaky junctions, and the explanation for these properties followed immediately from the high passive permeability of the junctions of these epithelia to ions. Conversely, the epithelia with high open-circuit voltages, high electrical resistances, and steep gradients maintained by ion transport proved to be the tissues in which the junctional gates are closed.

The teleological reasons why the gates are closed in certain epithelia and open in others are only partly understood. The reason why urinary bladder, frog skin, stomach, salivary and sweat duct, and distal tubule must have "tight tight junctions" is clear: the function of these tissues is to build up steep gradients of Na^+ or H^+, and this would be impossible if passive ion permeation down gradients were rapid. Not so clear is why gallbladder, small intestine, proximal tubule, and choroid plexus have "leaky tight junctions" and whether they would function equally well with the junctional gates closed. A possible reason is that leaky junctions are somehow involved in coupling of passive solute and water fluxes to fluxes of actively transported solute. Similarly unclear is the structural basis of differences in junctional tightness among epithelia. Is it that variation in junctional resistance is due to variation in the number of structural "strands" which the junction interposes between the lumen and lateral intercellular space? Is the variation due to different pore sizes of the junctional pathways? Or is it due to differences in charges which line the junctional wall and control ion permeability, as will be illustrated later in Fig. 3?

The fence. These gate studies showed that much of epithelial diversity arises from junctional diversity. However, epithelia also differ in their cell membranes, and this brings us to the question of the fence. The existence of a fence has been implicit in many discussions of epithelial physiology since 1950, but this problem has rarely been considered explicitly. Numerous studies have shown that the opposite-facing membranes of epithelial cells, the apical and basolateral membranes, have quite different properties. What is the fence that lets a cell maintain differences between two membranes that join each other and that presumably possess fluidity? Let us consider three examples of these differences, in order to appreciate how sharp is the dividing line at the putative fence?

1. The apical and basolateral membranes of epithelia differ biochemically. A well-known example is that the membrane-bound enzyme sucrase of the small intestine is confined to the apical membrane. Conversely, Na^+-K^+-activated ATP-ase is confined to the basolateral membrane in the intestine and kidney. In intestine the membranes differ in their phospholipid-to-cholesterol ratio.

2. In several leaky epithelia, such as small intestine and proximal tubule, the apical but not the basolateral membrane has a mechanism that serves the passive, coupled entry of Na^+ and nonelectrolytes, such as sugars and amino acids. The apical membrane of small intestine and gallbladder has a similar

mechanism for passive coupled entry of Na^+ and Cl^-. In contrast, the basolateral membrane of small intestine and gallbladder has an active Na^+ pump. The basolateral membrane of these epithelia may also have a Cl^- carrier: net lumen-to-blood Cl^- fluxes across this membrane are apparently down the electrochemical gradient, but the partial conductance of Cl^- is probably much too low to account for the flux without a carrier. Thus, the apical and basolateral membranes of these leaky epithelia differ markedly in their ion transport mechanisms.

3. Just as in leaky epithelia, the two membranes of tight epithelia also differ in their ion transport mechanisms. Until recently, quantitative assessment of these differences was much more difficult than in leaky epithelia, because the high resistance of tight epithelia meant that ion conductance at the damaged tissue edge could dominate measured properties. In the last few years Higgins, Cesaro, Gebler, and Frömter (1975), and Simon Lewis and I (1976), independently devised a method for virtually complete elimination of edge damage. With this new method Lewis and I found junctional resistance of rabbit urinary bladder to exceed 300,000 Ω -cm^2. Here is a tissue in which the tight junctions really are like cement, as classical anatomists assumed. The transcellular resistance of rabbit urinary bladder was shown by the new sealing methods to be up to 80,000 Ω -cm^2, and nearly as high resistances were obtained in frog skin and *Necturus* urinary bladder. However, these cellular resistances were found to vary greatly with physiological state. Active Na^+ transport is associated with an electrical conductance, such that epithelial resistance of rabbit urinary bladder decreases from 80,000 to 2,000 Ω -cm^2 with increasing short-circuit current. These conductance changes arise entirely in the apical membrane, which possess a Na^+ entry mechanism that is probably passive and is blocked by calcium and by the drug amiloride. (Amiloride acts as a diuretic because it blocks cellular Na^+ uptake, hence Na^+ reabsorption, in distal parts of the nephron). Whether this mechanism is a carrier or pore remains unknown. A similar Na^+ entry step is probably present in the apical membranes of most Na^+-absorbing tight epithelia. In contrast. the basolateral membranes of these epithelia have an active Na^+ pump, requiring HCO_3^- and inhibited by ouabain.

Let us now return to the question of the fence. Both in leaky and in tight epithelia, the apical membrane differs greatly from the basolateral membrane, as must be true for there to be net transport across the epithelium. Yet membranes are at least partly fluid. How is it possible that, within a few hundred Å, as one rounds the corner of the cell from the apical membrane to the basolateral membrane, one encounters such a change in membrane properties? Where is the fence that separates the amiloride-sensitive entry mechanism from the Na^+ pumps in tight epithelia, or that separates the Na^+ cotransport carriers from the pumps in leaky epithelia? Presumably the fence is at the tight junctions, which constitute hoops completely encircling each cell at this corner. Yet we have no direct evidence at all about the structural basis of the fence. Are the tight junctional structures that constitute the extracellular gate anchored to a hoop of membrane structures that constitute the fence? Is the fence part of a scaffolding that is distributed through the whole cell membrane, and that maintains the cell's shape? Cell asymmetry at the fence also raises questions of membrane assembly. Presumably there is on-going loss or destruction, balanced by synthesis, of the molecular constituents of pumps, entry mechanisms, and cotransport carriers in the steady state. As the cell synthesizes new molecules of these mechanisms, how do these molecules get steered to the correct side of the cell?

Despite these membrane differences across the fence, the two membranes must still transport the same solutes in series at the same flux rates, and must somehow know what each other is doing. This problem may be illuminated by the discovery, in rabbit urinary bladder, of feedback from the basolateral pump on the apical conductance mechanism. Decreases in pump rate, such as those produced by ouabain or removal of HCO_3^-, decrease apical conductance; increases in pump rate increase apical conductance (Lewis, Eaton and Diamond, 1976). Existence of such feedback is obviously important to cell volume regulation, since a decrease in pump rate without a compensating decrease in Na^+ entry would cause the cell to swell and burst. The feedback problem in the asymmetrical cells of epithelia is therefore relevant also to any symmetrical cell, where the pump and entry mechanism are not spatially separate. The mechanism of this feedback in epithelia remains unknown. One candidate is changes in intracellular Na^+ concentration. If so, however, the mechanism is somehow the opposite of the simple obvious effect of "high ion concentration → high conductance," as high intracellular Na^+ concentration would arise from a lowered pump rate, which proves to be associated with <u>low</u> conductance.

The existence of feedback is relevant to the unresolved question of aldosterone's site of action. As is well known, the hormone aldosterone stimulates Na^+ transport in many tight epithelia (e.g., frog skin, rabbit urinary bladder, amphibian urinary bladder, distal tubule, colon, salivary duct, sweat duct). This effect could result either from synthesis of new apical entry molecules, leading to increased cell (Na^+) and hence to increased basolateral pumping; or else from synthesis of new basolateral pump molecules (or of increased energy supply to the pump), leading to lowered cell (Na^+) and hence to increased apical entry. Discriminating between these two theories is difficult, because the presence of feedback means that aldosterone will increase both apical conductance and basolateral pumping, whichever mechanism is the primary target of aldosterone's action.

Although aldosterone acts on many tight epithelia, there is no leaky epithelium in which it has been shown to stimulate transport. This difference is not due to the aldosterone receptor being present but with its transport effects somehow shunted out in leaky epithelia: Nicolette Farman (personal communication) found that specific receptors for aldosterone can be detected biochemically in tight epithelia but not in gallbladder, a leaky epithelium. Thus, tight and leaky epithelia do not just consist of the same cells shunted by junctions of differing leakiness, but also differ systematically in their cell membranes. Two further differences between the cell membranes of tight and leaky epithelia are that only tight epithelia have the amiloride-sensitive Na^+ entry mechanism in their apical membrane, while only leaky epithelia have Na^+ cotransport mechanisms in their apical membrane. It is unclear why, teleologically, the distributions of these three epithelial mechanisms (aldosterone receptors, amiloride receptors, amiloride-sensitive Na^+ entry, Na^+ cotransport) should be so closely correlated with junctional tightness or leakiness.

Emergent Properties

Let us now consider how the roles of junctions as bridge, gate, and fence transform the emergent properties of the whole epithelium. Black-box analysis of epithelial permeability and coupling mechanisms can yield completely misleading conclusions about mechanisms at the membrane level, if one does not consider effects of epithelial organization. I shall illustrate this point by recounting misinterpretations which I proposed for two epithelial phenomena in the 1960's and which I must now dismiss as youthful follies: "electrokinetic phenomena" and osmotic water permeability.

Folly number 1: "electrokinetic phenomena." In 1962 I observed that osmotic water flow across gallbladders separating solutions of identical ionic composition give rise to electrical potential differences directly proportional to the flow rate, and hence formally identical to the flow-related potentials named streaming potentials and often observed in artificial membranes (Diamond, 1962). Other workers subsequently described similar phenomena in small intestine and choroid plexus. The electrokinetic phenomenon that is the opposite of streaming potentials and is also often observed in artificial membranes is termed electroosmosis. In 1969 James Wedner and I observed in gallbladders a phenomenon formally identical to electroosmosis: transepithelial passage of electric current gave rise to transepithelial water flow (Wedner and Diamond, 1969). While the epithelial observations do behave phenomenologically as electrokinetic effects, I drew in 1962 the incorrect inference that the "streaming potentials" also arose mechanistically as an electrokinetic effect at the membrane level--i.e., that they were due to frictional interactions between ions and water traversing the same membrane channels. We were spared this error when we observed "electroosmosis" in 1969, for we simultaneously made the observation that refuted this interpretation. When we applied a transepithelial current to obtain water flow, the voltage we recorded consisted not only of the expected IR step in phase with the current, but also of a voltage that developed more slowly and outlasted the current by many minutes. This slow voltage change showed that ion concentration gradients were being built up within the epithelium.

It turned out that both "streaming potentials" and "electroosmosis" in gallbladder are actually unstirred-layer effects within the epithelium. "Streaming potentials" arise because osmotic volume flow sweeps solute into or out of the lateral intercellular spaces, changing the ion concentrations there, and the local ion concentration gradient across the junctions sets up a diffusion potential. "Electroosmosis" arises because current flow changes ion concentrations within the epithelium through the transport-number effect (Barry and Hope, 1969a, 1969b), and the local osmotic gradient across the epithelium sets up osmotic flow. Both of these coupling phenomena arise from the whole organization of the epithelium and its internal unstirred layers, not from true electrokinetic interactions at the membrane level. No examples of true electrokinetic phenomena have been observed in any epithelium. If they do exist at all, they are below the limit of detection. The same unstirred-layer effects also contribute importantly to apparent electrokinetic phenomena in some artificial membranes.

Folly number 2: measurements of osmotic water permeability. Knowledge of the osmotic water permeability (abbreviated P_{osm}) of epithelia is of interest in several connections, such as in assessing mechanisms of solute-linked water transport. In the 1960's most epitheliologists, myself included, adopted a direct approach: impose an external osmotic gradient, measure volume flow in the steady state, and calculate P_{osm} as the ratio of volume flow to imposed gradient. For leaky epithelia such as intestine, gallbladder, choroid plexus, and proximal tubule, this method yields P_{osm} values ranging from 6×10^{-5} to 8×10^{-3} cm/sec, osmolar.

However, the reinterpretation of "streaming potentials" discussed in the previous section shows that imposition of external osmotic gradients leads rapidly to solute polarization within the epithelium. From the magnitude of the "streaming potential," reinterpreted as a diffusion potential, one calculates that the effective osmotic gradient to drive water flow is reduced at least an order of magnitude below its nominal value, because the internal gradient due to solute polarization is opposite to and nearly as large as the imposed gradient. The conclusion is that measured P_{osm} values underestimate true values at least 10-fold. In elegant experiments on the alga *Chara australia*, Barry and Hope (1969b) used a fast and sensitive method to measure water flow as a function of time, while they used a chloride electrode near the membrane to monitor solute concentration changes simultaneously. Readers eager to savor the full horror of the solute polarization effect, and the errors it produces in P_{osm} measurements, will find this paper by Barry and Hope satisfying (especially their Fig. 16).

Only slightly less horrifying (because volume flows but not concentration changes were measured as a function of time) is the direct demonstration by Wright, Smulders, and Tormey (1972) of how solute polarization distorts P_{osm} measurements in gallbladder. Measuring volume flow (J_v) with a time resolution of 5 min, these authors found that J_v is at least 10 times higher at a time 5 min after imposition of an external osmotic gradient than in the steady state 30 min later. The curve of J_v versus time is so steep in its early phase that the initial J_v value must have been at least 10 times higher again than the 5-min value. Thus, if one cannot measure J_v before internal solute polarization has decreased the effective osmotic gradient, the calculated P_{osm} will be an underestimate by a huge factor. Yet the solute polarization (as gauged by the time course of "streaming potentials") has a half-time of a few seconds in gallbladder, and probably a fraction of a second in perfused renal tubule. No method for measuring J_v in epithelia remotely approaches this time resolution. Even in renal tubule a measurement of J_v takes about 30 sec. The unfortunate conclusion is that available P_{osm} determinations for leaky epithelia are literally worthless, except to indicate lower limits. We have no idea how much higher than the highest measured value of 8×10^{-3} cm/sec, osmolar the true values actually are. Here too, as with apparent electrokinetic phenomena, the organization of the whole epithelium puts a quite different interpretation on measured black-box properties.

Solute-linked water transport. The two previous sections illustrate how epithelial organization can be a nuisance to physiologists. However, this organization is essential to one of the main functions of epithelia, the coupling of water transport to active solute transport.

Virtually all epithelia generate active transepithelial fluxes of solute. These solute fluxes are accompanied by and coupled to passive water flow. In some but not all epithelia, the ratio of water flow to solute flux is such that the transported fluid is isotonic to the animal's plasma. (The correlation is that leaky epithelia, like gallbladder, small intestine, and proximal tubule, and "medium-tight" epithelia, like stomach, colon, and

ADH-treated collecting duct, transport isotonic fluids. Tight epithelia, like urinary bladder, frog skin, and salivary and sweat duct, transport hypertonic fluids.) In four of these isotonically transporting epithelia (gallbladder, small intestine, pancreas, and Malpighian tubule) the further experiment has been performed of varying the bathing solution osmolarity, with the result that transported osmolarity is equal to bathing osmolarity over a 10-fold range. The only reasonable conclusion is that water transport involves complete osmotic equilibration of actively transported solute somewhere within the epithelium. That is, active solute transport into or out of some local space within the epithelium makes this space hypotonic or hypertonic, and water flows across the epithelium down the resulting gradient between the space and the external solution. (The one recent dissenting view, Hill's electroosmotic theory, will be discussed on p. 15). In proximal tubule and perhaps small intestine there is an added complication: besides actively transported solute, much additional solute passively diffuses or is dragged across leaky junctions into the primary transported fluid, and this carries more water by codiffusion (Fordtran, 1975; Boulpaep, 1975; Andreoli, Schafer, and Patlak, 1977).

Is P_{osm} high enough in leaky epithelia to account for complete osmotic equilibration of transported solute? If the local space where equilibration took place were well-stirred, the transported osmolarity Os would be given by the expression

$$Os = \frac{C}{2} + \sqrt{\frac{C^2}{2} + \frac{M_o}{RTP_{osm}}} \qquad \text{(eq. 1)}$$

where

C = bathing solution osmolarity

M_o = active solute transport rate

R = gas constant

T = absolute temperature (Diamond, 1964).

Insertion of the P_{osm} values measured 10 years ago into eq. 1 predicted hypertonic absorbates: the P_{osm} values were apparently too low for complete equilibration.

However, combined physiological and anatomical studies showed that active solute transport took place into (or out of) the long and narrow lateral intercellular spaces, which are unlikely to constitute a well-stirred compartment (Tormey and Diamond, 1967) (Fig. 2). Direct evidence for a role of lateral spaces in osmotic equilibrium was provided by Wall, Oschman, and Schmidt-Nielsen (1970), who were able to withdraw fluid samples by micropipet from lateral spaces of transporting insect rectum and thereby demonstrated that the spaces were hypertonic. Given lack of stirring, the length of lateral spaces makes existence of standing osmotic gradients along the spaces likely. William Bossert and I derived the relevant differential equations and calculated resulting Os values by computer (Diamond and Bossert, 1967, 1968). Subsequently, Segel (1970) obtained a limiting analytical expression for Os:

$$Os = C(1 - K_2) \qquad \text{(eq. 2)}$$

where

$$K_2 \equiv \lambda[\sinh(k/\lambda)]/k \cosh k$$

$$k^2 \equiv 2\,C\,P_{osm}\,L^2/rD$$

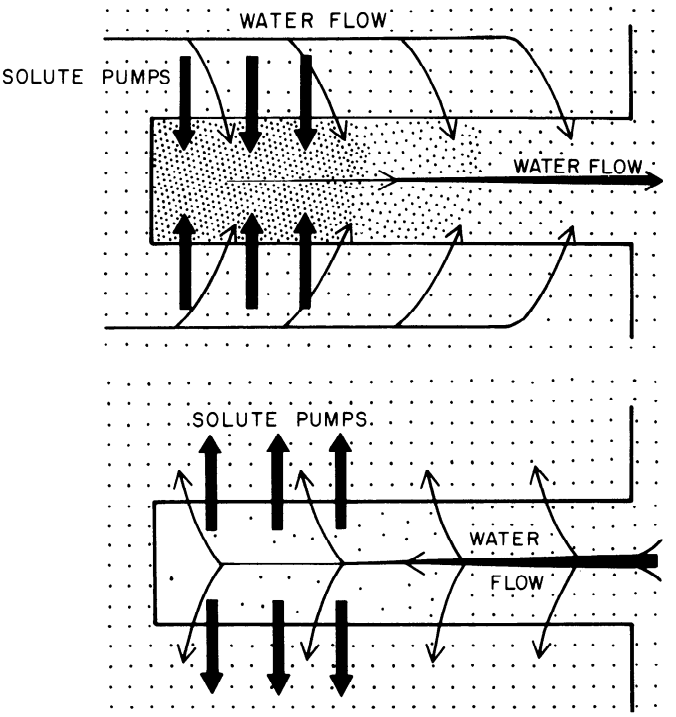


Fig. 2. Comparison of "forward" and "backward" operation of a standing-gradient flow system which consists of a long narrow channel closed at one end (e.g., a basal infolding, lateral intercellular space, etc.). The density of dots indicates the solute concentration. Forward operation (top): solute is actively transported into the channel across its walls, making the channel fluid hypertonic. As solute diffuses down its concentration gradient toward the open mouth, more and more water enters the channel across its walls due to the osmotic gradient. In the steady state a standing osmotic gradient will be maintained in the channel by active solute transport, with the osmolarity decreasing progressively from the closed end to the open end; and a fluid of fixed osmolarity (isotonic or hypertonic, depending upon the values of such parameters as radius, length, and water permeability) will constantly emerge from the mouth. Backward operation (bottom): solute is actively transported out of the channel across its walls, making the channel fluid hypotonic. As solute diffuses down its concentration gradient toward the closed end, more and more water leaves the channel across its walls owing to the osmotic gradient. In the steady state a standing osmotic gradient will be maintained in the channel by active solute transport, with the osmolarity decreasing progressively from the open end to the closed end; and a fluid of fixed osmolarity (isotonic or hypertonic, depending upon the parameters of the system) will constantly enter the channel mouth and be secreted across its walls. Solute pumps are depicted only at the bottom of the channels for illustrative purposes but may have different distributions along the channel. (From Diamond and Bossert (1968) with permission of Rockefeller University Press.)

In this expression L is the channel length, r channel radius, D solute diffusion coefficient, and λ the fraction of the channel length (measured from the blind end) over which active solute transport occurs.

Evaluation of eq. 2 requires knowledge of lateral space dimensions L and r, for which approximate ranges of values could be obtained from ultrastructural studies of epithelia by the mid-1960's. However, most of these studies either dispensed with statistical sampling and just selected "typical" electron micrographs for publication, or else relied on light microscopic techniques and were thus unable to resolve the narrower spaces. All of these studies dispensed with stereological analysis, which is essential for deducing measurements of three-dimensional structures from two-dimensional sections

(Weibel, 1973). Recently the first stereological analysis of lateral spaces in a transported epithelium has been carried out by Blom and Helander (1977), for rabbit gallbladder.

If one inserts into eq. 2 the L^2/r for rabbit gallbladder measured by Blom and Helander, together with the P_{osm} determinations of Wright, Smulders, and Tormey, one finds that osmotic equilibration along standing gradients would suffice, within a large margin of safety, to yield a virtually isotonic transported fluid (Diamond, 1977). If the equilibration space is too short for standing osmotic gradients to be significant, as may be true for proximal tubule, eq. 1 rather than eq. 2 applies. However, insertion of recent P_{osm} values for proximal tubule and gallbladder into eq. 1 still yields a nearly isotonic absorbate.

These calculations bring both good news and bad news to epitheliologists. The good news is that we are now close to a quantitative explanation of isotonic water transport in terms of measured channel dimensions and water permeability of epithelia. The bad news is that upwards revision of epithelial P_{osm} values since 1969 means downwards revision of the osmotic gradients expected to be present between lateral spaces and the external solution. The task of measuring these gradients in epithelia other than insect rectum has never seemed easy, because methods for rapid freezing, solute immobilization, and solute estimation in frozen sections must be developed. The smaller magnitude of the gradients than previously anticipated will make this task harder yet.

At this point mention must be made of two recent papers by A.E. Hill (1975a, 1975b). Many epitheliologists have been puzzled by these papers, in which Hill purported to show that "it seems virtually impossible that the intracellular and lateral spaces of fluid-transporting epithelia are in fact local osmotic coupling spaces" (Hill, 1975a, p. 99). Hill reached this conclusion by inserting what he claimed were typical P_{osm} and L^2/r values for epithelia into eq. 2. He went on to develop an electroosmotic theory of solute-linked water transport.

The explanation of this puzzle is as follows (Diamond, 1977). The P_{osm} value that Hill used, 10^{-5} cm/sec, osmolar, is nearly 1 – 3 orders of magnitude below the measured values for all leaky epithelia. It must be even further below the true values that take account of solute polarization. Hill justified the value of 10^{-5} cm/sec, osmolar on the grounds that it is representative of most cell membranes. In fact, it is below measured P_{osm} values of most cells (see for instance the tabulation by House, 1974, p. 165), and for cells other than erythrocytes these measured values are usually gross underestimates because of unstirred-layer-effects. Hill's L^2/r values were obtained from 12 publications, of which none employed stereological analysis, five only showed "typical" electron micrographs without measurements or statistical sampling, two relied on light microscopy, and one provided no morphological information at all. The L^2/r value Hill quoted for gallbladder proves to be what Tormey and I reported as the lowest extreme value rather than the average value. The resulting L^2/r values Hill used are far below that which Blom and Helander obtained by stereological analysis. Not surprisingly, Hill concluded that epithelial P_{osm} and L^2/r values are too low to account for water transport osmotically. His electroosmotic theory ignores the evidence indicating electroosmosis to be undetectably small in epithelia, and requires electroosmotic coupling efficiencies up to 550 water molecules per ion, one or two orders of magnitude above measured values for artificial membranes.

Uses of Epithelia to Physiologists

I shall conclude by considering a bridge between epithelial physiology and the rest of cell physiology. A prevalent attitude among physiologists in the 1960's went as follows: "If you want to understand basic things about cell membranes, study single cells, like nerve, muscle, and erythrocyte. Avoid epithelia because their organization is too complex."

Now that epithelial bridges, gates, and fences are better understood, physiologists can profit from some real advantages of epithelial sheets over single cells. These advantages include: durability (e.g., gallbladder withstands a pH range from 2.5 to 10.5, and osmolarities from about 60 to 600 mOsM); ready access to both sides of the preparation without need for perfusion; domination of electrical properties of leaky epithelia by a single channel, the junction; lack of the voltage dependence of ion permeabilities that makes nerve interesting but that is a nuisance for studies of permeability properties other than voltage dependence; drug control of ion permeability over one or two orders of magnitude, through amiloride; and pump-leak feedback between two separate membranes, rather than in the same membrane.

To illustrate these advantages, Figs. 3 – 7 present a brief smorgasbord of what epithelia (e.g., gallbladder) can contribute to basic permeability problems:

Fig. 3 illustrates the role of membrane charge in cation-anion discrimination. Cation conductance is constant above pH 5, then plummets with decreasing pH and is negligible below pH 3, while anion conductance changes in the reverse direction and at a lower pH. Evidently, cation conductance is controlled by membrane acidic groups with apparent pK_a near 4.5, and anion conductance is controlled by basic groups with pK_a below 3 (Wright and Diamond, 1968; Moreno and Diamond, 1974).

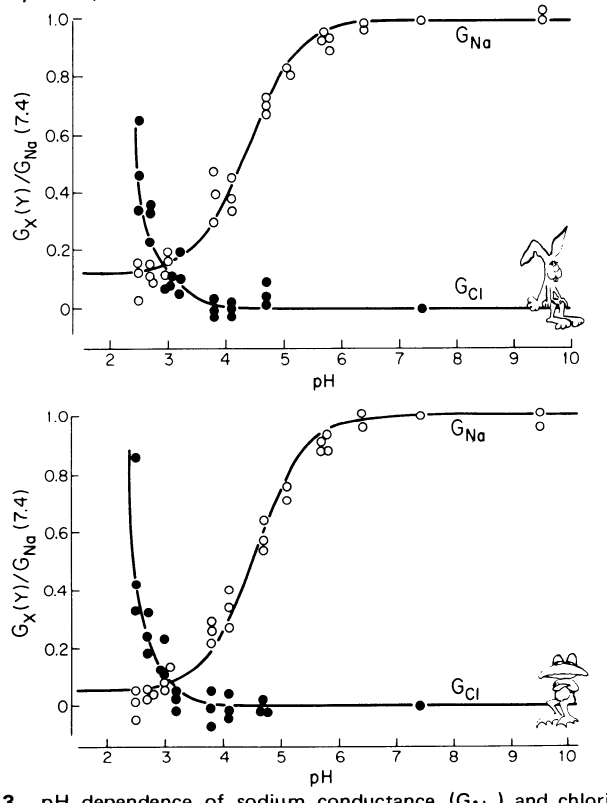


Fig. 3. pH dependence of sodium conductance (G_{Na}) and chloride conductance (G_{Cl}) in rabbit (above) and bullfrog (below) gallbladders. Ordinate is G_{Na} of G_{Cl} at the indicated pH, divided by G_{Na} at pH 7.4. After Moreno and Diamond (1974).

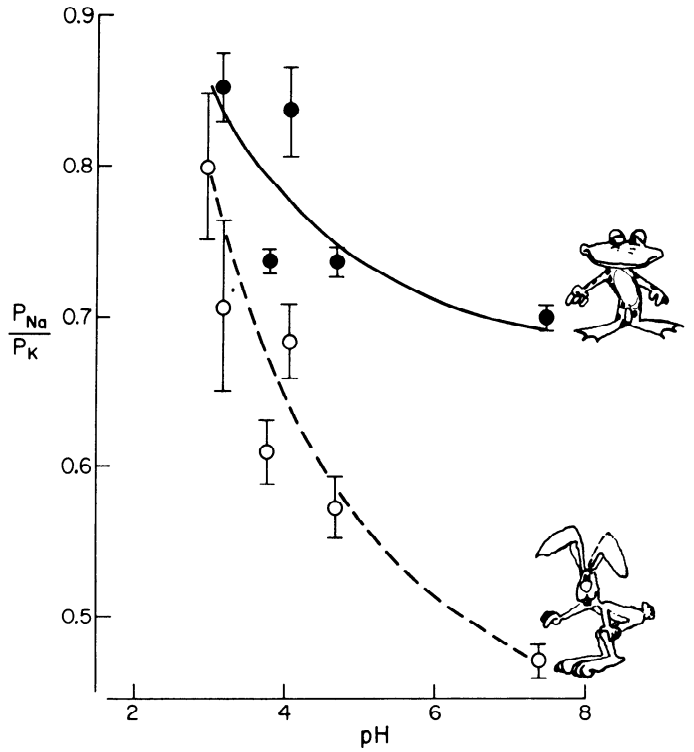


Fig. 4. pH dependence of the sodium-to-potassium permeability ratio in bullfrog (solid points and curve) and rabbit (open points and dashed curve) gallbladders. After Moreno and Diamond (1974).

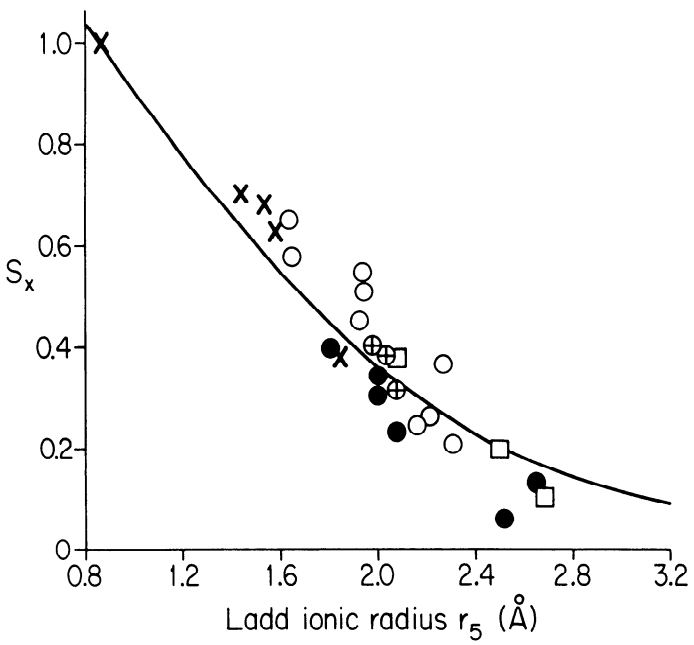


Fig. 5. Sieving of permeating cations by gallbladder tight junctions. Abscissa, the cation's ionic radius; ordinate, the cation's relative permeability coefficient in rabbit gallbladder divided by its relative permeability coefficient in bullfrog gallbladder, interpolated to the same site field strength in both species. Symbol X, inorganic cations; other symbols, organic cations. The solid curve is based on the Renkin equation with the best-fit values of effective pore radii (rabbit 5 A, bullfrog 8 A), (From Moreno and Diamond, 1975.)

Fig. 4 illustrates that electrostatic forces and membrane charge also play a role in cation-cation discrimination, as predicted by Eisenman (1962). The permeability ratio P_{Na}/P_K shifts with pH, as does P_{Cl}/P_{Na} (Moreno and Diamond, 1974).

From Fig. 5 one can conclude that cation-cation discrimination depends not only on electrostatic forces but also on steric effects. Ratios, between rabbit and bullfrog gallbladder, of relative permeability coefficients for numerous inorganic and organic cations vary with cation radius, once species differences in electrostatic forces have been removed. The variation suggests an effective channel radius around 5 Å for rabbit gallbladder, and around 8 Å for bullfrog gallbladder (Moreno and Diamond, 1975).

Fig. 6 depicts relative permeability coefficients of organic cations, corrected for the above-mentioned sieving. Permeability increases with the number of protons that the cation has available for hydrogen bonding, up to four protons. Evidently the membrane's cation binding sites are proton acceptors, presumably oxygen functions, that can form up to four strong hydrogen bonds with permeating cations (Moreno and Diamond, 1975).

In Fig. 7 we see that nonelectrolyte reflection coefficients (σ's) decrease with increasing oil/water partition coefficient, and that in some but not all membranes σ's are lower for small polar solutes than for other solutes with similar partition coefficients. This suggests that most nonelectrolytes cross membranes by dissolving in the lipid region, and that pores may also be present in some but not all membranes (Wright and Diamond, 1969; Hingson and Diamond, 1972).

All five experiments illustrated in Figs. 3 – 7 yield similar results if performed on nerve, muscle, or erythrocyte. However, the single-cell results are less extensive, harder to obtain, and cover a narrower pH range than the epithelial results.

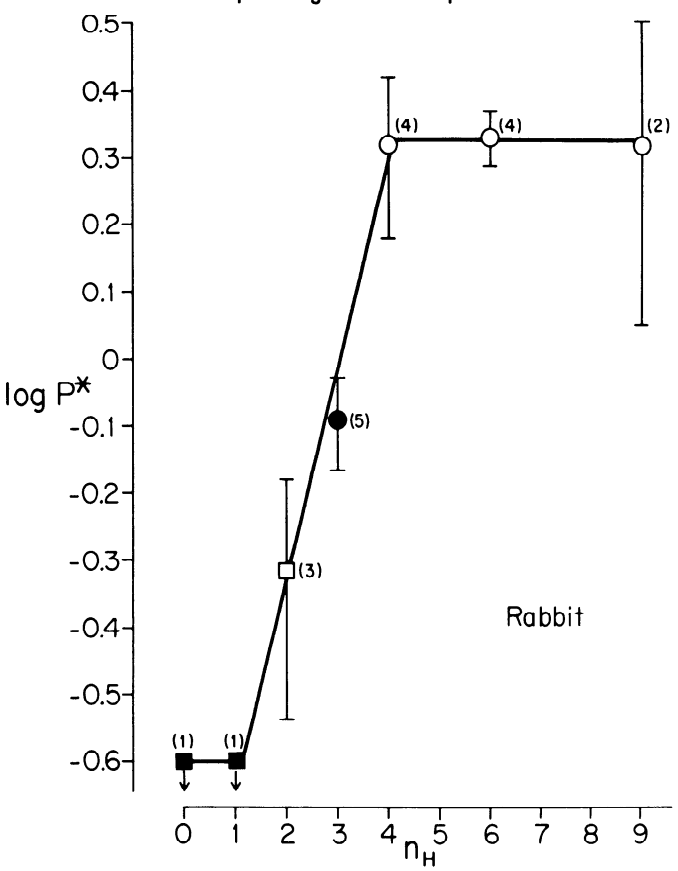


Fig. 6. Ordinate, relative permeability coefficients of organic cations in rabbit gallbladder, corrected for sieving on the basis of Fig. 5. Abscissa, number of protons on the cation capable of donation for hydrogen bond formation. Bars are standard deviations, numbers are the number of cations tested with the given n_H value. (From Moreno and Diamond, 1975.)

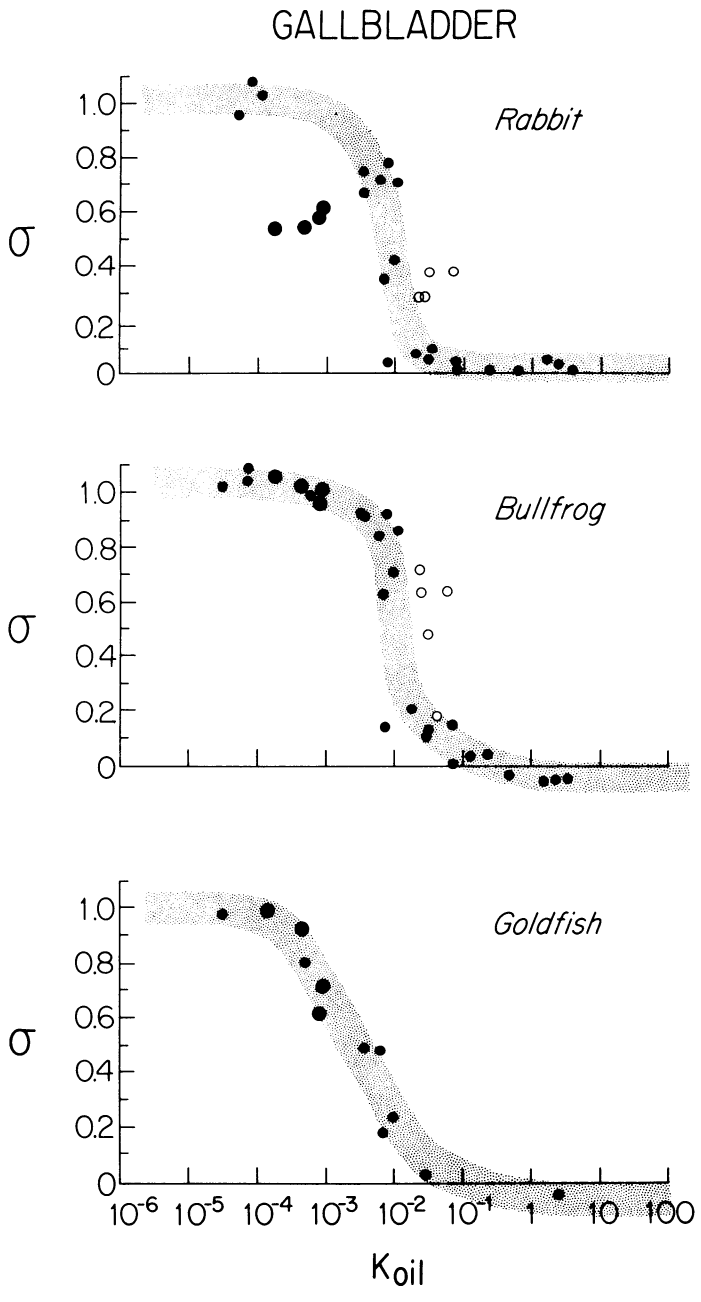


Fig. 7. Nonelectrolyte reflection coefficients (σ) in gallbladders of three species, as a function of the nonelectrolytes' partition coefficients between olive oil and water. Open circles refer to branched solutes. (After Hingson and Diamond, 1972.)

The moral of this smorgasbord is as follows. Perhaps you are not interested in the specific problems of epithelial organization; perhaps bridges, gates, and fences are all a nuisance to you; perhaps you wish to study basic questions common to all cell membranes, such as extraction of channels and carriers, or the origin of ion or nonelectrolyte selectivity. If so, consider seriously the advantages of epithelia!

With pleasure I acknowledge my debt to the colleagues who shared with me the excitement of studying epithelial organization: Peter Barry, William Bossert, Chris Clausen, Eberhard Frömter, Dickson Hingson, Simon Lewis, Terry Machen, Julio Moreno, John Tormey, James Wedner, and Ernest Wright.

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References

Andreoli, T.E., Schafer, J.A., and Patlak, C.S. (1977). Isotonic lateral intracellular spaces: a model for isotonic fluid absorption in the isolated proximal straight tubule. In: Coupled Transport Phenomena in Cells and Tissues. Edited by J.F. Hoffman, in press. Raven, New York.

Barry, P.H., and Hope, A.B. (1969a). Electroosmosis in membranes: effects of unstirred layers and transport numbers. I. Theory. Biophysical J. 9:700-728.

Barry, P.H., and Hope, A.B. (1969b). Electroosmosis in membranes: effects of unsitrred layers and transport numbers. II. Experimental. Biophysical J. 9:729-757.

Blom, H. and Helander, H.F. (1977). Quantitative electronmicroscopical studies on in vitro incubated rabbit gallbladder epithelium. Submitted to J. Cell Biol.

Boulpaep, E.L. (1971). Electrophysiological properties of the proximal tubule: importance of cellular and intracellular transport pathways. In: Electrophysiology of Epithelial Cells. Edited by G. Giebisch, pp. 258-263. Schatteur, Stuttgart.

Diamond, J.M. (1962). Mechanism of water transport by the gallbladder. J. Physiol. 161:503-527.

Diamond, J.M. (1964). The mechanism of isotonic water transport. J. Gen. Physiol. 48:15-42.

Diamond, J.M. (1977). Solute-linked water transport in epithelia. Chapter in book, Coupled Transport Phenomena in Cells and Tissues, ed. J.F. Hoffman. Raven, New York.

J.M. Diamond and W.H. Bossert. (1967). Standing-gradient osmotic flow: a mechanism for solute-linked water transport in epithelia. J. Gen. Physiol. 50:2061–2083.

J.M. Diamond and W.H. Bossert (1968). Functional consequences of ultrastructural geometry in "backwards" fluid-transporting epithelia. J. Cell Biol. 37:694-702.

Farquhar, M.G. and Palade, G.E. (1963). Junctional complexes in various epithelia. J. Cell Biol. 17:375-412.

Fordtran, J. S. (1975). Stimulation of active and passive sodium absorption by sugars in the human jejunum. J. Clinical Investigation 55:728-737.

Frömter, E. (1972). The route of passive ion movement through the epithelium of *Necturus* gallbladder. J. Membrane Biol. 8:259-301.

Frömter, E. and Diamond, J.M. (1972). Route of passive ion permeation in epithelia. Nature New Biol. 235:9-13.

Higgins, J.T., Cesaro, L., Gebler, B., and Frömter, E. (1975). Electrical properties of amphibian urinary bladder epithelia. I. Inverse relationship between potential difference and resistance in tightly mounted preparations. Pflügers Arch. 358:41-56.

Hill, A.E. (1975). Solute-solvent coupling in epithelia. A critical examination of the standing-gradient osmotic flow theory. Proc. Roy. Soc. Lond., B. 190:99-114.

Hill, A.E. (1975). Solute-solvent coupling in epithelia. An electroosmotic theory of fluid transfer. Proc. Roy. Soc. Lond., B. 190:115-134.

Hingson, D.J. and Diamond, J.M. (1972). A comparative study of nonelectrolyte permeation in epithelia. J. Membrane Biol. 10:93-135.

House, C.R. (1974). Water Transport in Cells and Tissues. Williams and Wilkins, Baltimore.

Keynes, R.D. (1969). From frog skin to sheep rumen. A survey of transport of salts and water across multicellular structures. Quart. Rev. Biophys. 2:177-281.

Lewis, S.A. and Diamond, J.M. (1976). Sodium transport by rabbit urinary bladder, a tight epithelium. J. Membrane Biol., in press.

Lewis, S.A., Eaton, D.C. and Diamond, J.M. (1976). The mechanism of sodium transport by rabbit urinary bladder. J. Membrane Biol., in press.

Loewenstein, W.R., Socolar, S.J., Higashino, S., Kanno, Y., and Davidson, N. (1965). Intercellular communication: renal, urinary bladder, sensory, and salivary gland cells. Science 149:295-298.

Moreno, J.H. and Diamond, J.M. (1974). Discrimination of monovalent inorganic cations by "tight" junctions of gallbladder epithelium. J. Membrane Biol. 15:277-318.

Moreno, J.H. and Diamond, J.M. (1975). Nitrogenous cations as probes of permeation channels. J. Membrane Biol. 21:197-259.
Sachs, G., Shoemaker, R.L., Blum, A.L., Helander, H.H., Makhlouf, G.M., and Hirschowitz, B.I. (1971). Microelectrode studies of gastric mucosa and solutated gastric cells. In: Electrophysiology of Epithelial Cells. Edited by G. Giebisch, pp. 258-263. Schatteur, Stuutgart.
Sakin, H. and Boulpaep, E.L. (1975). Models for coupling of salt and water transport. Proximal tubular reabsorption in *Necturus* kidney. J. Gen. Physiol. 66:671-734.
Segel, L.A. (1970). Standing-gradient flows driven by active solute transport. J. Theoret. Biol., 29:233-250.
Shiba, H. (1971). Heaviside's "Bessel cable" as an electric model for flat simple epithelial cells with low resistive junctional membranes. J. Theor. Biol. 30:59-68.
Tormey, J.M. and J.M. Diamond (1967). The ultrastructural route of fluid transport across rabbit gallbladder. J. Gen. Physiol. 50:2031-2060.
Ussing, H.H., Kruhoffer, P., Hess Thaysen, J., and Thorn, N.A. (1960). The Alkali Metal Ions in Biology. Springer, Berlin.
Wall, B.J., Oschman, J.L., and Schmidt-Nielsen, B. (1970). Fluid transport: concentration of the intracellular compartment. Science 167:1497-1498.
Wedner, H.J. and Diamond, J.M. (1969). Contributions of unstirred-layer effects to apparent electrokinetic phenomena in the gallbladder. J. Membrane Biol. 1:92-108.
Weibel, E.R. (1973). Stereological techniques for electronmicroscopic morphometry. In: Principles and Techniques of Electronmicroscopy. Edited by M.A. Hayat, 3:237-296. Van Nostrand Reinhold, New York.
Wright, E.M. and Diamond, J.M. (1968). Effects of pH and polyvalent cations on the selective permeability of gallbladder epithelium to monovalent ions. Biochim. Biophys. Acta. 163:57-74.
Wright, E.M. and Diamond, J.M. (1969). Patterns of non-electrolyte permeability. Proc. Roy. Soc. London B. 172:227-271.
Wright, E.M., Smulders, A.P., and Tormey, J.M. (1972). The role of the lateral intracellular spaces and solute polarization effects in the passive role of water across the rabbit gallbladder. J. Memb. Biol. 7:198-219.

A GENERAL APPROACH TO THE EVALUATION OF VENTILATION-PERFUSION RATIOS IN NORMAL AND ABNORMAL LUNGS*

By Peter D. Wagner
Department of Medicine, University of California-San Diego
La Jolla, California 92093

Ever since the central clinical importance of ventilation-perfusion inequality to gas exchange was realized many years ago, gas exchange physiologists have searched for methods by which to characterize the distribution of ventilation-perfusion ratios.

In terms of clinical usefulness, it was a major breakthrough when some 25 years ago, Riley and his colleagues (12-14) developed the 3-compartment analysis of venous admixture, physiologic deadspace and the ideal point. Even though it was fully appreciated that real lungs were highly unlikely to consist literally of just those 3 compartments, their scheme aided considerably in the understanding of gas exchange, and it has become not merely well-accepted, but regarded as one of the charter contributions to gas exchange physiology.

Much the same can be said for the similar efforts of Briscoe (1,2) and, for those interested in the application of non-respiratory gases to the evaluation of gas exchange, for the 2-compartment analyses of Farhi and Yokoyama based on measurements of inert gas exchange (4,5,16).

Then, in 1968, Lenfant and Okubo (8) argued that if more raw data could be prized from the lungs, enough might be obtained from which to determine approximate but continuous distributions of ventilation-perfusion ratios, and so break away from the traditional (and comfortable) 2- or 3-compartment analyses. While Lenfant and Okubo used as their forcing functions different levels of inspired O_2 concentration, very similar transformations were shown to be possible with other forcing functions such as the use of several inert gases of different solubilities (15). However, in both cases, the quantity and quality of the data were limited, and the concept of fitting such data with continuous or essentially continuous distributions has met with considerable resistance on theoretical grounds (9,10).

A major descriptive problem therefore exists, both with the multiple inspired O_2 and the multiple inert gas approaches. The problem is how to properly handle multiple gas data so as to gain the greatest amount of insight into the properties of ventilation-perfusion distributions, both without overstepping the theoretical limitations inherent in the particular technique and without throwing away useful information.

It is precisely this problem to which I will devote these remarks, with reference to data corresponding both to normal and abnormal lungs.

There is however a second coexistent problem, and that is one of communication. Each forcing function (that is, each level of inspired O_2 or each different inert gas) supplies one dimension, so that for example in the 6 inert gas test (15), we have to communicate in 6-dimensional space. While this may be simple for the digital computer, it cannot be accomplished in a comprehensible manner at the personal level. Accordingly, the entire framework of the ensuing discussion will be confined to only 2 dimensions, and will in fact make use of the respiratory gases O_2 and CO_2 and the O_2-CO_2 diagram of Rahn and Fenn (11). I would stress however that the approach to be presented is entirely general and is applicable not only to the multiple inspired O_2 method and the multiple inert gas method, but also to the Riley 3-compartment scheme, the 3-inert gas method of Farhi and Yokoyama and even to peripherally related tests such as the multibreath nitrogen washout test for estimating ventilatory inequality.

*Taken from the introductory remarks given at the session on Pulmonary Gas Exchange at the 1976 Federation Meetings.

Ventilation-Perfusion Ratio Line on the O_2-CO_2 diagram

Recall the O_2-CO_2 diagram (Figure 1A). Rahn and Fenn showed how a unique curved line could be slung between known venous and inspired points and that any point on this line was associated with a single value of ventiliation-perfusion ratio ($\dot{V}_A/\dot{Q}$). This "$\dot{V}_A/\dot{Q}$ line" is of course the graphical solution to the steady state mass balance equations in the lung (that is, the Fick principle). The line can be "calibrated" in terms of $\dot{V}_A/\dot{Q}$ ratio as shown.

An exactly corresponding line exists in another coordinate system, namely that of the corresponding blood contents for O_2 and CO_2 (Figure 1B). Similar calibration with $\dot{V}_A/\dot{Q}$ values can be performed. This line has a special property—it is concave. That is, its slope decreases (becomes more negative) as $\dot{V}_A/\dot{Q}$ rises. The importance of this concavity is that since we are hypothesing that all lungs can be thought of as collections of homogeneous compartments situated along the concave line, all combinations of such compartments will have to give rise to a mixed arterial O_2 and CO_2 content point lying below the line (provided the weight given to each such compartment, i.e., the compartmental perfusions, are all positive). Note that because of the nonlinearity of the O_2 and CO_2 dissociation curves, we have to use the O_2-CO_2 content diagram rather than the O_2-CO_2 partial pressure diagram when combining compartments to form the arterial blood.

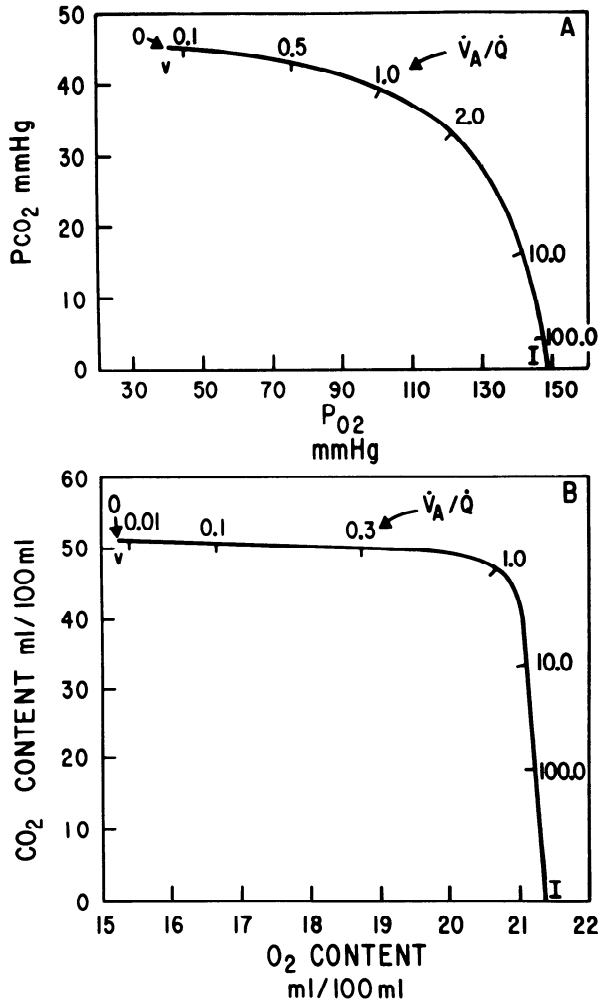

Fig. 1. O_2-CO_2 Diagrams. A. Standard diagram for P_{O_2} and P_{CO_2} showing the ventilation-perfusion ratio line calibrated with ventilation-perfusion ratios ($\dot{V}_A/\dot{Q}$). B. Corresponding $\dot{V}_A/\dot{Q}$ line on the O_2-CO_2 content diagram. Note the greater angularity of the latter. Both $\dot{V}_A/\dot{Q}$ lines are concave.

There is a limit to the area on the O_2-CO_2 content diagram that such combinations of compartments can occupy: it is given by the straight line joining the venous and inspired points. Thus, in Figure 2 is defined what we might call the region of possible outputs of lung models exchanging O_2 and CO_2. We are now ready to explore the problem referred to above. It is this:

As physiologists we would like to be able to take a measured arterial point and be able to recover useful information regarding the nature of the $\dot{V}_A/\dot{Q}$ inequality responsible for that point. We would like one model that fits the data and is useful, that is, more useful than just knowing the arterial point itself. Usefulness here might be diagnostic in that some pattern of inequality might be associated with a specific disease; it might be therapeutic if it gave an objective estimate of change in lung function after therapy more clearly than that obtained just from the arterial point alone. It might be prognostic in that with the model results, some predictions might be made as to the potential benefit or undesirability of certain therapeutic interventions. Furthermore, such a model may well lead to hypotheses that can be tested and so give more insight into the physiological abnormalities of gas exchange in disease.

However, as mathematicians, we would have to argue against the physiologists' preoccupation with a single model. This is because an infinite number of models will fit the data.

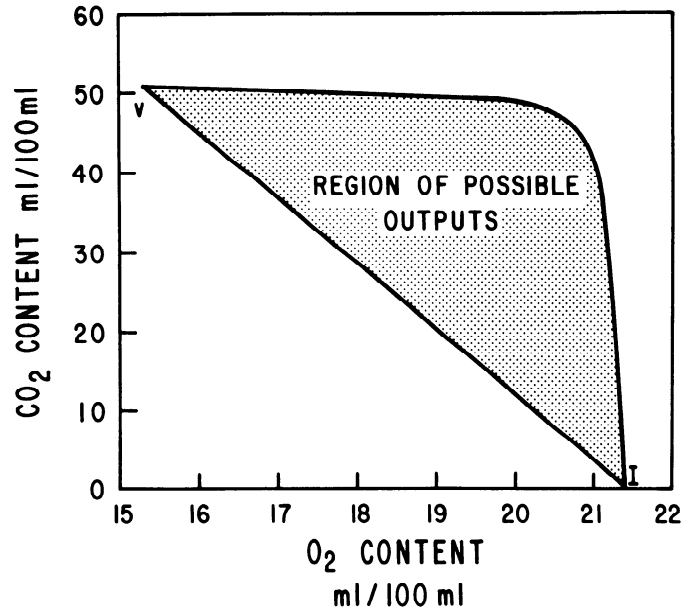

Fig. 2. Region of possible outputs. Stippled area defines possible locations of arterial O_2 and CO_2 content pairs formed by positive combinations of compartments along the $\dot{V}_A/\dot{Q}$ line.

Range of Possible Solutions

The O_2-CO_2 content diagram illustrates this dilemma especially well, based on a simple geometrical principle. Recall (Figure 3) that if one takes a straight line segment A-B and inserts a point C, the coordinate of C is given by an appropriately weighted average of the endpoints A & B. Turned around, if we know A, B, and C then we know the two weights that are associated with A and B to yield C. In this example, the weight of A is $\frac{4-3}{4-1}$ or 1/3; that of B is $\frac{3-1}{4-1}$ = 2/3. This principle was applied to gas exchange by Farhi and Yokoyama (5).

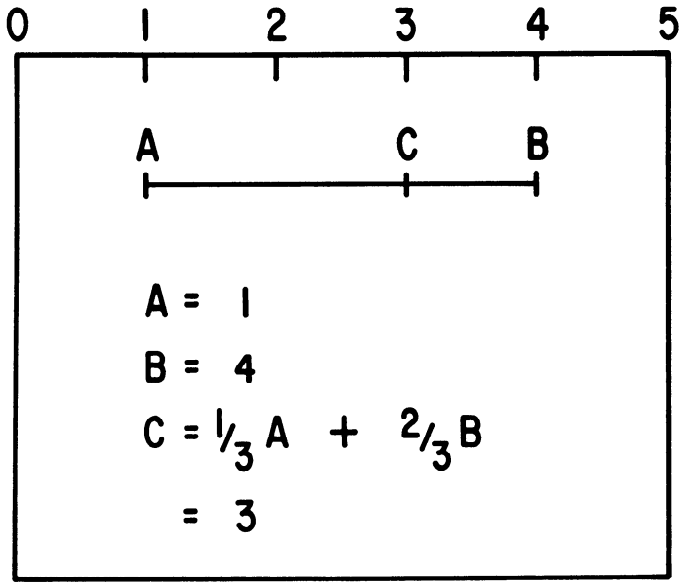

Fig. 3. Illustration of the quantitative description of a point C in an interval in terms of the endpoints A and B of that interval.

Applying the principle to an arterial point (Figure 4) it is immediately apparent that by rotating the intervals about the arterial point an infinite number of pairs of compartments exist that will explain the data point, and in each case the necessary fractional perfusions are given simply by the segment ratios as described above. Notice that some pairs contain quite high $\dot{V}_A/\dot{Q}$ ratios while others do not—yet all are precisely compatible with the same arterial point. It is important to note that the fractional perfusions given by this two-compartment analysis are in fact the maximum fractional perfusions that can be associated with each $\dot{V}_A/\dot{Q}$ value. Consequently by using this graphical approach upper bounds can be placed on perfusion in any region of the $\dot{V}_A/\dot{Q}$ spectrum.

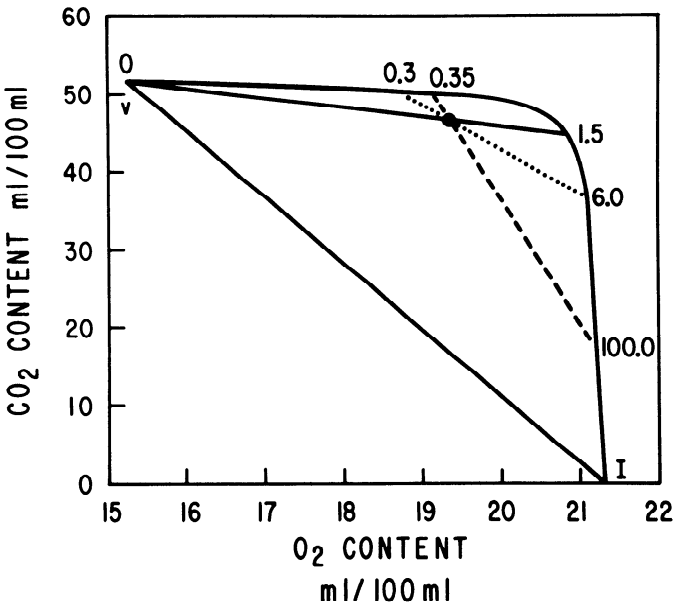

Fig. 4. Three possible two-compartment models precisely compatible with the arterial point given by the solid dot. The interval analysis of Figure 3 gives the fractional perfusions of the individual compartments (which are indicated by the intersection of each interval with the $\dot{V}_A/\dot{Q}$ line). Numbers are the $\dot{V}_A/\dot{Q}$ values of these compartments. Rotation of the interval about the arterial point by moving the endpoints along the $\dot{V}_A/\dot{Q}$ line from V to I gives an infinite set of precisely compatible two-compartment models.

At this point I would like to draw your attention to a semantic point that could cause confusion—the concept of uniqueness. Each compatible pair in Figure 4 represents a unique solution in that as soon as one $\dot{V}_A/\dot{Q}$ ratio is arbitrarily specified as a compartment, the other is defined uniquely by the straight line through the arterial point, as are the necessary fractional perfusions.

On the other hand, each particular two-compartment solution is clearly not the only one compatible with the given arterial point so that in the overall scheme, the given arterial point cannot be taken to be the result of any single $\dot{V}_A/\dot{Q}$ pair. (As will be shown it could also be the result of combinations of more than two compartments.)

Riley and his colleagues approached this problem by always giving the compartment pair in which shunt was maximized, and the value of shunt given by the present graphical analysis is precisely the venous admixture as defined many years ago by that group. This remains a clinically useful model in spite of tremendous problems of "non-uniqueness."

It is also possible to specify graphically sets of three-compartment lungs that are compatible with the arterial point of Figure 4. This specification will now be described, not as an intellectual exercise but rather because it points to a way of resolving the dilemma.

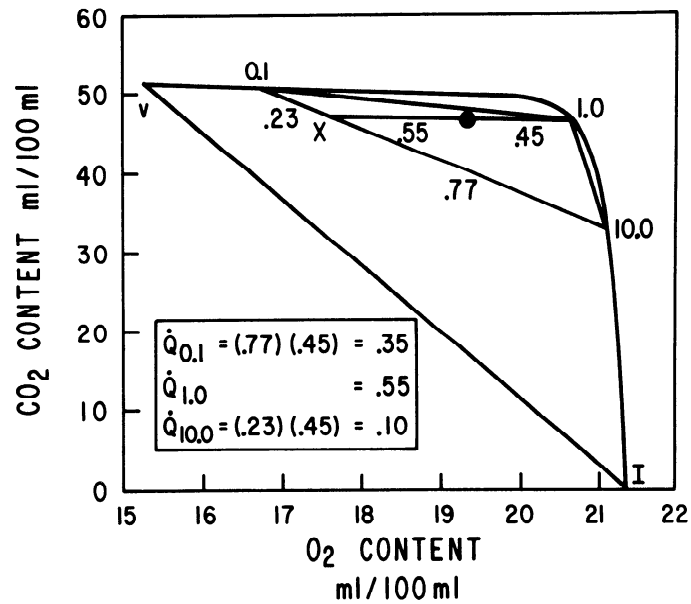

Fig. 5. One example of a precisely compatible three-compartment model. After choosing $\dot{V}_A/\dot{Q}$ values arbitrarily (here 0.1, 1.0, 10.0), their locations are joined to form a triangle and from the point of $\dot{V}_A/\dot{Q}$ 1.0 the interval is drawn through the arterial point to position X. The indicated segments and operations within the box give the necessary fractional perfusions.

Restrictions on possible solutions

A 3-compartment solution can be constructed as follows: choose 3 compartments arbitrarily (as in Figure 5 where $\dot{V}_A/\dot{Q}$ values of 0.1, 1.0 and 10.0 have been selected). Then draw the construction as shown. The segments indicated give the necessary fractional perfusions. Notice again that once the three $\dot{V}_A/\dot{Q}$ values have been chosen, the fractional blood flows are specified uniquely. But more importantly notice that such a construction is feasible only if the triangle formed by the 3 chosen $\dot{V}_A/\dot{Q}$ values does in fact contain the arterial point. Thus in Figure 6 the 3 compartments forming triangle A will explain the arterial point, but there is no way that the 3 com-

partments specifying triangle B can by themselves account for the arterial point, i.e., restrictions can be shown to exist on compatible models. In other words unique compartmental specification of distributions precisely compatible with a given data point is not possible, but it is possible to evaluate restrictions on possible models compatible with the data, and in the most general sense this suggests the way to proceed: choose one model that fits the data and is useful in the sense indicated above and then evaluate the restrictions that can or cannot be placed on other compatible models.

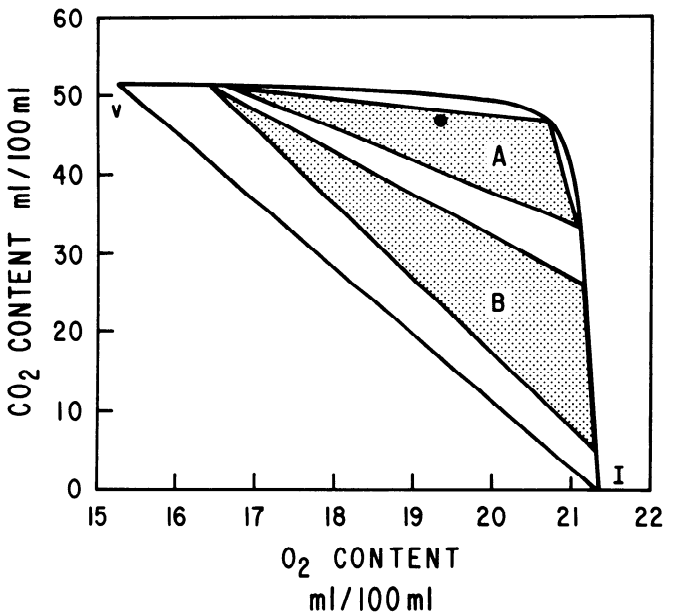

Fig. 6. Only sets of three compartments forming triangles that enclose an arterial point (●) can explain that point. Here, triangle A can account for the arterial O_2 and CO_2 contents but triangle B cannot, illustrating that in spite of lack of an unique solution, restrictions occur on compatible models.

A point of utmost importance regarding these restrictions can be made using the O_2-CO_2 content diagram, and is illustrated in Figure 7. If the arterial point lies precisely on the boundary of the region of possible outputs (A), the restrictions are complete: the point (in this two-gas example) represents a homogeneous lung of the associated $\dot{V}_A/\dot{Q}$ and is incompatible with any other compartmental arrangement. Point B is close to the boundary in the region of its maximal curvature. While in the strict mathematical sense uniqueness has been lost, fairly severe restrictions can still be placed on the values of compartmental ventilation-perfusion ratio and blood flow that will explain the point. By performing the rotational analysis of Figure 4 it can be seen that most of the blood flow must be in compartments of $\dot{V}_A/\dot{Q}$ close to 1, although small amounts of perfusion cannot be excluded from any region of the spectrum of $\dot{V}_A/\dot{Q}$. By contrast examine point C which is equally as close to the boundary as B, but in a region of very little curvature of the boundary. While essentially all of the perfusion could be in the $\dot{V}_A/\dot{Q}$ region close to 0.25, the point C could equally well arise as the result of a two-compartment lung with approximately equal perfusions at $\dot{V}_A/\dot{Q}$ ratios of zero and about 1. Thus the restrictions on point C are not nearly as tight as those on B. Finally, considering D, it is clear that for points deep in the interior of the possible region very little restriction can be placed on the compartmental distribution of perfusion.

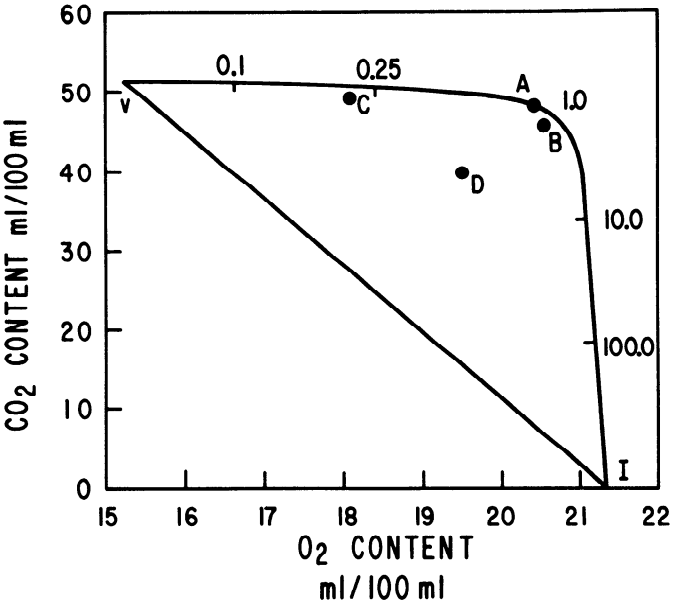

Fig. 7. Four hypothetical arterial points (A, B, C, D) are shown and in the text, the severity of restrictions on perfusion at any $\dot{V}_A/\dot{Q}$ is indicated for each point. In general, the closer the arterial point is to the boundary of the region of possible outputs, the tighter the restrictions that can be placed.

It is therefore evident that the restrictions that can be placed on compartmental models compatible with a given arterial point depend on the geometric location of that point within the region, so that a uniform description of the restrictions is quite definitely not possible. However, in general, the closer the data point is to the boundary of the region and the greater the number of forcing functions, the greater are the restrictions that can be placed on the compatible distributions. Figure 8 shows one example of the kind of restrictions that can be placed on arterial points calculated to result from narrow (A), bimodal (B) and broad (C) distributions of ventilation-perfusion ratios, each indicated by the solid line. The plots give the maximum fractional perfusion at each value of $\dot{V}_A/\dot{Q}$ in the spectrum both for the case where O_2 and CO_2 are the only test gases (O) and when the data of 6 inert gases are used (●). The calculation of maximum fractional compartmental perfusion in the latter case was performed by standard linear programming methods (3) that have been used for corresponding problems in other disciplines for many years. These plots show that for narrow distributions (whose arterial points lie near the boundary), even two gases greatly restrict the compatible distributions, but this is not the case for more interior points associated with broader distributions, where more gases are required for significant restriction.

Effects of random errors in the data

There has been studious avoidance of experimental error in the discussion up to this point, but no analysis of this type can be complete without allowing for random errors.

Figure 9A illustrates the effect of random error in the present context. If error is added to some known arterial point P then a circular cloud (corresponding to the normal distribution) is generated in two dimensions by adding random errors to P. Here it is assumed for simplicity that the standard deviations of experimental errors in the two gas contents are precisely the same (the cloud would otherwise be elliptical) and are in fact distributed normally. The relative density of this cloud in any region reflects the chance that if a measured

arterial data point, now containing error, lay in that particular region, it really came from the point A. Notice that in Figure 9A the cloud has points that lie both inside and outside the region of possible outputs. While we recognize that no lung model could give rise to such exterior points (in the absence of error), these points could well arise as a consequence of error, and the importance of their location will now be discussed.

Restrictions on possible solutions in the presence of random error

In Figure 9B, two measured arterial data points (X and Y) containing error are considered. Here we have no direct knowledge of the precise location of the real arterial point and our purpose is to develop a scheme for investigating the effects of error and finding the probable location of the real arterial point. Unlike the previous analysis of error-free data, where the various compatible models were all equally probable statistically, the analysis to be described introduces the concept of probability, since in general terms, the greater the distance between two points, the less likely is one point to be an explanation of the other.

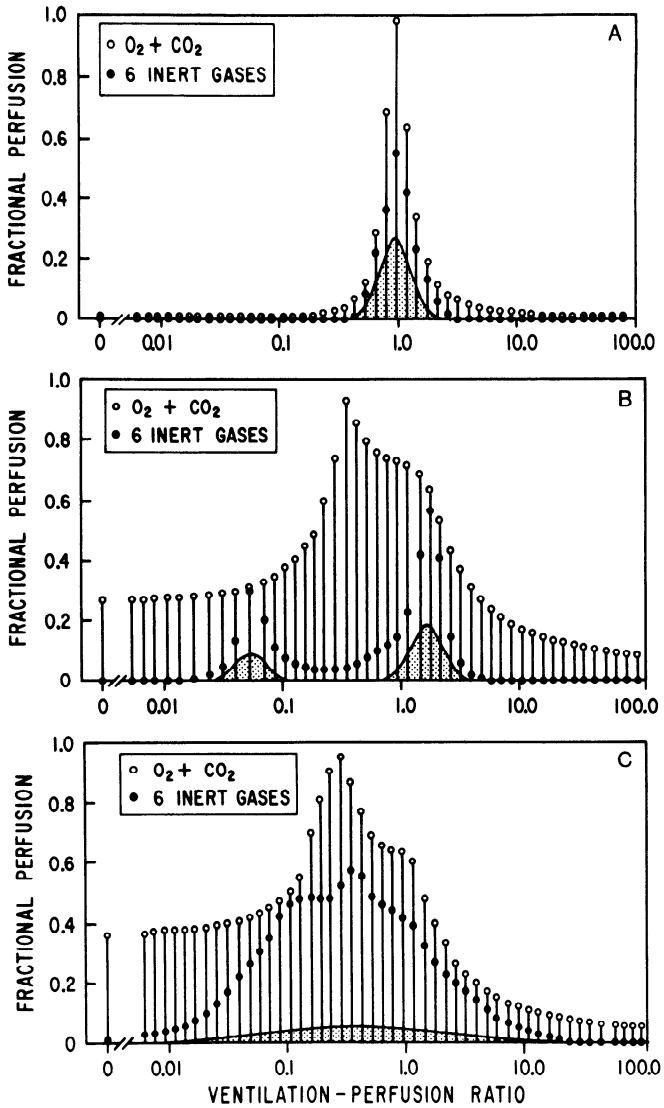

Fig. 8. Maximum possible fractional perfusion at several $\dot{V}_A/\dot{Q}$ values for each of 3 arterial points derived from narrow (A), bimodal (B) and broad (C) distributions. Results are given for the two-gas system (O_2 and CO_2 content, O) and for the 6 inert gas system (●). In each case, six forcing functions provide tighter restrictions than two, but in A the differences are of little physiological importance. A large improvement in resolution is afforded by 6 gases for the bimodal case (B), while in C the improvement in extending the data from two to six points is seen mainly at the upper and lower extremes of $\dot{V}_A/\dot{Q}$. All 3 examples clearly demonstrate the lack of resolution within a narrow range of $\dot{V}_A/\dot{Q}$.

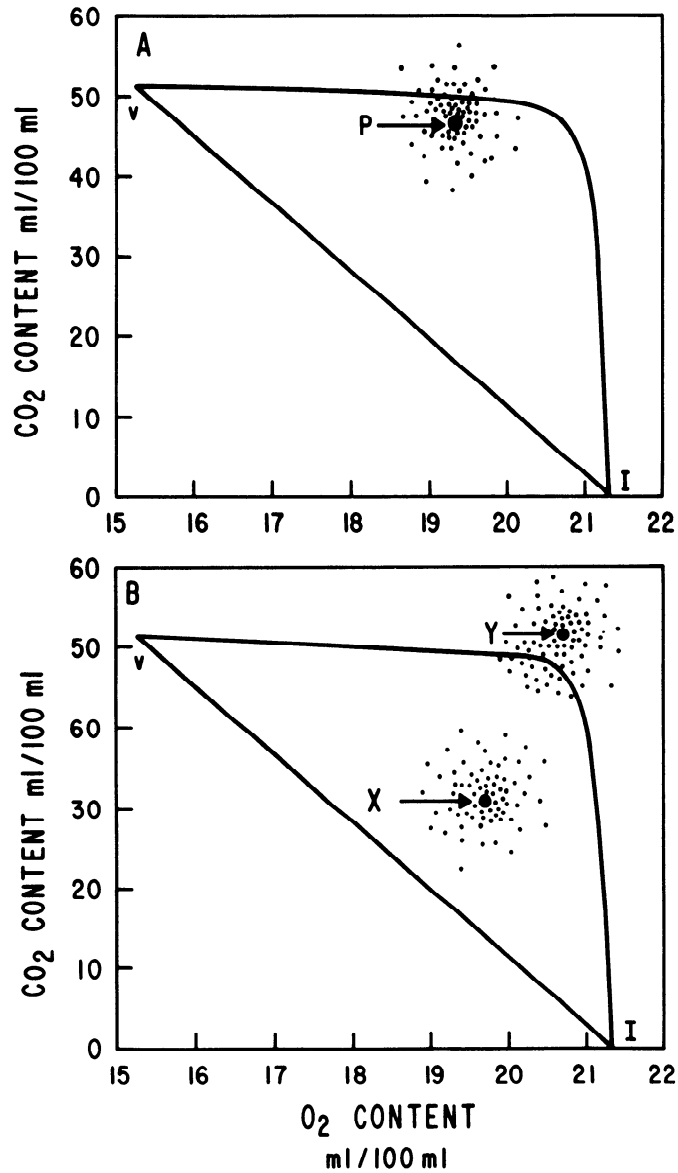

Fig. 9. Effects of normally distributed random error (assumed equal for O_2 and CO_2). A. Random error is added to a hypothetical known arterial point P. Note that some error-containing values so formed lie inside and some outside the region of possible outputs. B. Random error is subtracted from measured (error-containing) arterial data points X and Y. X lies deep within the permissible space; Y is an exterior point. The portions of the cloud of values lying within the permissible space in each case indicate in a probabilistic sense the region in which the real arterial point lies.

For the interior data point X, random error has been subtracted many times from X to form a density cloud which gives the probabilistic description of where the arterial point of the real lung could lie given error of a certain magnitude. Since in this example virtually all such points are found to lie within the permissible region, it is a straightforward matter to consult the X^2 table for two degrees of freedom (as the data consist of two observations) and establish the probability that the real arterial point lies within a certain distance of the

measured point X. Thus, we could select an appropriate probability, say 90%, and draw a circle of the corresponding radius (obtained from the X^2 table) around X. Statistically, this area will enclose 90% of the arterial points that through addition of error could have given rise to X.

We should now explore each point within that circle along the lines of the graphical analysis given earlier and in this way build up a picture of the restrictions that could be placed on distributions compatible with a given data point X. This picture will have taken account of the problem of non-uniqueness and also of experimental errors.

Unfortunately (from the mathematical standpoint) such a simple scheme for analyzing effects of error is not applicable to the exterior point Y, and the reason is evident on inspection of the density cloud of points centered on Y: Many of those points lie outside the permissible region, and it is accordingly not possible to find models that fit these points. Only those points lying within the permissible region require our attention as candidates for the real arterial point responsible for Y. Consulting the X^2 table in this case ignores the restrictions imposed by the geometry, and it is therefore not the appropriate test to use. If the measured data point in practice often lies outside the permissible space then we must develop an alternative scheme that will locate only those points in the density cloud that lie within the space. While such considerations may not often be necessary for O_2 and CO_2 as illustrated, they become increasingly important as more forcing functions are used. This is because for these more complex methods the relative volume of the permissible space is greatly reduced compared to the simpler case under discussion. Using the method employing 6 inert gases measured data points are virtually always found to be outside the permissible space.

Let us now consider what to do for the situation where the measured data point does lie outside the region of possible outputs. Given such a data point Y (Figure 9B), it is not difficult to locate a large number, say 50, of points lying within the permissible space, by repeatedly subtracting error from Y randomly and retaining only those points that fall within the space. Interior points are distinguished from exterior points by the inability of the latter to be fitted by any compartmental model using standard quadratic programming methods (7). This set of 50 interior points has sampled statistically the area from which the real lung giving rise to Y originated. Now we can explore as before the compatible distributions of each of these 50 data points to look for restrictions that can be placed on the amount of perfusion that could be located in different regions of $\dot{V}_A/\dot{Q}$ spectrum. Such analyses yield both qualitative information on the possible form of the distribution and quantitative probabilistic information on the variability of patterns of distribution.

This kind of analysis, which we may call "bounds analysis," is essential in order to understand and interpret information on $\dot{V}_A/\dot{Q}$ inequality obtained from any method involving gas exchange—whether it be the venous admixture analysis of Riley and coworkers, the compartmental analyses of Briscoe, King and coworkers based upon O_2 and CO_2, the analysis of Lenfant and Okubo in which progressive increases in inspired P_{O_2} were applied or the more recent multiple inert gas analyses (as evidenced by the work of Jaliwala et al. (6) and of Olszowka (9)). The appropriate "region of possible outputs" is definable for each of these various procedures and the corresponding bounds analyses can then be carried out. An example of this analysis for 49 such interior points calculated by subtracting error from the arterial retentions of 6 inert gases corresponding to a bimodal distribution is given in Figure 10.

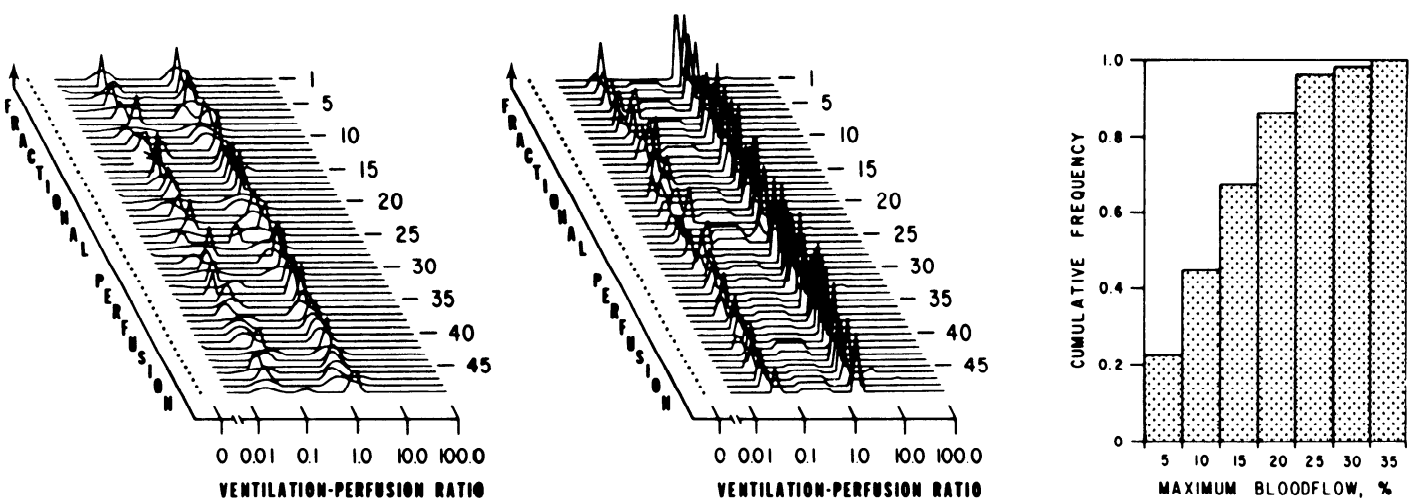

Fig. 10. Analysis (for 6 inert gases) of 49 arterial points lying within the region of possible outputs, randomly generated by subtracting error from the arterial point of the bimodal distribution shown in Figure 8. Left panel: 49 distributions corresponding to each such set (found using the ridge regression method with essentially no smoothing). Bimodality is strongly suggested. Middle panel: Maximum perfusion in the intermediate $\dot{V}_A/\dot{Q}$ region studied by linear programming methods as discussed in the text. Right panel: cumulative frequencies of these maximum perfusions in the intermediate $\dot{V}_A/\dot{Q}$ region showing that only 10% of the time will the maximum blood flow exceed 20% of the cardiac output.

Representative Solutions

There are however practical disadvantages to the routine use of bounds analysis, particularly with the more complex techniques involving several gases or O_2 at several inspired levels. They are tedious and expensive to perform even using specially designed routines and require considerable digital computer time. Moreover, the clinician is given the restrictions that apply to his patient, but no single model with which to make diagnostic, therapeutic or prognostic calculations. While bounds analysis is of great importance, some choice of one particular model should be made for the reasons given earlier. The problem is of course how to make that choice. A reproducible and objective method is required and Figure 11 suggests at least two such methods illustrated here for an exterior data point (Y).

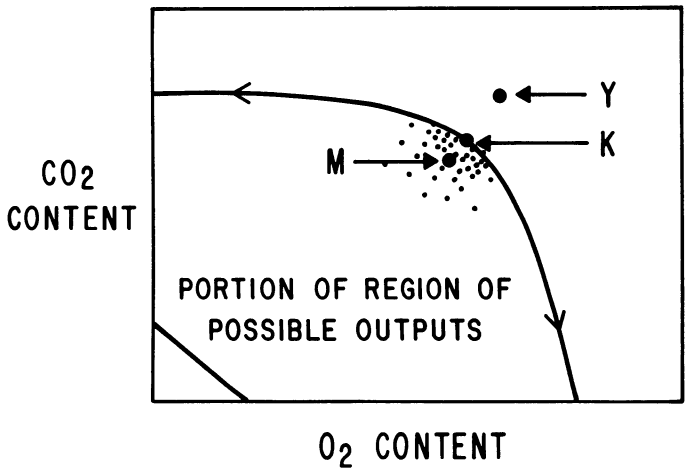

Fig. 11. Choice of one representative arterial point for the common case of the measured arterial point (Y) lying outside the region of possible outputs. Standard quadratic programming (least squares approach) will locate the boundary point (K) closest to Y. The ridge regression technique locates a point close to M (the center of mass of the region that in a probabilistic sense is the region of origin of the arterial point of the real lung) and is suggested as an appropriate choice.

One is to find the nearest point (K) in the permissible space to the data point Y. There is certainly no technical difficulty with this choice of a representative point: quadratic programming involving the least squares approach (7) will give this result. Note that the result (K) will always be a boundary point of the permissible space. Its principle advantage is that it definitely provides the best fit to the error-containing data point. However it is also precisely on the boundary of the region defined previously as the probable region of origin of the real arterial point and it gives no information about the rest of that probable region. In addition, for the case of O_2 and CO_2 illustrated here, K always represents a homogeneous lung and this is generally inappropriate. In the case of 6 inert gases, K, being on the boundary, represents a model consisting of no more than three ventilated and perfused compartments (or two ventilated and perfused compartments together with shunt and dead-space). Consequently, this choice of a representative solution will often conceal much of the available information. For example, when applied to error-perturbed data of cases B and C of Figure 8, this approach will give similar results for both, and the investigator may well fail to become alerted to the possibility that these two cases are different (as bounds analysis indeed shows). Finally, the results will be unstable in the presence of error, and changes in compartmental values may thus be interpreted incorrectly as real when in fact they only reflect random error.

A more representative and informative choice of a single compatible data point is the center of mass (M) of all the (50) points lying in this probable region. There are two ways to estimate the center of mass of these points. The first is simply to sum their coordinates and divide by their number, but while this operation is trivial, initial identification of the 50 points requires somewhat tedious analysis as indicated above. A second way of estimating the center of gravity is by the technique of enforced smoothing described in standard mathematical texts as the method of ridge regression (7). It is found empirically that when the amount of smoothing used in the ridge regression technique is just sufficient to stabilize results in the presence of random error, the associated data point closely approximates the center of mass of the probable region.

This approach involves the use of an arbitrary number of $\dot{V}_A/\dot{Q}$ compartments in the model since the matrix equation that is solved is always exactly determined (number of equations equals the number of forcing functions) whatever the number of compartments. This means that in the 6 inert gas method for example, where the model used has 50 virtual $\dot{V}_A/\dot{Q}$ compartments, the recovered 50-compartmental solution can never exhibit more than three modes. This would also be the case if the model contained 100, 1000 or any other number of compartments. While these general properties of the ridge regression method must be kept in mind, this multicompartment approach has advantages in addition to providing a stable result and a close approximation to M (Figure 11). The solutions found using this approach for case B and C of Figure 8 are very different in case B being bimodal and in case C being broad and not bimodal. This result is in contrast to the above direct least square approach, and does suggest differences between the two cases that can be tested by bounds analysis.

Experience with real data (from multiple inert gas studies of patients with asthma, chronic obstructive lung disease and interstitial lung disease) has confirmed the value of the ridge regression approach since in most cases, the grouping of lung units into two (or three) modes as suggested by ridge regression has been confirmed by bounds analysis.

As a final comment, while only the direct least squares and the ridge regression methods have been considered here in detail, it is not implied that no other reasonable representative choices could be made and defended.

In summary, several kinds of difficulty arise in the search for methods to depict $\dot{V}_A/\dot{Q}$ inequality both qualitatively and quantitatively. First, $\dot{V}_A/\dot{Q}$ inequality is generally estimated through methods of gas exchange, necessitating the construction of models as a framework. Any application of such methods must then be interpreted in the light of the associated assumptions (such as a purely parallel arrangement of compartments being perfused and ventilated continuously). This aspect has not been dealt with here. Second, in the absence of an infinite amount of data, complete (unique) specification of models compatible with data will not be possible even if there is no experimental error. However, graphical analysis of such a situation indicates that definite restrictions exist but will depend in a complex fashion both on the number of forcing functions (inert gases, levels of inspired P_{O_2}) used and on the location of the particular arterial point under study within the

space of permissible locations (that is, the extent and pattern of the ventilation-perfusion abnormality present in the lung).

Third, random experimental error loosens the restrictions that can be placed on compatible models. Probabilistic evaluations can be made and these should take advantage of the special geometrical features of the particular model being employed.

Consideration of these problems in the present geometric frame of reference suggests two complementary approaches in order to satisfy both the clinicians' need for a single working model and the mathematicians' objections to the non-unique nature of the problem:

It is possible to give a single representative model (for example, the approximation to the mean value of the probable region of origin of the arterial point). This requires very little computing time, gives generally stable results, and can be interpreted properly with experience.

It is also possible to determine restrictions on the class of compatible models by techniques referred to here as bounds analysis, taking account of both non-uniqueness and experimental errors. This is regarded as essential to proper interpretation of the data but is quite tedious owing to the large number of calculations required.

Since these methods, generally applicable to respiratory gas techniques such as those of Riley and Cournand, Briscoe, Lenfant and Okubo, to multiple inert gas techniques such as those of Farhi and Yokoyama and others and also to nitrogen washout techniques, give restrictions that depend heavily on the particular data, they need to be applied to actual data in each case before final judgment can be passed on the usefulness of these various tests in clinical practice.

Acknowledgments

It gives me much pleasure to acknowledge the important contributions of Dr. J. B. West and especially of Dr. J. W. Evans in the development of this work. Supported by NIH grants HL 17731 and HL 00111.

References:

1. Briscoe, W. A. A method for dealing with data concerning uneven ventilation of the lung and its effects on blood gas transfer. J. Appl. Physiol. 14:291-298, 1959.
2. Briscoe, W. A. Comparison between alveolo arterial gradient predicted from mixing studies and the observed gradient. J. Appl. Physiol. 14:299-303, 1959.
3. Dantzig, G. B. Linear Programming and Extensions. New Jersey: Princeton, 1963, pp. 94-108.
4. Farhi, L. E. Elimination of inert gas by the lung. Resp. Physiol. 3:1-11, 1967.
5. Farhi, L. E. and T. Yokoyama. Effects of ventilation-perfusion inequality on elimination of inert gases. Resp. Physiol. 3:12-20, 1967.
6. Jaliwala, S. A., R. E. Mates, and F. J. Klocke. An efficient optimization technique for recovering ventilation-perfusion distributions from inert gas data. Effects of random experimental error. J. Clin. Invest. 55:188-192, 1975.
7. Lawson, C. L. and R. J. Hanson. Solving Least Squares Problems. New Jersey: Prentice-Hall. 1974, pp. 160-164, 190.
8. Lenfant, C. and T. Okubo. Distribution function of pulmonary blood flow and ventilation-perfusion ratio in man. J. Appl. Physiol. 24:668-677, 1968.
9. Olszowka, A. J. Can $\dot{V}_A/\dot{Q}$ distributions in the lung be recovered from inert gas retention data. Resp. Physiol. 25:191-198, 1975.
10. Peslin, R., S. Dawson and J. Mead. Analysis of multicomponent exponential curves by the Post-Widder's equation. J. Appl. Physiol. 30:462-472, 1971.
11. Rahn, H. and W. O. Fenn. A graphical analysis of the respiratory gas exchange. The American Physiological Society, Washington, D.C., 1955.
12. Riley, R. L. and A. Cournand. 'Ideal' alveolar air and the analysis of ventilation-perfusion relationships in the lungs. J. Appl. Physiol. 1:825-847, 1949.
13. Riley, R. L. and A. Cournand. Analysis of factors affecting partial pressures of oxygen and carbon dioxide in gas and blood of lungs: Theory. J. Appl. Physiol. 4:77-101, 1951.
14. Riley, R. L., A. Cournand and K. W. Donald. Analysis of factors affecting partial pressures of oxygen and carbon dioxide in gas and blood of lungs: Methods. J. Appl. Physiol. 4:102-120, 1951.
15. Wagner, P. D., H. A. Saltzman and J. B. West. Measurement of continuous distributions of ventilation-perfusion ratios: theory. J. Appl. Physiol. 36:588-599, 1974.
16. Yokoyama, T. and L. E. Farhi. Study of ventilation-perfusion ratio distribution in the anesthetized dog by multiple inert gas washout. Resp. Physiol. 3:166-176, 1967.

FULBRIGHT-HAYS AWARDS IN BIOLOGY

For thirty years the Fulbright-Hays program has provided opportunities for university lecturing and advanced research abroad. In recent years 450-500 awards per year have been made to American scholars and other professionals—25-35 to specialists in life sciences. The program also includes awards to foreign scholars for lecturing and advanced research at U.S. institutions.

Announcement of the awards available for 1978-79, in the 31st annual competition, will be published in March 1977. The general composition of the program involving more than 70 countries is expected to be similar to that of recent years. Registration for personal copies of the announcement is now open; forms are available from the Council for International Exchange of Scholars, Suite 300, Eleven Dupont Circle, Washington, D.C. 20036.

Among the 76-77 grants, 24 awards in animal and plant science were made to American scholars for work in Asia and the Pacific (10), Europe (8), Latin America (5), and the Middle East (1); 12 scholars from abroad will be in the U.S. from Australia, Belgium, Denmark, India, Iran, Norway, Pakistan and Sudan. Grantee lists will be sent upon request.

Nominations for 1977-78 awards are now being forwarded to the 12 countries which programmed grants in biology for announcement last spring. However applications are still being received for prospective positions in the U.S.S.R.: Plant physiology, movement control mechanisms and measurement of electrical activity of brain cells. These appointments require U.S. citizenship and university or college teaching experience. Qualified persons interested in applying should write immediately to the CIES for further details and application forms.

THE RELATION OF MEDICAL DEPARTMENTS OF PHYSIOLOGY TO OTHER PROFESSIONAL SCHOOLS*

By Jere E. Goyan
Dean, School of Pharmacy
University of California, San Francisco

I am very pleased to have this chance to discuss with such a distinguished group a problem which seems to bedevil every school whose basic science departments are called upon to present courses to other schools.

I do not claim to be an expert on the affairs to be discussed, merely a battle-hardened veteran. I have had the opportunity of working with seven basic science chairmen in our School of Medicine over the last ten years, have earned and awarded several purple hearts, and wish to freely admit that our interactions have always been challenging and only occasionally vituperous.

To illustrate, let me quote from a letter, dated June 26, 1967, which I received from the chairman of the Department of Microbiology:

> "Because of the steadily rising costs of instruction and the absolute necessity to devote some resources to significant academic development of the department, we shall be unable to continue laboratory instruction to students of pharmacy unless significant budgetary provisions can be made immediately. The staff of the Department of Microbiology regrets the need for this step, but finds that laboratory instruction to students in the School of Pharmacy will have to be curtailed drastically in 1968 unless some financial support for personnel and materials becomes available."

In my usual statesmanlike fashion, I replied with a memo to the dean of medicine, indicating our long-standing support of the department and closing with the statement, "I can only reject his argument as egregious, and request that we meet at an early date to discuss his demands."

A few days later, I received a copy of his reply to the dean of medicine:

> "Several days ago I received a copy of the letter of July 19, 1967, sent to you by Dean Jere E. Goyan of the School of Pharmacy. In this letter Dean Goyan applied the term 'egregious' to my arguments regarding the necessity to curtail laboratory instruction for students in the School of Pharmacy, unless additional budgetary support could be provided. I looked up 'egregious' in the dictionary and found the meaning 'conspicuously bad,' also 'distinguished' (archaic). I chose to consider the archaic meaning."

As you can tell, our exchanges are always very "high-toned."

However, our continuing need to live together has led to accommodation, and over the past few years we have had a basically harmonious relationship, not just with the individual cited, but with the other basic science chairmen. Nevertheless, our relationships with each of these departments have essentially grown like topsy, and consequently our arrangements are considerably different in each department.

I would like to launch into my topic by making an assumption which few of you would challenge: that every health professional school has, and needs, varying amounts of instruction in the basic sciences in its curriculum. For the purpose of this discussion, let's narrow it to physiology, although the scheme I will present could serve as a paradigm for all of the basic sciences.

Let's assume that I am the dean of a school of pharmacy, and I want physiology taught to our students. How do I go about doing it? There are many ways, but let me take this opportunity to provide you with my opinion of the ideal way, a way many of my colleagues in dentistry, nursing, and pharmacy agree with philosophically.

The ideal way I will present is based upon five beliefs which I hold.

Belief No. 1: There should be only one physiology department on a campus; it should be located within the school closest to its natural mother (medicine in this case); and it should be responsible for any course in physiology taught within any school. For example, it has always struck me as silly for a school of pharmacy to have its own separate and independent department of physiology, or to tuck a physiologist into one of its other departments, if there is a department of physiology in a school of medicine within easy access. Such cubbyholes are wasteful duplications and tend to isolate such individuals from the mainstream of events within his or her discipline. Such individuals do not easily, if ever, earn the respect of their colleagues in the primary department.

Belief No. 2: A school requiring instruction in physiology should have in its budget a sufficient number of FTE to support the personnel required, and this should be made available to the department supplying the instruction on a recharge basis. There is method to this recharge madness; it gives the school some control over course content. I also believe that the amount of resources made available on recharge should be the result of negotiation with the dean of the school in which the Department of Physiology resides, and not with the chairman of the department. He or she is in a far better position to judge the overall needs of the department.

Belief No. 3: No one person should be totally responsible for the teaching of physiology in a given school; the discipline is best taught by choosing from the strengths of many persons, and this should be a departmental decision.

Belief No. 4: When a position becomes available the search committee should be composed of persons from the department and the school requiring instruction, and the person chosen should be acceptable to both groups. As indicated earlier, I do not believe that such a person should have the total responsibility for the course, although he or she might oversee the course to make sure the jigsaw pieces fit together.

Belief No. 5: Joint appointments should be made whenever possible. In our school, for example, we have a number of faculty who hold joint appointments in our Department of Pharmaceutical Chemistry and the Department of Biochemistry in the School of Medicine. It would also seem reasonable that individuals in schools of pharmacy with an interest in pharmacokinetics might well hold joint appointments in the Department of Pharmacology of a school of medicine. Such interactions are obviously dependent upon joint interest between faculty members in a common research goal and serve

*Presented at the Fall Meeting of the Association of Chairmen of Departments of Physiology, San Francisco, November 11, 1976.

to strengthen not only the bonds between the schools, but also the quality of research in both schools.

Consider, if you will, the composite of what I have suggested: a single department strengthened by the resources of all of the schools, sharing its strengths with them, and working toward mutual goals. A basic science department built in this manner should have little difficulty in relating to the other schools, and, indeed, of seeing in the relationship an opportunity for growth and development.

That is my ideal scheme, and there are some obstacles in attaining such a nirvana. It is fraught with problems, some of which may not be solvable. However, I would like to identify some of the dilemmas which those of us with administrative responsibilities outside of schools of medicine encounter. The number one problem, and undoubtedly the most difficult to resolve, is the attitude of the basic science faculty who hold appointments in schools of medicine, and who are required to instruct in other schools. I have sat on too many school of medicine committees in which I was the only non-medicine member not to be aware of the basic ingrained prejudices which I take some delight in identifying as "physicianism." This prejudice evidently starts with the belief that school of medicine faculty enjoy the highest status, that the highest of all callings to the teaching profession is to be involved in the training of future physicians, and to be required to train a "lower status" health professional is per se denigrating. I find that this attitude is held by many basic science teachers regardless of whether they are M.D.s or not. In my opinion, this attitude has resulted in numerous incidents in which slighting remarks have been made about the profession of pharmacy in front of our students. An example which comes to mind is: "Well, I guess that you really don't need to know this to sell garden hose." Such remarks as this are doubly infuriating, coming as they do from persons who know little, if anything, about the modern practice of pharmacy, and, for that matter, probably know little about modern medical practice. Another outcome of this basic attitudinal problem—and I wish to assure you that it is commonplace—is that in many cases the department chairman looks around for the least productive scientist or the least effective teacher and uses the other school as the dumping ground for his or her predecessor's recruitment errors.

How do we resolve this particular problem? Clearly, everyone in this room is in an excellent position to have some effect because your faculty will, to a larger degree than you would care to admit, reflect your opinions. First, learn something about the quality of the students your faculty will be instructing in the other schools. You may be surprised to learn, with few exceptions, that entering GPAs have been going up in all of the health professional schools over the past several years. They may be smarter than you think. In our school, for example, the average entering GPA for our first-year class in the last three years has been 3.3 (based on 4 equals A).

Secondly, make some effort to learn something about the nature of the profession for which the students are being trained. I assure you that pharmacy is presently marching to the beat of a far different drummer than it did just a few short years ago.

Thirdly, students' egos are always fragile, at least in the profession of pharmacy. The one thing they don't need is some ignorant authority figure slicing up their chosen profession. What I am asking is that you communicate all of the above to your faculty.

Next, let's talk a little about the level of presentation of the course. Too often there is little, if any, communication between the parties concerned, relative to this matter, and consequently there is a good deal of difficulty, with both the students and instructor becoming frustrated and unhappy. The easy way is, of course, to simply teach the same course as presented to medical students, perhaps concurrently.

Dr. Cecil Sheps, in an article on the problems of establishing a health-care team, notes that members of the team do not need "to think alike, but rather to act together." In other words, each health professional should bring some area of expertise to the team which is unique to his training. Thus, it follows that little is gained in trying to teach all students in one classroom exactly the same subject matter.

In trying to identify the proper presentation for the various health professionals, it seems helpful to me to subdivide teaching into the three categories suggested by Dr. H.S. Broudy of the University of Illinois—namely, didactics, heuristics, and phyletics. Dr. Broudy defines didactics as the imparting and reinforcing of skill and knowledge; heuristics as that part of our teaching designed to promote discovery by the pupil; and phyletics as love of the teacher by the learner and presumably vice versa.

Taking physiology as an example, I believe that the didactic portion necessary in modern pharmaceutical education is essentially the same as that in medicine. The heuristical portion, on the other hand, should be quite different since problem solving in medical school courses is usually related in some way to diagnosis, whereas the problem-solving portion of the pharmacy course should be related to drug therapy insofar as possible.

Lastly, we come to phyletics, which, it seems to me, is at least somewhat related to role models—that is, an individual with no background in pharmacy is going to find it difficult, although not impossible, to inspire pharmacy students in this fashion. I would hope that the professional faculty of the non-medical schools can accept the primary responsibility for this role. For example, our students have shown a great increase in interest in physiology over the past few years, partially because of their perception that it is important to their understanding of drug therapy, a notion which is brought home forcibly to them by our clinical pharmacy faculty. Perhaps this is what Jacques Barzun meant when he said, many years ago, that the virtues which we hope to instill in the minds of our students "come not from the course, but from the teacher; not from the curriculum, but from a human soul."

The foregoing analysis indicates that innovative faculty and department chairmen should recognize that much of the didactic training of today can be presented in a number of ways other than the classical lecture. Thus, assuming that the basic physiology of the kidney is important to both pharmacy and medical students, it is possible to design various multimedia presentations which would greatly facilitate learning of this material by the student and even perhaps make unnecessary the usual lecture presentation. Since there is reasonable agreement between renal physiologists, it should even be possible to have such presentations used on several different campuses. We should not look at this as a threat in the sense of possibly replacing the college professor, but rather as a golden opportunity for the faculty member to participate in helping the individual learner with his or her problems in understanding the didactic material, and taking the responsibility for the heuristical and phyletic portion of teaching.

One of the most troublesome problems between us has always been the level of support which the non-medical school should provide, as illustrated in my correspondence with the chairman of the Department of Microbiology. Unfortunately, the established student-faculty ratios in the other health profession schools are generally much higher than they are in schools of medicine. For example, let us assume that a pharmacy school has a student-faculty ratio of 12:1, whereas a medical school with which it's affiliated has a student-faculty ratio of 4:1. The department chairperson in a basic science department assumes that additional resources will accrue to him or her on the basis of the 4:1 ratio, whereas the dean of the other school has to see it on the basis of 12:1. This discrepancy, which is oftentimes larger than the 3:1 quoted, makes it difficult for both sides. This is one of the reasons negotiations should take place between the deans rather than between the department chairman and the dean being served.

This difficulty is, of course, not limited to our interactions, but on a given campus it may cause problems between a department of biochemistry on the general campus and a department of biochemistry in the school of medicine, where individuals in the school of medicine may well not only have lower teaching loads but higher salaries! In many institutions schools of medicine have used the need for 1:1 student-faculty interaction at the clinical level as an argument for much lower student-faculty ratios than those in other schools. However, they have then used resources obtained by this argument to enrich a given basic science area in order to improve their image. It seems clear that this practice is going to be seriously questioned in the future not only by university administrators, but also by legislators and others concerned about the cost of education. Please do not misunderstand. I recognize the fact that there are also basic science departments which have not received adequate resources to meet their teaching responsibilities, but I do believe that the other problem also exists. Thus, the problems we have to deal with are difficult, but they are not insurmountable.

SOCIETY OF TOXICOLOGY SELECTS AIHA TO HANDLE ADMINISTRATIVE OPERATIONS

The Society of Toxicology has announced that effective immediately American Industrial Hygiene Association will serve as the society's administrative base of operations.

The arrangement will afford the Society of Toxicology (SOT) a full-time administrative operations center and enable it to provide ongoing services for its growing membership. SOT, founded in 1961, in the past had utilized volunteers from within its own membership to coordinate its programs, publications and other endeavors. Now AIHA, based in Akron, will perform all administrative functions, under the directorship of William E. McCormick. Mr. McCormick also serves as managing director of AIHA.

"This was a natural undertaking for SOT, since about a third of our members are also members of American Industrial Hygiene Association and AIHA has available manpower and facilities to provide professional coordination for our society," said SOT president Robert Scala, Ph.D., a toxicologist with Exxon Corp., Linden, N.J.

SOT's membership has grown to more than 900 specialists in toxicology, representing industrial, governmental and academic organizations throughout the United States and other parts of the world.

Under the arrangement, AIHA will provide membership services, assist in communications programs and oversee other day-to-day operations.

Although SOT will continue to produce and edit its bimonthly newsletter, AIHA will coordinate the publication's business functions. SOT education seminars and the society's annual meeting will be coordinated under AIHA auspices.

"We want to make it clear that the Society of Toxicology will continue to be a separate professional entity," said Dr. Scala, "and that this new arrangement with AIHA is to fill our broadened administrative needs and also to better serve the needs of our membership and society through AIHA's available resources."

Mr. McCormick will serve as executive secretary of SOT. In addition to Dr. Scala, other principal officers of the society are Gale Boxill, Ph.D., secretary, of Wyeth Laboratories, Paoli, Pa.; Hans P. Drobeck, Ph.D., treasurer, of Sterling-Winthrop Research Institute, Rensselaer, N.Y., and Harold M. Peck, M.D., president-elect, Merck Institute, West Point, Pa.

Headquarters for the Society of Toxicology are 66 South Miller Rd., Akron, Ohio 44313. Phone (216) 867-3755.

COUNCIL ON EPIDEMIOLOGY AND PREVENTION

The Council on Epidemiology and Prevention of the International Society of Cardiology announces its 10th Ten Day International Teaching Seminar on Cardiovascular Epidemiology and Prevention, to be held in Ghana, August 21-September 2, 1977. Approximately 30 Fellows can be accepted. Final selection will be made by the Council's Seminar Committee. Nominees should be at the postdoctoral level, with some residency training or its equivalent, and be interested in cardiovascular epidemiology. Except in unusual circumstances, preference will be given to younger candidates, with little or no formal training in epidemiology. Limited funds may be available to give partial assistance with travel costs for accepted Fellows. Room and board are provided, without cost, to Fellows. Fluency in English is an absolute essential.

Candidates are selected on an individual basis, and not as representatives of their institutions. Therefore once selection has been completed, should the candidate be unable to attend, no substitutes not reviewed by the Seminar Committee may be sent as alternates by the institution.

Three documents are required for application and should be sent at time of application: A letter of nomination submitted by chief of department or institution, a personal letter of application from the nominee, and the applicant's curriculum vitae. These should be received prior to the deadline for application, May 1, 1977.

They should be sent to:

Jeremiah Stamler, M.D., Chairman
Council on Epidemiology and Prevention, ISC
Northwestern University Medical School
Ward Building – Room 9-105
303 East Chicago Avenue
Chicago, Illinois 60611

The Seminar is held under the auspices of the International Society of Cardiology, in association with the World Health Organization, and local hosts.

NEWS FROM SENIOR PHYSIOLOGISTS

Victor Guillemin wrote Bruce Dill:

It was mighty kind of you to remember my 80th birthday. I felt remiss at not remembering your 85th. All I can say is that I shall try and do better on your 90th.

I do not have a job with a name on it but I am putting in quite a few hours on my new book every day. It is progressing nicely and I am learning a lot. Eileen and I are leading a quiet, pleasant life, taking walks in all kinds of weather, reading a lot and seeing our children now and then. We both send our greetings and best wishes to Chloris and to you.

Chauncey Leake to Bruce:

How good of you, dear Bruce, to write me on joining the 80 Club. I never thought I'd make it! And there's still so much to do! I hope this reaches you before you get off on your trip, for I want to urge you to come back this way. I'll be glad to put you up at the Bohemian Club. There, On Wed. Sept. 29, the Pharmacologists are giving me a dinner, and that morning at 10:00 AM, inaugurating a lectureship named for me. Irvine Page will be the lecturer, with lunch and reception in afternoon. None of this do I deserve, but it thrills me anyway! Come, join us!

May your good work ever thrive, and joy to you and yours.

Helen Bourquin's reply included reminiscences about early days at Aspen:

I do appreciate your birthday cards more than I can tell you! And also that you included me in news from senior physiologists! I did not expect that. Thank you!

In answer to your request for information about my experience in the schools in Aspen, they were considered excellent but I remember very little about them. My mother read to me much about the great artists and their art, authors and what they had written, composers and their music and, above all, scientists and the contribution which their research had made before I had even gone to school. Instead of athletics I spent the time hiking, bicycling and climbing in the mountains with my father and sister enjoying their grandeur and beauty.

Clara Fenn sent Bruce a copy of the W.O. Fenn booklet composed of tributes to Wallace from friends and associates. She writes that it is not for sale but many copies have been distributed and some remain "in a closet of the Physiology Department and the secretary and I are a good team at mailing them out."

I suggest that Chairmen of Departments without this book write Clara Fenn for a copy.

Ernst Fischer to Hal Davis:

I thank you very much for the birthday greeting of the APS on my 80th birthday. I celebrated my birthday with four old friends of my student days in Rio de Janeiro. After Rio, we Fischers visited one of these friends on his coffee plantation in Parana for three weeks. Then we travelled to the Amazon wilderness and enjoyed the interesting fauna and flora there. Finally we visited Bogota, Cartagena, Baranquilla and Santa Marta in Colombia. We were very lucky with weather and saw interesting city and country life reminiscent of Spanish style.

Back in Richmond I am still attending seminars at my old institution, and I am kept busy with desk work and library work for various journals.

I read recently that you received the National Medal of Science, accept my sincere congratulations.

Ruth Conklin to Hal:

Thanks for the Physiological Society birthday greeting. It is nice to be remembered, especially when one is no longer active. I am active in other ways, though, and still take care of my house and garden and do volunteer work. Vassar has a fine new Biology building, with equipment that would be the envy of most schools.

No news, except of a personal nature. Florence McDonough and Jane McCarrell were my overnight guests recently and we were speaking of you. Florence was on her way to visit her son in Washington, and Jane was on her way to Frederick, Md., where she still lives after her retirement from Hood College. She was one of my first master's students at Vassar.

Warfield Firor to Hal:

How gracious of you and the American Physiological Society to take notice of my eightieth birthday. Although a surgeon, I became a member of your society before I was taken into the American Surgical Association. It may sound very strange to you but since retirement my interests and reading have been centered in theology.

E. A. Spiegel to Hal:

Thank you very much for your kind birthday wishes. My teacher Obersteiner once told me: When scientists are getting old, they frequently write biographies or other historical essays. It seems that I have become a victim of this trend. I am at present surveying the development of stereoencephelotomy in the human.

Herrman Blumgart replied to Hal who had sent him a birthday greeting and had remarked on how much he had enjoyed the tribute to Herrman in The Harvard Medical Alumni Bulletin, May/June, 1976. The authors were A.S. Freedberg and M.W. Halmolsky. Their four-page illustrated article was summarized as follows: "It has been two years since Dr. Blumgart suffered a cerebrovascular embolic accident. While improved, he has not been able to return to the work that had made his emeritus years virtually no different in their productivity from those that went before. It had been hoped to present an interview with Dr. Blumgart so that the reader who did not know him could develop a more personal view of him and what he represented. Since this has not been possible, we have constructed a picture of him based on our experience, on what he has said and what others have written about him. We see him as he once was and still remains for us who were fortunate to come under his tutelage."

Paul Reznikoff to Hal Davis:

Thank you very much for your cordial greeting on my 80th birthday. I am still as active as possible, seeing patients, attending school and hospital meetings and trying to keep up with hematologic advances, which I find more and more complex with advancing age.

We are winterizing our summer home at Woods Hole, Mass., where I spent many happy summers at the Marine Biological Laboratory and I expect to "retire" to this place in the not too distant future.

Carl Bunde to Hal:

I am happy to know your investigations into the happenings of we old ones is continuing. I note that my previous reply was two and one-half years ago when, as a Medical Research Consultant, I was working about half time. That was a little more than two years after retirement at 65.

Now I am putting in more than half time as recently I took on the responsibility of setting up and operating a 24 bed clinical research unit. It is exciting and absorbing so I do not mind too much that it interfered with my fishing and hunting this fall.

The wish I have for my retired colleagues is that their aging should be as gradual as mine has been.

Tom Magath wrote Hy Mayerson that he does his gardening and travels a good deal. He and Hiram Essex celebrated their joint birthdays together at a little party with some friends of their vintage. They have been doing this for a long time.

Gertrude van Wagenen to Hy:

Your good wishes and birthday note were so surprising and enjoyed that last May the acceptance of it was overlooked.

Lucky me—I'm still in an office in the department and do keep busy with leftovers of research from the time I had an active primate colony.

Walter Alvarez to Maurice Visscher:

Many thanks for your kind letter. I often wish that I could hear more from the journal that I worked for for so many years. When changes in managership come I wonder what they will do to the journal.

Please excuse my poor writing but I am now over 92 and just got over a bad spell of flu. I still enjoy life. I am just getting out another book and planning others.

Theo Boyd to Hy:

Thanks for your birthday remembrance. I retired almost 10 years ago because my eyesight and hearing were failing. The change has been so gradual that I have had time to become adjusted. Now I can read only with the aid of a special bright light and a magnifying glass. My wife reads to me and is the family chauffeur.

I still have the physical strength for mowing grass and cutting wood. Like you, I rake leaves and do gardening. But in this rural area I can grow only such vegetables as the wild animals allow me to. Squirrels eat my corn before the ears are ready for the table. Rabbits eat my bean plants. Any vines that survive and climb my poles are chewed off by deer. I used to have melons and cucumbers, but a colony of woodchucks moved in. Now those plants never reach the blooming stage. Fortunately no local varmints molest tomatoes, squash, okra, peppers or potatoes. So I still grow them in plenty.

At 83, I reflect on how lucky I am to have lived in this century, when we had so much oil and so much fun inventing machines to burn it. Sometimes I worry, though about how our grandchildren will keep warm in winter when they reach our age. Anyhow, we shall leave them elegant superhighways on which to ride their bicycles.

Abe Cantarow to Hy:

It was good to hear from you and to be made to feel that there is still some interest in members of our generation.

Now in the tenth year of retirement from my first career of forty years in academia, I have thus far not experienced any evidence of the anticipated trauma of transplantation into the foreign soil of a government bureaucracy.

I am the administrative head of a group of scientists on the staff of the Director of the National Cancer Institute, concerned with analyzing the research programs supported by the NCI and assisting in formulation of new programs. This can probably not be considered scientific activity, but at least it keeps me in contact with the scientific activity of others. Apparently the authorities here believe I am still able to make a useful contribution to the mission of the NCI, for which I am grateful. There is little that is required of me that I do not enjoy doing, so I am having a happy time and an enjoyable experience. I can endorse the statement attributed, I believe, to that wise man, Benjamin Franklin: "There is nothing wrong with retirement as long as it does not interfere with your work."

Sid Harris to Hy:

Nancy and I enjoyed your personal note very much. Some of the statements would fit our own situation. We too are in good health, are involved in gardening and continue to have a strong zest for travel.

I have not done any writing for publication since the two papers that were published in 1974 and 1975 in collaboration with Doctors Albert J. Bocage (deceased) and Humberto Otero. I still am on the Editorial Board of the American Heart Journal, and continue to participate in the weekly grand rounds conferences of the professional staff of the Community Hospital of the Monterey Peninsula.

I read a great many books in a variety of fields of literature from history and archeology, e.g., The Greek Treasure and The Source, to biography, e.g., Beyond the Presidency, to boisterous humor, e.g., MASH Goes to New Orleans and Mrs. 'Arris Goes to Moscow.

In the scientific literature I try to stay reasonably well informed in the few fields with which I am expected to be acquainted and have the strongest interest. We are planning to attend the meetings of the American Heart Association in Miami Beach, November 15-18, 1976; the Eighth International Symposium on Cerebral Function, July 1, 1977; and the International Physiological Congress in Paris, France, July 18-23, 1977.

No, Hy, I am not interested in a job.

Cliff Stickney to Hy:

Thanks for the kind and understanding note. May you also enjoy doing what you want to do. To paraphrase a statement made by the late General MacArthur: "Old professors never die; they just fade away!"

Dwight Ingle to Hy:

I am beginning my 4th year of retirement. Our home is Wabigama, a club started by Ajax Carlson and friends from the University of Chicago 53 years ago. Each winter we move to a different university campus.

We spent last winter at the University of Idaho, my undergraduate school. I participated in teaching a course called "Science, Fantasy and the Unexplained." Whereas our students at Chicago were inclined to be skeptical of both fact and fiction many of those at Idaho hold strong faiths in one or more forms of pseudoscience. A protagonist of special creation spoke on the campus against the concept of biological evolution and many members of the large audience embraced the concepts of the speaker. You may know that the Institute for Special Creation is located in San Diego and sends speakers to our colleges and universities. The following of the Biblical account of creation is growing steadily. Anti-science is not dead.

I had another interesting experience last November. I attended a conference sponsored by the Reverend Myung Moon. It is not surprising that he has a following among the young; so did Hitler. I am more distressed by the fact that some world

leaders in science are unaware of his demagoguery and lend support to his international conferences.

I have written a book which was published as a paperback last spring (Is It Really So? Westminster Press, Philadelphia). It is written for beginning students and for laymen. It is a primer on the principles of science and the logic of science and argument.

My hobby is sailing and racing a little catamaran. The behavior of air and water is less complex than any biological system but I haven't mastered sailing by any means. But I have improved a bit each year. There are times that I have the illusion of being young again but these feelings are ephemeral.

This winter we will go to Gainesville. And in the future we hope to explore more of our universities.

Leon Chesley to Hy:

I still have two years to go until mandatory retirement at age 70, but hope that the computer loses track of me when the time comes.

I am still carrying the usual teaching load in Obstetrics and Gynecology at the State University of New York Downstate Medical Center, still producing papers, and still working on a book "Hypertensive Disorders in Pregnancy." The book should be finished before the end of the year after more than five years of effort.

The last thing I would want ever is an administrative position but I would be interested in a research opportunity two years hence. Depending upon what such a position might offer, I would consider moving from my home although I'd prefer not to.

Arthur Grollman to Hy:

In conformity with the rules of the university I have given up my laboratory activity and the department of experimental medicine and am now associated with the department of pathology on a part time basis. After over fifty years devoted to experimental studies and teaching in departments of chemistry, physiology, pharmacology, and internal medicine it is difficult to assume a life of leisure and I am therefore keeping busy writing, teaching and maintaining a consultant practice which I plan to continue after the present academic year when the rules of the university demand my assumption of an "emeritus" status.

I am preparing for press, papers on "Comparison of Response of Auricular Smooth Muscle of Heart of Hypertensive and Normotensive Rat," and "Theory for the High Incidence of Hypertension in the Black."

Yes, I am interested in a position enabling me to continue my scientific and/or teaching and writing activities. I am free to move to anywhere in the U.S.A. or abroad.

Jessamine Hilliard to Hy:

How very nice to get your friendly, chatty letter! We old people like to be remembered . . .

This senior citizen will be 70 years old in December, so some physical changes have transpired. In 1970, I had a silent heart attack and last fall a CVA with left side paralysis. Fortunately, my brain damage was not severe and I am now able to drive a car and do my own housework. I swim every day and have started to take piano lessons to strengthen my left hand.

I am frequently asked to referee articles for endocrine journals and have maintained a membership in the American Medical Writer's Association (AMWA).

I have two volunteer jobs at local Orange County Hospitals where I do library biographical research for staff members.

My husband, Dr. John K. Hilliard, who will be 75 next month, has just opened his own acoustical consultant office in Santa Ana.

Retirement was not satisfying to either of us so we both keep as busy as possible.

My kindest regards to you and all senior Physiologists.

Joseph Peters to Hy:

I am engaged in preparing classes for a freshmen zoology course, in designing some experiments dealing with the electrical activity of the brain and heart under the influence of drugs in developing chicks, and in counselling college students seeking careers in biology or the health sciences. I have no interest in moving elsewhere, or in seeking another position. Here at Xavier University I am an emeritus professor, teaching approximately a half-load, with opportunities to continue research. I would wish similar "happy" conditions to my colleagues of the same age. Among members of your Committee the person I know best is Dr. Hallowell Davis: he has exerted considerable influence for good in many areas of physiology in the United States. May he and others continue the good work.

Gordon Ring to Hy:

I occasionally give a talk at the University on Gerontology but spend a good deal of my time on gardening and hobbies like hooking rugs and talking to groups about my travels. Our latest trip by freighter (Yugoslav line) took us to Marseille, Casa Blanca, Trieste and Dubrovnik. It is the only way to travel if you hate to go in and out of airports, customs and the like.

Thanks for doing such a good job keeping up with the oldsters.

Harold Wayland to Hy:

I am still actively in harness at Caltech—our formal retirement age is 68, but I get an extra year, having been born on July 2, so I don't retire until June 30, 1978. With luck, I may be permitted one or two half-time years after that.

My major problem is that, being in a Division of Engineering and Applied Science I see no assured continuity of my work on transport and diffusion in living microcirculatory beds since there are no faculty members in the academic ladder at Caltech who are interested in this type of work, and I see little likelihood of this type of appointment being made. I do intend to hang on here until I can see a satisfactory disposition of my laboratory facilities, and then I would like to retire from laboratory direction and, hopefully, do consulting on the use of modern technology in physiological research.

I was in Japan for three and a half months in 1973 as a Visting Professor at Shinshu University, Matsumoto, and just yeasterday Dr. M. Hasegawa, Associate Professor of Physiology from Shinshu arrived to spend this year in my laboratory. I am afraid he is primarily interested in rheology, but I would like to get him interested in evaluating the PS product for the walls of terminal lymphatics in the mesentery, which I think can readily be done with our fluorescent tracer techniques.

Sam Reynolds to Hy:

I do not improve my golf but that's the fun of having a green off our patio and the 8th tee just beyond. Actually I exercise that way, between writing two to three papers a year (which seem worthwhile), an occasional lecture about the country, but most fun I find in the Division of Reproductive Biology in Ob-Gyn at Hershey Medical Center. That and the

resources of the library I find make retirement a pleasure. You know, the APS is the only society I know of that adds a warm personal touch for its retirees. Who invented it? He should take a bow from grateful associates while he can still smell the flowers.

Jim Hardy to Hy:

It was a great pleasure to receive your note inquiring about the activities of this "senior physiologist." Although I was retired two years ago the Pierce Foundation still provides me with a nice office so that I may write, have scientific discussions, or just plain bull sessions. In this way I keep in touch with my younger colleagues and occasionally have a suggestion which stimulates some additional research. Also, I serve as a sort of sounding board against which they can test their various ideas.

I was very proud to receive the Ray Daggs Award from the American Physiological Society last spring and have the attractive plaque mounted on my wall in my office. Indeed it gives me a warm feeling not to be forgotten. I have also been reactivated as an editor of the Journal of Applied Physiology so that perhaps you are right, I am "still at it." Actually I take off considerable time during the week to play golf and I certainly do not arrive in my office as punctually as of old. Fortunately, I can do experiments if I wish and have recently published a paper on the effects of acupuncture on pain sensation. I was stimulated to do this experiment by one of my former colleagues, and the results finally appeared in the Journal of Anesthesiology. It was clear that in the laboratory environment, acupuncture had no effect on pain sensation or temperature sensation. However, our conclusions certainly cannot be extended to either the operating room or the clinic. I plan to continue at my office as long as my health holds out and news of other senior physiologists indicate that this may be for a few years to come.

I am delighted to know that things go well with you and that you look back on your experience as a hospital administrator with pleasure. Administration really has its rewards.

Jim enclosed for Society Archives an up-to-date Curriculum Vitae which was prepared by Dr. Eleanor Adair on the occasion of his retirement.

Nathan Rakieten to Hy:

Since 1947 I've spent my major efforts in the related disciplines of Pharmacology, Toxicology and Biochemistry rather than Physiology and have been in my present post since 1950. The South Shore Laboratory is a Rakieten owned independent laboratory which presently does studies in Pharmacology, Toxicology, Biochemistry, Pathology, Bacteriology, Immunology and Hematology for the Food, Pharmaceutical and Cosmetic Industries as well as Clinical Pathology and Public Health. From 1957 through 1974—when NIH funds were slashed—we had a contract with the Pharmacology division of the DTC of the NCI studying the Preclinical Pharmacology and Toxicology of Anticancer Agents. These studies were challenging and rewarding and led to many joint publications with our colleagues at the NCI.

Ella and I have four children and nine grandchildren. Visits back and forth keep us young and active. Both my wife and I are avid golfers—you'll note I wrote avid not good. In addition we frequently attend the theater and concerts in the City.

I am not in a position at the moment to move to another area nor am I interested in an administrative position.

Ray Zwemer to Hy:

Three weeks ago Dorothy and I moved to Rossmoor Leisure World in Silver Spring, Maryland. We are enjoying the many kinds of activities available as well as a good bit of leisure.

I am still continuing scientific activities as the Chairman of the American Association of Anatomists Committee on Anatomical Nomenclature, as well as treasurer of the International Anatomical Nomenclature Committee.

I drop in at the APS office now and then to see Orr Reynolds and did a job in February for the physiologists by certifying the count on the mail vote for officers, which is now tabulated by computer.

Just a year ago in August we went to the Xth International Congress of Anatomists in Tokyo and I had a good time seeing Japan again after 58 years when I was there as a 16-year-old.

James Irving to Hy:

I am continuing with scientific activities and writing. An enlarged edition of my book, Calcium and Phosphorus Metabolism, was published by the Academic Press in 1973, and judging from the sales seems to have been a success.

I have an annual appointment at Harvard and am working with a group on bone loss in experimental periodontal disease, using mostly gnotobiotic rats. Since osteoclasts have long been my favorite cell, this is a very congenial occupation! In addition I have been organizing seminars in Oral Biology, giving a few seminars myself. The NIH have given me a sizable grant, which always helps.

I have been to conferences this year, the most interesting being on Membrane Transport at Zurich in Switzerland, where I picked up a lot of new ideas.

I continue as an editor of the Archives of Oral Biology which is also an interesting occupation as it keeps me abreast of the literature in Oral Biology. Also I am associate editor of Calcified Tissue Research.

I might be free to move to another area at the end of this academic year, but would much like to maintain my present research activities in some part of the bone and calcification field.

Irvine Page to Hy:

Sorry to report that I continue my errant ways of writing and talking too much. The great advantage of old age is that people seem to suffer it with less pain.

We spend about a quarter of our time in Hyannisport and still maintain cordial speaking relations with Ted Kennedy, despite our philosophical confrontations. It is a kind of tired detente.

I still have far too much to do and enjoy it by being allowed to complain bitterly about it. I seem to be "viable-wise," as the young would say! I attribute my seeming good health to jogging, tennis and a pleasant daily cocktail hour. I wish I were continuing laboratory work, but the Verboten sign on my laboratory appeared a decade ago. The sixty-five limit still rankles.

Perhaps the greatest sin I am committing is the writing of a book which will be titled something like, "The Mosaic Theory of Hypertension." If that gets published, I shall spend the rest of my life provoking Washington and trying to preserve the Republic, a sure sign of senility.

I am delighted that you have one of my colleagues—Ed Frohlich—at the Ochsner Clinic.

Nathan Shock to Hy:

Your letter caught me at a period of transition. As of December this year I will have reached that magical age of 70 and will retire as Chief, Gerontology Research Center, and Scientific Director, NIA. Although no formal action has been taken as yet, I will probably remain at the GRC as a guest worker to get on with data analysis and writing up of data that has accumulated over the last 15 years in connection with our longitudinal study of aging in 650 community-residing men.

Since I will no longer be a government employee, I will be free to accept invitations to give lectures and seminars and serve as a consultant.

Both Margaret and I are in excellent health, so we also plan to do some traveling.

George Clark to Hy:

I am doing a little teaching and as much research as I want to do. Since the research is inexpensive and is locally financed, the number of obligatory reports and deadlines is minimized. I'm having a lot of fun. This will probably continue as long as my health remains good. I am making contingency plans in case it becomes necessary to limit my activity.

George enclosed for Society Archives a curriculum vitae and a list of his publications.

Richard Bing to Hy:

I am still "doing my thing," not too far away from where Phil Bard is now located, from whom I heard recently. I am still on the staff at USC as Professor, at Caltech as Visiting Associate, and here at the Hospital as Director of Intramural Medicine and Experimental Cardiology.

I derive my greatest pleasure from the combination of seeing patients and working in the laboratory, each complementing the other. I feel that a scientist could derive the greatest benefit of his later years by shedding some administrative power and devoting himself to the more fruitful things in life, which are contact with patients, teaching young people, and investigating the insoluble problems of nature.

Personally, I should add to this, writing music, an occupation which has been my solace during my whole lifetime.

Anna Goldfeder to Hy:

I am happy to say that I am continuing my research problems pertaining to cancer and radiobiology. The recent publication in Cancer Research, as well as in other journals, serve as documents of my activities. In the January 1976 issue of Cancer Research is a concise autobiography comprising my 50 years in Cancer Research. Anna enclosed a recent reprint for Society Archives.

Bob Cleghorn to Hy:

I am working five days a week, trying to keep up with the expanding basic sciences as they apply to psychiatry. My chief clinical interest now is the study of manic depressives and the use of lithium.

I am not entertaining any geographical move, and am glad to be rid of administrative duties.

Philip Dow reported to Hy that he joined 20 others in an 18-day search for European bridges that they had missed on two previous trips:

Now I have the job of editing 550 color slides down to a number that anyone else would be interested in seeing. The trip included Iceland, Luxembourg, Germany, Austria, Liechtenstein, Switzerland, a little bit of France, and a few minutes in Italy when we took a wrong road. Earlier this summer, I made a solo trip to the European Microcirculatory Congress in Antwerp, and on a side trip to Bruges I climbed the 366 steps to the bell tower.

As related in my previous response, my removal from the School Budget to the Retirement Fund was mandatory in 1972, but I have remained here in a gradually decreasing Emeritus status. My professional output now scarcely justifies Bob Little's hospitality, which I enjoy daily. When George Burch or Matt Levy or Brian Hoffman gets too swamped he sends a manuscript my way and I enjoy the updating usually involved. Otherwise just reading and some committee work—including the school building namer, whose predecessor put Bill Hamilton's name on the new wing of our Basic Science Building. And I am to tell next week's Department Seminar about the "Hamilton Days."

So, right or wrong, I am not clamoring to be uprooted. While I must expect changes to occur in my personal situation, I do not foresee them specifically enough to make any different plans. I am in excellent hands medically and surgically, and in spite of a horribly brown thumb I keep the yard and shrubbery presentable, if not quite like my late wife's. I don't get to the golf course or the duplicate bridge table often enough to preserve game well. Rotary and Sailing Club are valuable outlets, and I am a perennial "treasurer type" for other organizations. I got a Colt last year and have much enjoyed the return to old driving styles.

I'm sorry for the change they had to make in the Journals and will let my longstanding JAP subscription lapse, since it no longer contains the "Special Communications." I found no stimulus for a trip to the India Congress, but I am tentatively working on the Paris project. Will I see you in Chicago?

Here are all best personal regards and warm thanks to all your colleagues on the Committee who are doing such a fine job for the Society and for us Oldtimers.

Howard Burchell to Hy:

I came officially emeritus from the University of Minnesota last July but I am continuing to work in the teaching unit at Northwestern Hospital. Last winter I had the opportunity of being visiting professor at Stanford University Center in the Division of Cardiology under Dr. Donald Harrison. It was a very worthwhile period and I plan to return this coming winter quarter again.

I am enticed by the invitation to spend some time at the National Library of Medicine analyzing the basic science underpinnings for developments in clinical medicine, specifically cardiology, and may do this in the spring quarter. The investigations would be somewhat akin to those of Julius Comroe but the perspective would have to be different due to my long term clinical orientation contrasted to a laboratory one.

Aurin Chase to Hy:

Due to a population explosion in the Biology Department my retired colleague and I lost our really luxurious quarters a year ago and now we each have only a small office which can double as a lab. We are still invited to attend the regular staff meetings and we have secretarial help and modest research funds.

I haven't done any actual lab work in physiology or biochemistry for several years but am doing some writing and lots of reading. One of my "extracurricular" activities has involved building a model sailplane and learning to fly it by remote radio control, but that got me interested in the way turkey

vultures travel by utilizing thermals. Consequently I've spent quite a little time this past year spying on a flock of about fifty vultures that roost around here. I've been photographing them with a movie camera and following individual birds by car on their daily flights for food. I'm especially interested in their soaring ability. They're actually too heavy for sustained flapping flight. I enclose an abstract of a talk I gave about them.

My wife and I made several trips during the summer up to the family farm in New Hampshire, where we did a little work around the cottage, went on a few of the less precipitous mountain trails and enjoyed the salubrious atmosphere in general. We both seem to be in good health and my only difficulty during the year was a hernia operation, which has left me much improved.

I am still enjoying my retirement. With my set-up here at Princeton I would not want to change anything, so am not anxious to move or undertake any sort of job elsewhere. I appreciate your inquiry, though, and think this is a wonderful thing that you and the others on the Committee on Senior Physiologists are doing in keeping in touch with all of us this way.

John Sampson to Hy:

I am still on the active teaching faculty of the Dept. of Medicine at California-San Francisco, and continue practice of internal medicine. This past month I completed a four-year term as president of the Inter-American Society of Cardiology —presiding at the Board, Assembly and Executive Committee Meetings at the Tenth Cardiology Congress in Caracas, Venezuela. In the four years I have been on the Executive Committee of the International Society of Cardiology I have had at least one publication on cardiology each year and continue to present papers on compliance of cardiac patients and the diagnostic value of evaluation of serum enzymes. I am not interested in any new academic or administrative position or in leaving San Francisco.

Dugald Brown to Hy:

On retiring I was left with a series of unpublished studies on muscular contraction. Since then I have been busy working up the raw data and analyzing the results in the context of the role of conformational changes in the cross-bridge proteins in contraction. I'm now preparing for an early publication. I have no personal physiological hang-ups except the usual lack of horsepower and look forward to continuing activities in this field.

Following retirement we moved to Woods Hole, where we had spent many summers with access to the scientific programs of the M.B.L. and especially its excellent library. We also acquired a house in Florida where we now spend the winter months. This is located close to the Mote Marine Laboratory which proves very helpful in many ways.

After being deployed for many years about half-time in administration it has been a great pleasure to concentrate on research and writing.

M. C. Chang to Hy:

I became an American Citizen in 1952 but I always look forward to a good relation between China and the U.S.A. so I visited the People's Republic of China in 1972 and 1975. Because of my early work on the development of oral contraceptives, the government, scientists, and friends there did not consider me as a deserter but treated me very kindly as "a worker of the world." The French reproductive biologists invited me to be the president in a plenary scientific session on the Biochemical Aspects of Capacitation and Gamete Survival at the 6th International Congress of Animal Reproduction in 1968 and the Polish scientists invited me to chair a plenary scientific session on the progress in the Biology of Gametes at the 8th International Congress of Animal Reproduction in 1976. The Society for the study of sterility in the U.S.A. gave me an Award in 1950 and again in 1961, and I received the Research Career Award from NICHD in 1962. The Society for the Study of Reproduction in the U.S.A. gave me the Hartman Award in 1970 and the British Society for the Study of Fertility gave me the Marshall Medal in 1971.

I am doing experimental work on mammalian fertilization and testing various antifertility compounds. I plan to retire within three years but I have not decided what to do after my retirement. I have been very fortunate to be in the U.S.A. for the past 31 years and appreciate the kind treatment of my friends at the Institute where I carried out my work, the people in NICHD, and the Ford Foundation.

Younger colleagues: if one works hard and is considerate of other people's feelings, one will always be happy and get along anywhere in the world.

George Glass to Hy:

I am still active; my retirement pertained only to my clinical duties as the Head of Section of Gastroenterology of the New York Medical College. I have retained my activities in the Gastroenterology Research Laboratories, which I am Chairing and whose continuous work has just been supported by a three-year grant from the National Institute of Arthritis, Metabolism and Digestive Diseases and by a three-year grant from the National Institute of Alcoholism and Alcohol Abuse. Both these grants permit me to continue several research projects and to staff them with two Research Associate Professors in Biochemistry, Drs. L. and A. Slomiany, as well as younger research workers, and to continue our work on glycoproteins, intrinsic factor, alcohol injury to the gastric mucosa and immunology of atrophic gastritis.

I retain my active title, Professor of Medicine in this School (not emeritus) and office space and secretary which I am using for my current publications, as well as preparing Volume 3 of the Progress In Gastroenterology, the first two of which have been published by Grune & Stratton in 1968 and 1970. The time interval between the second and third volume was due to my publishing the Volume on "Gastric Intrinsic Factor and other Vitamin B_{12} Binders" which was published by George Thieme Verlag in 1974.

You might be, also, interested to know that in October 1975, I was invited by French National Institute of Health to tour some 10 gastroenterological research institutes of the French National Institute of Health in Paris, Strasbourg, Lille, Lyon, Marseilles, Toulouse and Nancy. The correspondence on this will be published in the January issue of the American Journal of Digestive Diseases. This year I have presented papers at several international and national meetings in Gastroenterology.

Today, I feel that life is much too short, and looking back I haven't seen one single day when I was bored, tired of work or looking for other aims than the ones which I have cherished all my life.

John Scott to Hy:

I have retired after 52 consecutive years at the same insti-

tution, Hahnemann. I do not recall having missed any assignments during that period. At the moment I am enjoying the absence of any commitments or definite plans for the future.

Charlie Winter to Hy:

Although I spend much of my time in such activities as gardening, do-it-yourself projects, practicing for lessons on a newly acquired piano and the like, I've not entirely forsaken scientific pursuits. During the past year, my newly revised "Opportunities in Biological Sciences Careers" has been published by Vocational Guidance Manuals. In final stages of preparation is a monograph (with Dr. T. Y. Shen) on "Chemical and Biological Properties of Indomethacin and its Analogs," for the series "Advances in Drug Research" (Academic Press). Dr. Shen and I were also honored as recipients of the "Directors' Scientific Award" by Merck & Co. for our many years of work on this series of compounds.

Most surprisingly, I was invited to serve as Visiting Professor in the Department of Biological Sciences at the University of California at Santa Barbara during the Winter Quarter last year, and to return this year. I help teach in U.C.S.B.'s unique program offering a major in pharmacology for undergraduates. Although initially skeptical of the value of such a program, the experience converted me. Teaching such enthusiastic and responsive students is really thrilling, but we have to spend too much time filling in their deficient knowledge of mammalian physiology. I wonder how many physiology courses are taught in such a way that after completing them, the students may know a great deal about such things as the exchanges that take place at a cell membrane in a particular organ without learning the overall function of that organ and the system of which it is a part. Is it a violation of academic freedom to suggest to physiology teachers that they ought to spend some of their time in giving the students a broader view than just the instructor's own research interests?

My wife and I feel that in spending the winter term at Santa Barbara and the rest of the year in the Pacific Northwest, we have the best of both worlds! At our advanced ages, and with good health, what more could anyone ask?

George Ungar to Hy:

I retired from Baylor on August 1 but continue my research here at the Department of Biochemistry of the University of Tennessee Center for the Health Sciences. Work will certainly be on a much reduced scale but I shall be able to complete some unfinished studies and keep in touch with future developments. I also have plans for writing that will keep me busy for whatever time is ahead of me.

Joe Howland to Hy:

Your letter of greetings from all of my friends and associates in the American Physiological Society was received with considerable interest. To bring my record up to date, I took terminal leave from the Department of Radiation Biology and Biophysics at the University of Rochester Medical School to assume the position of Physician Director at the Alcohol Rehabilitation Center. The original agreement was to spend 50% of my time in clinical work and the remainder in research on alcoholism—which has long been one of my "blue sky" areas of research. As things will go, the job turned out to be 99% clinical and 1% frustration—but I must admit that I did learn a great deal from pure clinical observations some of which at present is being put to use. After 26 months of this I retired from full time activity. I did, however, retain a part-time appointment at the University of North Carolina Medical School (Department of Medicine). One of my prompt findings was that medical research is a "young man's game" and we "old fogies" are more apt to be tolerated than used. Certainly no laboratory space is available and most people are slaving under committed research from one grant or another. So for approximately 6 months I have been working on relearning the frustrations of golf, gardening (a Chapel Hill Disease) restoring my piano and organ technique to a reasonable degree, writing some poetry of questionable merit and making new friends. Having all my life been plagued by too many hobbies, I am shifting from one to the other at sporadic times—woodworking, electronics, etc. However I am continuously thinking during all this manual work of scientific ideas and in a way keep abreast by reading all the throwaways and sections of good magazines on scientific problems so that before long I hope to be back in the field in at least a part-time way.

From the professional viewpoint I have been engaged in a lot of thinking about many problems: for example 1) I have written a precis concerning the improvement of physician-patient relationships and restoring the art of medicine to the almost complete scientific method in which medicine is now practiced; 2) I have outlined an article for the semi-scientific press, i.e., Saturday Review, Atlantic or some such on the protean nature of alcoholism with its polyvalent contribution social, psychological and medical factors; 3) certain friends here are working on getting me involved in the philosophical approach to the development of the scientific method i.e., the nature of reason, the control of personal bias and the like; another possibility is to return to the study of adolescent medicine and those endocrine factors which are important: chronological vs. physiological aging; 4) I have the great temptation to return to my original training in ichthyological ecology and its relation to the environmental changes which are now so important. I would judge that there are many other things which may intrude on the above ideas, but with my horizontal type of interest in many disciplines who knows in which direction I will concentrate. Certainly Chapel Hill offers a tremendous challenge to the older scientists with two major universities, U.N.C. and Duke plus the developing Research Triangle and N.C. State is at Raleigh—some 25 miles distant.

In these days of completely sponsored research, one of the major problems for the elder scientist is to find financial support and space in which to work. One possible idea was generated by a cursory review of my files, most of which I moved to North Carolina (for some strange reason except that one hates to part with "old friends"). In these I have found a large number of unpublished papers and projects many of which are as original as when first conceived. Possibly a section could be inserted in one of our publications detailing a list of partially completed research efforts which for one reason or another never did get finished. Examples from my files include: 1) the relationship of bone-seeking radioisotopes in bone healing—certain experiments with plutonium many years ago showed astonishing results; 2) the nature of the alteration in bone structure following exposure to 2850 MHz microwave exposure—a tremendous hardening occurs which is impossible to explain; the nature of alcohol in the aging process particularly with the relation to collagen changes—a marked aging occurs in the chronic alcoholic and collagen changes are frequent. These form a few examples of what I mean. During my experience as Chief of Medical Research at the Manhattan District, I main-

tained a sort of journal of this type of thing which was circulated to the various interested laboratories and found that it excited tremendous cooperation and interest. It is possible that we elder scientists can help the "young" by the mere suggestion of ideas to them. I had suggested this sort of thing to Dr. Chuck Dunham during his tenure as Chief of Biology and Medicine at the A.E.C. but nothing developed along this line—probably a question of priorities.

I would appreciate hearing from you and your distinguished committee many of whom I know personally (from long ago, it seems) and will look forward to your elaboration in The Physiologist. Since they are building an institute at the Research Triangle for the Humanities—perhaps a similar type of thing could be developed for we "old fogies" who apparently have outlived our usefulness in the current scene.

Please excuse the delay in answer to your inquiry but as you see, the pressure of many things has kept me away from the typewriter for some time—visitors, yard work, unseasonable weather and an attack of "la grieppe" to mention a few interferences. Also extend all my best personal regards to your committee.

Dave Abramson to Hy:

Thank you very much for inquiring about me. It gives me a warm feeling to know that at least one scientific society is actually interested in the welfare of its senior members. I have read with interest the accounts in the "Physiologist," written by our colleagues.

With regard to myself, I retired from my job as head of the Department of Physical Medicine and Rehabilitation at the University of Illinois in September, 1972 but continued in the private practice of peripheral vascular diseases in the loop in Chicago until December 1975. At that time, I closed my office with some reluctance, for, being the only man in the specialty of medical vascular disorders, I enjoyed keeping the vascular surgeons in line. I am afraid that now someone else will have to take over this important chore in this area.

At present I am continuing to act as a consultant at the West Side V.A. Hospital and the Hines V.A. Hospital, spending two mornings a week teaching medical students and house staff, who have very little background in the field of vascular disorders, some of the fundamentals required for treatment of patients with such disorders.

In some of my free time, I work in my shop in the basement, making improvements in the house, like putting a shower stall in the basement and renovating the whole area. I also enjoy working on old but well-constructed furniture, removing all the paint, varnish, and stain, and refinishing the piece, even to the point of upholstering it.

At the present, I spend the rest of my free time writing a primer on vascular disorders of the limbs aimed primarily at students and house staff. About a year ago I had a 900-page book published on this subject, but because of its size and the elaborate manner in which the publishers presented it, the cost of the volume is so high that no one but an affluent physician in practice can afford to buy it. This is why I intend to make the primer about one-third the size of the other book so that it can be sold for a reasonable price. I have to complete it by July 1977 and I anticipate no difficulty in this regard.

With our two daughters leading their own lives, one in New York City and the other in Boston, Louise and I are left in a very comfortable, but much too large, home in a suburb of Chicago. However, I can't see ourselves living in a very impersonal high-rise apartment on the north side of Chicago and having to give up our garden which I enjoy very much. And so we will stay on, at least, for the present.

My future plans involve a book on the vascular aspects of orthopedics, a subject about which the men in this specialty have unfortunately very little knowledge. Then I may even revise a book, which I edited, on "Blood Vessels and Lymphatics" which was published in 1961. You may recall that you contributed a section to it. So you can see, I have enough chores to keep me busy for a while, so long as my health remains good.

I was happy to learn that you are also in good health and at last having enough free time to do some of the things that give you pleasure.

Lawrence Bennett to Hy:

Retirement life without teaching, laboratory, clinical or research responsibilities is just great. I have served on the Penrose Hospital Human Rights Committee but that has been minimal duty—though interesting. I drive a bus occasionally to pick up 4-year-olds for a preschool maintained by our church for underprivileged children. I have a good shop equipped for wood and metal working, and recently added lapidary and silversmithing, plus light welding. We are delighted with Colorado Springs and many wonderful friendships here. Soon we shall take off, as usual, for 5 months in our Airstream in Arizona where I keep up the lapidary and silversmithing plus swimming and golf.

Kacy Cole to Hy:

I still work at NIH about 4½ hours a day. I have complaints and minor coups—such as five papers in six months last year. I'm on an annual trek West and South—La Jolla, Berkeley, Galveston and this year the Biophysical Society in New Orleans.

J. S. Denslow to Hy:

About eight years ago I left the laboratory for my present appointment to become active in the social/legislative aspects of the biomedical sciences through Comprehensive Health Planning, Regional Medical Programs, Hill-Burton Programs, etc. I have served, or am serving on, the various Governing Bodies involved. Currently I am a Member, and Chairman of the Planning Committee, of the Governing Body of Area II Health Systems Agency of Missouri, Inc. Size-wise this area is horrendous, covering sixty of the one hundred and fourteen Missouri Counties and over one million people. I also serve as a Consultant to the National Center for Health Statistics and for DHEW Regions V and VI.

Recently I have returned to the laboratory to collaborate with a young anatomist, John Krogh, Ph.D., of our Faculty, to continue my earlier work on spinal cord reflexes. We anticipate the development of models (using the dog) for further studies of reflex activity including, not only viscero-somatic reflexes, but such others as somato-visceral, somato-somatic and psychosomatic reflexes as well. Our Faculty includes a good mix of junior and senior investigators and we are quite enthused about the work that is going forward.

Clinton Woolsey to Hal:

Since my role here as Biomedical Unit Coordinator, as for any appointment for an Emeritus Professor, must be renewed annually, I was pleased that this has been done for next year. In other respects we continue busy. I have nearly completed work-up of the human material I presented at the O'Leary

Symposium. I have greatly changed the mode of presentation and am introducing figurine maps, which, instead of employing "Zipatone," show next to the figurines the evoked responses obtained when various cutaneous sites were stimulated.

We have also been invited to participate in a Symposium on Vision to be held in Bogota, Columbia, next January. I plan to present some new material on the multiple visual areas of the rabbit.

A. Van Harreveld to Hal:

In your letter of Sept. 6 you write that you are still working. I am convinced that this is the key to a satisfactory life at advanced age. I am following my prescription and am daily pursuing my old studies on the changes in water and electrolyte distribution in the central nervous system and its consequences for brain function.

Hy Mayerson to Hal:

Why should I try to get out of writing to you? I have received so many delightful replies to my letters that I agree it is only fair that I be courteous to you!

I'm not really loafing. I'm having a good time. As you know, like Frank Sinatra, I "retired" again last year, on my 75th birthday, September 10, 1975. I had invested some 40 years at Tulane and 10 years at Touro Infirmary, a 560-bed teaching hospital. I went over there as Director when they fired the occupant—didn't know anything about running a hospital, of course, but I know a lot about people (students are people, you know) and for about six months I had a lot of fun untangling the situation. I then brought in a former student, an experienced hospital administrator, and I demoted myself to Research Director for Professional Services, retaining primarily the teaching program. Of course, this all meant that I was out of the laboratory but I did have some vicarious pleasure in being involved in the administration of the hospital research program which is quite extensive (I still am consultant to the research committee).

And so I finally decided that 50 years of service to society was probably enough, that I had paid my dues and was now entitled to some of the privileges. It hasn't taken long to learn to put off to tomorrow what can be done today. It is so good to be free of deadlines, reports and other people's problems. My garden occupies some time, plants don't talk back, complain or yell—if they don't like what's going on, they just lie down and die. I still am on several community organization committees, cancer, etc. Three years ago I was elected to the Board of Trustees of St. Mary's Dominican College, ±500 student (women) body. I have just been elected to another 3-year term. As the only member of the board with academic experience, I can be useful and so I get involved with the faculty and honestly think I have been helpful. I just helped get a new dean who is working out well, etc.

And, of course, we have been traveling. We got out to the Pacific Northwest last fall—had a delightful evening with Jack Brookhart and his lovely spouse—and had a swell time exploring the area. Last spring we planned to visit Guatamala but the earthquake got there the day before we had planned to go—so we went back to Mexico instead. And on Thursday, we leave for southern Spain and France and will be gone for 3 weeks.

Now as to the leading questions—obviously the answers are in the negative. I'm all for letting the young'uns run things, for better or worse, they need to make their own mistakes like we did. I'm content to watch from the sidelines. I read the journals, struggle with new vocabulary, and honestly feel lost—so much is going on that's exciting. At any rate, Hal, Caroline and I are in good health—so are the children and grandchildren and we'll just continue to coast along, grateful to be here.

Allan Grafflin to Hal:

I very much appreciate your letter of September 6th, and trust that all goes well with you, as it does with us. I have at long last retired from practice, and am nearing the end of disengaging process as far as patient referrals, etc., are concerned. I preferred to leave when I might stay rather than run the risk of continuing too long.

Rex Ingram to Hal:

I retired the first of January 1973, and haven't had a vacation since. I've continued to act as consultant in some research projects and in the writing of papers. Also, I have helped somewhat in the laboratory portion of the neuroanatomical portion of a so-called neurobiology course. I also have worked at writing a book—A Review of Anatomical Neurology, which, to my relief, should be off the press at the end of November. It is being published by the University Park Press of Baltimore. This is intended, in a hopeful way, to assist residents in neurology, advanced medical students and graduate students who wish to enter the neurological field and who need a deal of reinforcement in depth following subjection to the current minicourses. It is strongly functionally oriented and, I think quite up-to-date. At any rate, it is finished and may or may not prove attractive. It does have a rather unusual style.

During this period I had the pleasure of spending three winters at the medical school of the University of Arizona in Tucson. Friends there gave me space to work and the privileges of a good and convenient library. Believe it or not I had the courtesy title of visiting professor in the Department of Pathology. This was a very happy arrangement for which I am grateful to Professor Jack Fayton and his colleagues. Also, Mrs. Ingram and I have real affection for the Sonoran desert. As of now, I am catching my breath and trying to catch up on the current literature. We're going back to Arizona for a visit next month, to see our son, who practices radiology in Phoenix, and his three sons. From there we plan a visit to Guadalajara and related parts of Mexico.

In answer to your queries: at the present I am not interested in another position. I cannot at the moment make any forecast. People here at Iowa are busy. There are new headship appointments in Physiology and Biochemistry and there will soon be another in Microbiology. Anatomy was refilled in 1973. The signs are reasonably healthy except for the compression which confines the basic sciences. Perhaps unfortunately in some respects the quote "O Tempora! O Mores!" seems to hold.

Fred Jung to Hal:

Please give my special greetings to Dr. Adolph, to whom I am especially indebted for inspiring me to become a physiologist. At age 78 I find that I have already outlived not only most of my former teachers but even many of my former students. A widower since 1961, I finally gave up my house a year ago and was fortunate in finding an outstanding retirement home. Now I am active mostly in the American Association of Medical Writers. My speaking engagements in the past

year included a sermon at the Evanston Unitarian Church on the struggle for freedom as represented in the life of the physiologist Michael Servetus.

At this age, I see more clearly than ever that it was a privilege to teach in a medical school. It is rewarding to see the conspicuously fine work done by one's former associates, and as a recent hospital patient I learned again how reassuring it is to find that so many of the hospital staff, from physiotherapist to surgeon, are former students whom I respected and liked.

One learns to appreciate laboratories and libraries when access to them becomes more difficult. Techniques that were standard years ago now seem prehistoric. Real or fancied impairments of vision, hearing, and memory discourage long-range commitments. For these reasons I now confine myself to writing, at every opportunity, against pseudoscience and to helping young investigators to avoid old fallacies. That may sound strange, but I so vividly remember a meeting of the APS at which the late Graham Lusk, in his quavering voice, complained about some work on the respiratory quotient: "These young people are putting mistakes into the literature faster than I can get them out again." I remember him before the advent of electric hearing aids, sitting in the front row with his big ear-trumpet. For a young member giving his first paper and suffering from stage-fright besides, that ear-trumpet added something unforgettable to the scene. I wonder how many other members still remember it.

Jim Pinkston to Hal:

My wife, Peggy, and I moved to Staunton, Virginia, in August. Peggy, who is 16 years my junior, completed the requirements for a doctorate at City University of New York in July, then accepted a professorship in that field here at Mary Baldwin College, where there seems to be a very strong teaching program in the sciences.

Since both Peggy and I are from the South originally, we have not found it difficult to adjust to our new environment. We were fortunate to find a lovely old home, colonial style, within easy walking distance from the College, so we are now happily and comfortably settled. A small greenhouse has been erected, and is now functioning satisfactorily, consequently, as a plant enthusiast, I am busier than ever growing some of the fascinating gesnernads, with never a dull moment. In fact, I have found retirement to be anything but boring!

Chet Hampel to Hal:

It was indeed most pleasant to get your note and to realize that we old "Cat and Kymograph" physiologists have not been completely forgotten.

After twenty-nine years at New York University, I retired in 1971 while on sick leave due to rather severe acute depression. I have had a couple of bouts with it since and have had enough Electro Convulsive Therapy—a Medieval and barbarous treatment—to last me quite a time.

I do enjoy the opportunity to read a great deal of the time in this beautiful rural village and am only slightly handicapped in walking.

Howard Bartley to Hal:

It was good to hear from you. I became an emeritus in 1971 at the age of 70. An interesting thing I did just before that was to produce a paperback called "Perception in Everyday Life." It wasn't meant to be a text, but a little brother to my "Principles of Perception." It was during the time that students were at their height in rebellion and were asking for "reality." This meant to me that what we were trying to teach them in books needed to get closer to them. So the paperback was a device via anecdotes and specific applications of the principles in the text for that purpose. It seemed to do the job.

Since 1972 I have been on the campus at Memphis State University first as a Distinguished Visiting Professor and then as Distinguished Research Professor, with no specific commitments. I have been doing a little teaching and holding a couple of seminars, but mainly writing. This has included an autobiography, meant to disclose the odyssey of a little boy who had no playmates and lived in the world of things and imagination instead of a world of people.

We hated to leave East Lansing and Michigan State, but needed to get away from the ice and snow and long winters. I had been invited several times to come to Memphis, so since this was my wife's old home town we made the move.

I spend some of my time painting, and have quite a lot of them to show for it, in spite of those given to my relatives and friends. I was in several shows in East Lansing and have had two one-man shows here and several paintings in another gallery.

Although I belong to several other professional and scientific groups, I can say that physiologists have one of the top places of warmth and regard in my feelings.

I don't have quite the same reason for visiting St. Louis and Washington University as when Bishop and O'Leary were still on the scene. I am trying to devise a painting wherein George Bishop, Jimmy O'Leary and Pete Heinbecker and myself are seen as four old cowboys. Would you have a title for the painting?

Harold Kaplan to Hal:

I am retiring (by statute) from the Physiology Department at Southern Illinois Universtiy this coming September after 28 years of teaching (and research) there, at undergraduate and graduate levels as well as in the SIU Medical School.

I founded the Department and was its chairman for 22 years. This tenure of office, as you know, required some intricate survival tactics. I published some 180 papers and am trying to complete a revised laboratory manual in mammalian physiology, and also in anatomy and physiology for speech pathology. I would like to continue teaching if an opportunity presents itself in any desirable area of the country. As you can see, my sprit fortunately hasn't caught up with my chronology. I am pleased to see The Physiologist used as a vehicle for this kind of correspondence and I am glad that you catalyzed me to contribute.

Any correspondence should be directed to my home address: 106 No. Almond St., Carbondale, IL 62901.

Bob Dow to Hal:

I have enjoyed the letters from the older members of the American Physiological Society which have appeared in The Physiologist. I have never been anything but an amateur physiologist although I have treasured my membership in the Society. I continue to practice neurology and do clinical electroencephalography at Good Samaritan Hospital and Medical Center in Portland, Oregon.

The Laboratory of Neurophysiology, which was established over 15 years ago at our hospital, continues to prosper now as the Neurological Sciences Institue of Good Samaritan Hospital and Medical Center, and I have relinquished the directorship of the laboratory to Dr. Donald S. Rushmer, who is Acting Direc-

tor of the Institute. It has grown until we now operate with 8 full-time members and a large number of research projects, mostly in some aspect of motor control. Total grants and contracts contribute over $400,000 annually to its support. We still hope for an angel who will give us an endowment for its permanent support. The Good Samaritan Hospital and the University of Oregon Health Science Center's Neurology Resident Training Program merged in 1969, and is prospering under the new leadership of Dr. Frank Yatsu who arrived from San Francisco in July 1975 to become head of the Department of Neurology at the University of Oregon Health Science Center.

We have been able to recruit some outstanding neurologists to help in our teaching program during the academic year 1976-77, while the hospital is engaged in the search for a new Chief of Neurology in anticipation of my retirement in a year or so. Dr. Karl VonHagen from USC, Dr. Russell DeJong from Michigan, Dr. Adie Sahs from Iowa and Dr. Alex Ross from Indiana are to serve as Acting Directors of Neurological Education in rotations for periods of 3 months to 6 weeks each, beginning in a few days.

Our Department at Good Samaritan Hospital and Medical Center was successful in obtaining a contract for a comprehensive center for epilepsy for Oregon, which is now in its second year of operation.

With all this activity going on I am fully occupied. However, we have built a second home in the eastern slope of the Cascades, near Bend, Oregon, and Willetta and I spend long weekends there every chance we get with lots of golf, fishing, and during the winter, cross-country skiing. In a short time, these weekends will gradually become longer and longer.

Those members who have retired and are doing some western travel should look us up when they come to Oregon. It is a great place to enjoy a good life.

Bob Morison to Hal:

I retired from Cornell July 1, 1975 and have been here on our family farm ever since. During term time I went downtown for 2 or 3 days a week to perform the varied but largely self-selected duties of the "class of 1949 visiting professor." I also continue on a few boards and committees which keep me up in the air rather more than I would like.

Most of my writing and talking in the last few years has been on topics related to "Biomedical Ethics" or other matters relating to the interaction of Science and Society.

I certainly don't want another administrative position. Indeed in my opinion no one over 65 should try to administer anything or anybody except himself.

I don't want to move to another area. New England is just too beautiful in the fall. My wife is still active in house and garden though handcuffed by the fragilities of osteoporosis and a moderate hardness of hearing.

Leon Saul to Hal:

How great to hear from you. Again, congratulations on the medal and on being in such fine shape at eighty. We also appreciate your notes on the children—none nearby, it seems, but just so all are thriving, which is the main thing.

I am still in private practice to make a living. But since this involves studying patients it provides the happy situation of continuing this kind of clinical investigation and what I find, I write about. One book is in press, due to be published in January 1977 "The Childhood Emotional Pattern" and two other books are in progress "The Psychotic Character" and a longitudinal study of a life, no title yet chosen. Tentatively, "The Maturing of Corey Jones."

Angina prevents getting around much, especially in winter, but walking a mile before lunch and another before dinner daily, plus a post-lunch nap, seem to keep the innards in pretty good working order.

The old Scotch method of "doing something other" after seventy, seems excellent but, if my egotism does not deceive me, what I am learning and publishing seem worthwhile contributions. Having my office at home and being blessed with a harmonious marriage there is no wish to change or move.

Of course I miss the old days with Hal Davis, studying the brain, especially the auditory pathways . . . but we only have seventy—ninety years. Blessed is he who has found his work.

Ray Daggs to Hal:

After retiring four years ago I had a grand time working with rare woods, doing pottery with Mary and some gardening. Then I had a bout of illness, G.I. mostly, which the doctors in Bethesda could not diagnose even after a host of tests and a couple weeks in the hospital. When I got a bit better Mary and I decided to find a nice retirement village nearer our children and grandchildren (we even have a great-grandchild). We sold our home in Bethesda and moved to a very nice retirement village nearer our family. It is called Clearbrook in Cranbury, N.J. relatively near Princeton. We have a ranch style condominium which serves our purposes very well. There are all sorts of activities for those who wish to participate. All the outside chores, such as cutting grass, shoveling walks, etc., are done for you, yet there is space around the house for flower gardens which we enjoy.

We found that the Health Center here at Clearbrook is very competent making the medical emergency I had in July smooth as silk. The Medical Center and Hospital at Princeton was efficient and the facilities for treatment and diagnosis are very modern. I am slowly on the mend after surgery for gallbladder and intestinal blockage. Am beginning to enjoy hobbies again. For the winter we are going to try to grow orchids under lights. There is always something to keep us busy and our children visit us frequently. It is a very nice retirement life and I recommend it to other oldsters.

H.H. Cole to Hal:

I greatly appreciated receiving the letter from the Committee on Senior Physiologists, a truly outstanding group of Seniors.

I gave up my research grant a year ago but am still involved in writing up the findings for publication. Excepting for occasional lectures, I have not taught for the past two years.

In 1974, I completed editing the book, "Animal Agriculture," with Dr. Magnar Ronning. This book encompasses the nutritional, genetic and physiological aspects of livestock management and is a radical departure from the early livestock production texts based on the art rather than the science of husbandry. The fact that it has been well received is only one evidence of the revolution which has occurred in the teaching of livestock husbandry—and as a matter of fact, of its practice.

Currently, I am in the final stages of editing, with Dr. Perry Cupps, the 3rd edition of "Reproduction in Domestic Animals."

For several years, I was chairman of a Hormone Subcommittee of the American Society of Animal Science concerned with evaluating the safety of the use of estrogens as growth promotants in ruminants, a procedure which increases the efficiency of the article appearing in Bio Science in 1975, that the use of the hormone does not constitute a health hazard. I have just asked to be relieved of this committee assignment.

Because I am just too busy in Davis, I do not wish to take on any other activities. I think, however, that the activities of your committee in attempting to provide new opportunities for physiologists following retirement are most laudatory because I see so many retired faculty resigned to boredom. I do not wish to infer that my life consists solely of work. Despite a hip replacement a year ago, or more accurately because of it, I play golf twice weekly.

Ted Liberson to Hal:

In my opinion clinical neurophysiology can contribute a great deal to rehabilitation medicine and I have been very active in this field for many years. I have developed techniques of functional electrical stimulation in hemiplegics and paraplegics which have been applied successfully in a number of centers. I have also been active in research in electromyography and evoked potentials. At present I "oscillate" between Miami and Brooklyn.

In Brooklyn, I am in charge of Rehabilitation Service carrying a load of clinical and research electromyography; I am also reading difficult EEG's. I am attempting to develop a standardized technique of Evoked Potential Electroencephalography (new version of "functional EEG," a concept which I developed a long time ago). This technique involves random rhythmic application of visual, auditory and electric stimuli as well as "blank stimuli" with a computerized simultaneous recording from eight different areas of the head. Incidentally, your committee may be interested in knowing that my data suggest a decrease of the brain volume in its posterior half (not frontal!) in an advanced age. I am also reviving my techniques of simultaneous recording of palmar and plantar skin galvanic potentials in order to derive some notion concerning the conduction velocity in the corresponding C fibers.

In Miami, I am preparing to apply the same techniques for patients of advanced age in a geriatic rehabilitation center. There I am aware of the importance of electric response audiometry in order to help these patients' rehabilitation!

I am not interested in an administrative position, thank you. Of course, if I had an opportunity of devoting my entire time to research, I would welcome it, but these opportunities are rare to come by.

Chandler Brooks to Hal:

I am in good health and carrying on the activities of a physiologist. The Administration of the Downstate and my successor, Vahe E. Amassian, have been kind enough to let me continue to occupy facilities and carry on research and subjects of interest to me. I am, of course, seeking simple problems which I estimate within the scope of my present abilities, and strangely enough I am finding some interesting effects of nerves on the heart which I had not anticipated previously. I work, also, a bit on the hypothalamus and on the autonomic system and I will be participating or helping to manage a joint U.S.-Japan Symposium on the Autonomic System to be held in June of 1977.

Incidentally, the product of our Symposium on Walter B. Cannon has attracted some interest and I think the volume may soon be out of print; or in other words, all of those we had printed will have been distributed or sold. This pleases me very much because I think it was an interesting meeting and some of the things said were very worth preserving.

I do still give a few lectures—at least one a year—to our medical students. I feel a little bit, as I enter the classroom, as though I am an antique object on display, but I am pleased to have this opportunity to talk with the students. I lecture more frequently to our classes in nursing and paramedic fields, and I have a couple of elective courses that are attended by those few students who feel they have a bit of time to specialize in fields a little beyond those meeting the minimal requirements for graduation.

During the summer of 1975 I had a rather unique experience. I was invited to return to Dunedin, where I worked with Jack Eccles in 1946 and 1947. And I spent our summer months and their winter months teaching several courses to those spendid and friendly New Zealand students. It was a bit of strain on me because they thought I knew something about motor control, a subject I hadn't reviewed for quite a few years. It was a pleasure to review it again and Mrs. Brooks and I enjoyed our time there. New Zealand has not changed remarkably in 30 years and it has retained many of its most delightful characteristics.

This April I did go to Argentina to renew some of my acquaintanceships in South America. I still have a two-ended grant which permits cooperation between the Department of Downstate and that at Cordoba, Argentina. So I have a bit of grant money and facilities and equipment and some friends and students—life is pleasant for me at the present time.

Herbert Jasper to Hal:

I have just retired from my Professorship in the Department of Physiology at the Universite de Montreal and also retired as the Director of the Medical Research Council Group in the Neurological Sciences here. Our group has grown over the past ten years to be an important multidisciplinary unit and it is to be carried on with the new Director, Dr. Yves Lamarre.

The Faculty of Medicine and the University awarded me the honor of Professor Emeritus in the Convocation of May 1976, which was greatly appreciated, I can assure you. This is a rather rare award for this University.

I retain positions as Consultant in the neurosciences at the Universite de Montreal and Consultant in neurophysiology at the Montreal Neurological Institute of McGill University. Facilities for limited work are provided in both of these institutions and I have an opportunity to keep up my interest in the neurosciences in both places. I plan to make myself available for consultations and seminars and to carry out some clinical neurophysiological work at the Montreal Neurological Institute where I have been since 1938.

Shep Walker to Hal:

From the time of retirement in July 1974 until May 1976, I did research, wrote and published four papers. In May 1976, I experienced macular scotoma in both eyes and discontinued laboratory work. I was pleasantly surprised to find several agencies and instruments for visual aid to those with low visual acuity. However, more work needs to be done on perfection of lenses with high magnification that could be used as reading and writing aids in the office and the home. I am now interested in the possibility that the low energy requirement associated with lengthening contraction of muscle might warrant the development of a lengthening contraction machine to be used for persons convalescing from severe muscular weakness created by prolonged muscular disuse. We wish to add an expression of appreciation for the splendid work of the Senior Physiologists Committee and for the replies of Senior Physiologists previously appearing in the Physiologist.

Fred Mettler to Hal:

One area of my present activity may be of concern to fel-

low members. I am associated with Anatomy Associates, Box 376, Blaistown, N.J., which is concerned with professional and procedure liability litigation, as well as with industrial medicine, radiation effects and pathology. This organization would be pleased to hear from members interested in consulting who are qualified as expert witnesses in toxicology, in any of the clinical subspecialture of medicine or surgery or in the fields of prosthetics and supplementary devices. A list of pertinent publications should be submitted.

Morris Bender to Hal:

I became Professor and Chairman Emeritus in October 1973. Since then I have been teaching on a graduate level and doing some clinical research.

He enclosed an announcement of the investiture on November 29, 1976 of Bernard Cohen as the first Morris B. Bender Professor of Neurology at the Mt. Sinai School of Medicine, City University of New York.

Samuel Tipton to Hal:

My wife, Dr. Isabel H. Tipton, retired Professor of Physics, and I are busy with our Bird Study program here in southeastern North Carolina. We fill our time with Bird Banding in the U.S. Fish and Wildlife program, and general Breeding Bird Surveys which we run every year, with our travel, occasionally to foreign countries and more often to see our grandchildren in Tennessee.

The general situation and success of land birds in this coastal area has had very inadequate study. We believe that our data will contribute significantly to that area. We plan to devote much of our time and energy to these studies, with special interest in the success of the painted bunting here in the northernmost limits of its breeding area, for the next few years. So, I am not interested in other research or administrative positions.

L.P. Herrington to Hal:

I held one of the original appointments at the John B. Pierce Foundation in New Haven, coordinated with teaching at Yale. I retired 16 years ago following injuries received in the collision of two minimally insured vehicles, in one of which I had been a passenger for a few minutes. This was after 31 years of research and teaching; I was granted retirement as Director Emeritus for life.

Five years ago my wife, who was librarian of the Yale Department of Epidemilogy and Public Health succumbed following an operation for a metastasis. Since then I have lived alone, "house-bound," save for fifteen to thirty minutes a day, to a radius of circa 400 yds.

My focal activity involved human environmental physiology, cross-disciplined by features from some areas of biophysics and engineering. My last bibliography (1958) noted some 110 publications, several monographs, a book, and a volume of collected papers.

Currently I use available time and energy on two projects. The first is a long and tedious survey of the authority and auspices which supported non-commercial research in the past two centuries with especial emphasis on the psychophysiological and socio-economic factors which supported the various endeavors and their contemporary "rationalization."

A second writing on an analysis problem is a less tedious survey of the situations and factors which have been statistically most common in the planning, execution and publication of research in the general field of my chief interest.

The greatest problem, with the exception of voluminous notes and diary material, has been the essential break in reliable street transportation or central parking within "stride" distance of several excellent libraries.

Since a large number of our long term members have earned pensions, Social Security, or both, prior to 1960, they have abandoned subscription to handbooks and journals. At present the last notch out of kilter with the 1925-1960 period, economically, in which such livelihood was earned, is that of dues.

Roy Greep to Maurice:

My fond greetings to you and to the Committee of Senior Physiologists. This being my first and belated response as an elder, I should explain that admitting one has been, by reason of age, benched, sidelined, shelved or put out to pasture or whatever, is not something that comes easily though it be naturally. I reached mandatory retirement age in '72 but was allowed to stay an additional two years as Professor of Anatomy and Director of the Laboratory of Human Reproduction and Reproductive Biology at the Harvard Medical School. After that I worked full time a further two and one-half years directing a world-wide survey of research and funding in reproductive biology and contraceptive development sponsored by the Ford Foundation. A two-volume report was sent to press in March and I have since been a free man, perhaps more fittingly described as unemployed. The really strange and sometimes shocking initiation to retirement as I find it is to get up in the morning and not prepare to go to work.

I continue to do some editorial work, manage the Laurentian Hormone Conference, write and give an occasional lecture here and there on population problems and fertility control. Otherwise, it has been easy to keep occupied with gardening and other outdoor work through the summer, but I am facing the first winter "at home" with some qualms as my health and appetite for doing are not as yet much worse for the wear. After a couple hours of splitting logs I do notice a sense of fatigue unlike when I was a youth on the farm and wood was not an ancillary source of fuel. Whenever I sense a feeling of frustration coming on I draw comfort from a small poem by F.S. Cohen which I carry around in my billfold. It reads:

I dread the thought of growing old,
It fills me full of fear —
But compared to the alternative,
The choice is loud and clear.

On the matter of seeking a position elsewhere I am ambivalent. My wife has roots down in the Boston area and we are newly and comfortably settled in a lovely prerevolutionary farm house with acreage in woods, brook and pond, and an abundance of birds and some wildlife. We are in Foxboro, Massachusetts, about mid-way between Boston and Providence, Rhode Island. I hope I am not being immodest in admitting, however, that I would consider moving for a major opportunity elsewhere, mainly administrative. Barring that I hope soon to become adjusted to not beating my brains out to meet deadlines or the exigencies of the day or hour and to doing my own thing in some kind of constructive and satisfying effort.

Paul Nicoll to Maurice:

I'm still working full time at teaching and research. More and more my research turns toward the lymphatic capillaries and associated collecting ducts. The bat wing remains ideal as a biological in vivo site and definite data on physical parameters involved in lymph formation should soon result.

Sol Rosenthal to Maurice:

I am just finishing my book, "BCG Vaccination, Tuberculosis–Cancer." I have expanded it greatly from the first edition to include work on treatment of cancer and particularly immunization against cancer and leukemia. I have given papers in the last few years at seven international meetings where I presented my original studies on the stimulation of the reticuloendothelial system following BCG vaccination and on retrospective studies on vaccination of the newborn. Over a 20-year period, there was a 74% reduction in the mortality from cancer and leukemia in the vaccinated as compared to the non-vaccinated subjects. A group of us have established an international committee to study this problem all over the world.

Getting back to one of my old loves, and one in which you were involved, is histamine as the chemical mediator for pain. I was invited to give a paper in October at an international symposium on the subject, so the concept is still very much alive. Graham Weddell of Oxford has indicated that he would be willing to co-author a book on the chemical mediation for pain.

Outside of that, I have remarried (four years ago) and have a two year old daughter named Sara, the delight of my life.

My words of wisdom to pass on to younger and older colleagues is to become involved in a risk exercise sport (RE). As for myself, I ride horses, fox hunt and swim almost everyday. I have written extensively on the subject of RE and my thesis is that RE is necessary for our well-being to supplant the stimuli that our ancestors were evolved with in foraging for food and maintaining their territorial rights. My theory also states that we are suffering from a deficiency because of the lack of this type of stimulation. RE is the modern concept of fulfilling this need.

Wallace Armstrong to Maurice:

I have been at the NIH since September, 1974 as Acting Scientific Director of the Dental Institute under the provisions of the Intergovernmental Personnel Act which, in my case, is an arrangement whereby I am loaned by the University of Minnesota to the NIH. Since I am not an HEW employee my title has to be that of "Acting." I had planned originally to spend only one year here but I was invited to spend a second period of a year. I shall return to Minnesota early in September and enjoy the fruits of retirement if any can be discovered.

My work here has been quite intensive and I have been very busy. I have learned a great deal about the operation of NIH and I have developed a high regard for many of the activities in the Intramural programs and I have met and enjoyed a number of quite remarkable people. I had thought that the complexities of administration and of the bureaucracy of the University of Minnesota were large but I can tell you that the bureaucracy of the NIH is about 10 times more intricate than that of the University.

Bill Clark to Maurice:

I have your letter (+Bruce Dill + Hallowell Davis) re. The Physiologist and old cronies.

Yes I am very busy–both in research and writing. I have very little money but I do have a splendid and highly productive and creative psychopharmacologist, an Indian, Krishna Menon. We are working on: better central dopamine receptor agonists, thus better antiparkinsonism drugs; amphetamine antagonists (thus possibly new approaches to better neuroleptic drugs); mechanisms of action of hallucinogens; mechanisms of action of analgesic narcotics.

My writing includes papers on the above, and finishing up the 2nd edition of my "Principles of Psychopharmacology," Academic Press, 1970. The 1st edition received fine reviews and is used widely and internationally for teaching. The 2nd edition is much better. The 1st edition had 2 printings and a Spanish translation by La Prensa Medica, Mexico City. I hope to have the 2nd edition (out early '77) translated into several languages.

UCLA finally caught up with my age and so now I'm emeritus there (67 limit). The govt. isn't so strict. Altho' you're supposed to retire at 70, you can appeal. I intend to if my health keeps up as it has. I'll be 70 in a little over 2 yrs.

For hobbies, I paint some, study Latin and Greek, do photography, go swordfishing occasionally, and travel (my wife does the gardening).

Words of wisdom for younger colleagues? Nothing except keep up with modern technology. Don't rely on "Current Contents" for complete coverage of the literature. Also scan those sections of "Excerpta Medica" which cover your fields. It covers many more journals than "Current Contents."

Joseph Hinsey to Maurice:

It was thoughtful of you folks to inquire about me and what I am doing. Since I closed my office in 1969, I have ceased carrying on any academic responsibilities aside from an occasional review or comment on some subject. I still carry on quite an active correspondence with former students and colleagues whom I have known over the years. Since 1964, I have had to depend on canes for ambulation as the result of a mid-line disc at four lumbar for which I waited too long before surgical intervention. My activities have been more circumscribed than they would have been otherwise.

I have been concerned with certain present trends in medical education: expansion without adequate support, inadequate support and time for the basic medical sciences, changes in the conduct of clinical teaching, and undue political pressures. However I realize that I belong to an older generation whose objectives may have been different.

I deeply appreciate the work of your committee and I read carefully what you publish in The Physiologist.

Richard Richards to Maurice:

I am "consulting professor" in Anesthesia, Pharmacology and Medicine at Stanford University. This gives me opportunities for some teaching, some research with an occasional publication and clinical activities. Every week I make rounds as a clinical pharmacology consultant at the Palo Alto V.A. Hospital which is staffed by Stanford faculty. Furthermore I am a part-time consultant for Syntex Research and a member of several committees.

Advancing age takes its toll in resistance and productivity; experimental work, which I occasionally do, gets harder and more tiring. Still I am grateful for what I can do, though I realize that inescapably one falls behind in modern skills and methods.

I am very happy to continue receiving "The Physiologist" from the society and to see the continuous vigorous development of this science.

I sincerely hope you and the other members of this committee are well and that all of us may have the benefit of your wisdom and initiative for many years to come.

Charley Best to Maurice:

I am not doing research but do give a few lectures each year to the medical students on some aspect of endocrinology.

My wife and I are writing a history of our family and of my scientific work over the years with the hope of combining this into a book.

We have many invitations to give lectures in other countries but have not accepted them recently apart from certain ones in the United States. In October, for example, we are going to Boston to help dedicate a major addition to The Joslin Clinic. I have lost track of the number of times we have gone to Boston since 1922 when I lectured to the Harvard Medical Students with Professor Walter Cannon in the Chair.

Our next trip is to the Maine-New Brunswick coast where we are interested in selling the property there which we have owned for many years. Our most enjoyable holidays now are spent in Bermuda and in Coral Gables, Florida.

I am not interested in an administrative position and would not care to move to another area. I hope that you will send my very best regards to Bruce, Hal, Hymen, Edward and Phil. Margaret joins me in sending very warm regards to you.

Heinrich Necheles to Maurice:

I am touched by your interest and encouraging words. I will be eighty next year; but I still feel young and happy with ambitions and hopes for successful work in my field.

To answer your questions:

I am living happily with my wife in a garden city in California. I have recovered from a slight heart attack and am feeling well now.

I am writing my autobiography now and am participating in seminars and lectures on cancer and gastroenterology. I am doing research with my old group at Michael Reese Hospital on an ulcer factor. When and if we receive a research grant, I plan to fly to Chicago at regular intervals. My research group at Michael Reese Hospital is intact and keen to continue our work.

Hudson Hoagland to Maurice:

I retired as President of the Worcester Foundation for Experimental Biology at the end of 1968, but I have retained my office, to which I come quite regularly. I retired at the age of 68 with some reluctance, but felt I should do so since, as co-founder with Gregory Pincus, who died in 1967, and as the executive officer, I should follow rules we had laid down about our retirement, which we had agreed should take place at age 65, or, at the latest, 70. At the time I was collaborating with colleagues here on studies on psychopharmacology, particularly in regard to schizophrenia, but I had actually done nothing in the laboratory myself for some years. I acted rather as a director of our program in the field of biobehavioral science.

In my office over the last eight years, my activities have consisted largely of reading, giving a few lectures, and writing an occasional short paper dealing with the impact of science on certain social problems. I do seem to have a fairly extensive correspondence that I keep up with the the help of my secretary, who has been with me most of the years since 1931, and now comes in two days a week. My reading and interests have shifted from neurophysiology, psychopharmacology and neuroendocrinology, which involved my scientific papers, to an amateurish interest in archeology and anthropology, and I have spent some time traveling to sites concerned with these interests. There is nothing creative about this for me. I am, however, stimulated by what I have learned in a totally different field outside of physiology. I find in my professional field, not having kept up with the literature, that I am unacquainted with the young scientists who are doing exciting things. I call everyone under 65 a young scientist! Most of my contemporaries are either retired or dead.

I am still, however, active on some boards. I am a member of the Council of the American Academy of Arts and Sciences, of which I was President in the early 1960's, and am "Principal Investigator" on a planned Academy series of symposia on the history of human population growth, financed by NSF. I am a member of the Corporation of the Woods Hold Oceanographic Institute, of which, until I was 70, I was a trustee and member of its Executive Committee. I am also a member of the Corporation of Frank Schmitt's Neuroscience Program. Strangely enough, I am a director of a major bank in Worcester.

You mention you are interested in getting biographical material for the Society's Archives, and I am enclosing a small book called "The Road to Yesterday," which is autobiographical and also contains a history of the Worcester Foundation.

James Bradbury to Maurice:

I retired from the University of Iowa in 1974 and moved to Bozeman, Montana where I graduated in 1928. The University has appointed me Adjunct Professor in Biology and I am participating in the Physiology course for the medical students. There are 20 students here for their Freshman year and then they go to Seattle for the last 3 years at the University of Washington. Seattle takes students from Washington State, Alaska, Montana and Idaho in this W.A.M.I. program. My contribution is primarily in the Endocrine lectures during the winter quarter. I have also been on the advisory committees for several graduate students so I feel very much at home here at my old alma mater. Furthermore the climate of the Big Sky country is preferable to that of the Midwest. Hermann Rahn was here for a workshop on respiration 3 weeks ago, a very nice program.

A. B. Taylor to Maurice:

I have been retired from departmental teaching and other duties since September 1972. Fortunately I am in reasonably good health and continue to work in the laboratory almost every day I am in Urbana. Using the transmission electron microscope I am studying the ultrastructural changes associated with cellular aging in such cells as intestinal epithelium, liver and kidney from animals of various ages. In addition, in collaboration with Ladd Prosser, of my department I am studying the junctional area between the longitudinal and circular muscles in the small intestine of the cat hoping to be better able to explain the electrical activities associated with these muscular layers.

When not in the laboratory I do a limited amount of gardening and as a part of our activities I do some traveling with my wife. I could be interested in a position which would enable me to continue my scientific activities but would not desire an administrative position. I am free to move to another area.

It is most interesting to read of the activities of senior physiologists as presented in The Physiologist. Thank you for your greetings and inquiries about my activities.

Charles Kochakian to Maurice:

I have two more years before reaching mandatory retirement age; I am still active in the laboratory and the office. I hope to continue laboratory work and writing after retirement either here or elsewhere. Last autumn (1975) I completed a volume entitled "Anabolic-Androgenic Steroids" on invitation of the Editorial committee of Springer-Verlag. The volume is in the final stages of printing and should be in circulation by about December, 1976. Approximately half of the book was written by myself on subjects related to my basic studies. The rest of the book is related to the clinical application of the anabolic action of androgen-like compounds. I was particularly pleased to edit and write the several chapters in this book because it brings together the growth and development of the accumulated knowledge of the anabolic-action of androgens which was first reported by John R. Murlin and myself in 1935.

Hans Selye to Maurice:

I have been renamed a full professor at the University of Montreal for the coming academic year. Although financial difficulties have made me curtail my laboratory work and teaching, I am fully active, doing research mainly on the psychosocial applications of the stress concept.

This year I completed an extensive encyclopedic treatise entitled "Stress In Health and Disease" (Butterworths, 1976) which takes up 1256 pages and quotes about 7500 key references among the 120,000 reprints and books which we have accumulated in what we believe to be the largest existing documentation service on stress. I am also working on the foreign editions of my popularized book "Stress Without Distress." This volume outlines the behavioral code derived from stress research and was published in hardcover (Lippincott, 1974) and later in a large paperback edition (Signet Books, 1975).

My major preoccupation at present is the recently created International Institute of Stress, devoted primarily to the coordination of stress research throughout the world and the dissemination of information from our library through lectures and publications.

I do accept a certain number of visiting professorships outside of Montreal for short periods. However, having passed by five years the obligatory age of retirement, I find myself with less desire for or availability of free time than ever before, and thus prefer the format of lectures and national hook-up television conferences that reach comparatively large audiences. My health being excellent meanwhile, I really wonder where all this compulsive drive will eventually lead me!

Robert Gaunt to Maurice:

I have served as a half-time consultant for the CIBA-Geigy Corporation.

As of September 1, that came to an end and I have now moved my library to my home and set up an office-workshop there. Aside from doing just what comes naturally—which includes a sizable amount of time in travel, on my golf course, my lawn and in my little woods—I will continue to use CIBA-Geigy help and facilities to keep some writing and editing commitments.

Thus far the release from time-defined responsibilities for the first time since ploughing corn in North Missouri in the early 20's provides a welcome feeling. My rule of thumb is that I must get some work done but must hurry about nothing. We'll see how it goes.

Evan McChesney to Maurice:

I continue to hold the rank of Research Professor in the Institute of Comparative and Human Toxicology of the Albany Medical College, but since the beginning of 1975 I have retired from the laboratory to my office, where I have been involved in various types of scientific writing. The nature of this Institute's research activities and its sources of support require that rather frequent and voluminous reports be submitted. These cover both past and proposed future activities. I have been chiefly occupied, for several years, in compiling these reports and in composing most of their narrative parts. Naturally, I am grateful to the local authorities for according me the opportunity to carry on this useful and challenging work. How long this will continue is anyone's guess, but the present projection is: at least until mid-1977.

E. S. Nasset to Maurice:

I'm still working in GI physiology and still publishing scientific papers. I'm not now, nor have I ever been, interested in an administrative position. Since 1945, I've rejected 3 offers of chairmanships and 1 deanship.

My wife and I are both healthy and we enjoy life in Berkeley. Last week we attended the 1st International Symposium on GI Hormones held in Pacific Grove, California. This field has had an explosive growth in the last decade and it is bound to continue for some time. I'm glad to have had a hand in some of the pioneering efforts four decades ago.

Carl Dragstedt to Maurice:

Thank you and the other committee members for your greeting. I had a touch and go situation with "acute cerebral ischemia" plus cardiac irregularity this summer but I am doing fairly well.

I belong to a group of about 20 semi-retired here who meet for lunch once a week and I try to come up with rhyme. That's my main occupation.

Carl, our society rhymester enclosed one of his latest:

EIGHTY-ONE

How does it feel to make eighty-one?
Its something, I'm sure, that shouldn't be done;
According to history, and many wise men
All that is scheduled is three-score and ten.
So if you're that old, get ready to leave
Prepare for the verdict you're due to receive,
Ash-can or coffin are waiting for you,
And they don't have much patience for things overdue.

Stanley Garn sent Maurice for Society Archives a list of his 23 publications in 1975 and added:

At this moment, working with some of the chronic renal failure patients, I have combined both work on bone and bone loss (that started in 1960) and on hemoglobin, the difference between blacks and whites (that began to emerge 5 years ago).

As soon as we have enough black patients with transplanted white kidneys and white patients with transplanted black kidneys, we will have the perfect experiment!