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The Physiologist

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

Volume 22, No. 6, December 1979

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On the Cover: This issue's illustration suggests areas of interest in the field of gravitational physiology. Drawing by Dan Winter.

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April 12-17, 1981	—	Atlanta, GA
April 18-23, 1982	—	New Orleans, LA

Fall

October 12-17, 1980	—	Toronto, Canada
November 1-6, 1981	—	Boston, MA
October 10-15, 1982	—	San Diego, CA

28th International Congress

July 13-19, 1980	—	Budapest, Hungary

For travel information to the International Congress in Budapest, please write to:

Chevy Chase Travel
4715 Cordell Avenue
Bethesda, MD 20014

Regular Members	4,198
Honorary	8
Emeritus	458
Associate	631
Corresponding	40
Student	157
Total	5,492

DEATHS REPORTED SINCE THE 1979 SPRING MEETING

James Brodley III (R) - 1-6-79 - Cooperstown, NY
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Abraham Cantarow (E) - 9-1-79 - Natl. Cancer Inst.
Walter Fleischmann (E) - 3-23-79 - Johnson City, TN
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Louise M. Heim (R) - - County Coll. of Morris, Dover, NJ
Theodore L. Jahn (E) - 5-1-79 - UCLA
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Heinrich Kluver (E) - 3--79 - Univ. of Chicago
Grayson P. McCouch (E) - 8-2-79 - West Chester, PA
Heinrich Necheles (E) - - Walnut Creek, CA
Robert E. Semple (R) - 7--79 - Queens' Univ., Kingston, Ontario
Erma A. Smith (E) - 6--79 - Wichita, KS
David C.H. Sun (R) - 1-23-79 - Phoenix, AZ
Anastasios Tsakiris (R) - 10-25-79 - Univ. of Sherbrooke, Quebec
Cornelius A.G. Wiersma (E) - 5-19-79 - Calif. Inst. Tech., Pasadena
Alvalyn E. Woodward (E) - 7-16-79 - Charlotte, NC

NEWLY ELECTED MEMBERS

The following, nominated by Council, were elected to membership in the Society at the Fall Meeting, 1979.

REGULAR MEMBERS

ARBEL, Emanuel R.: Cardiovacular Inst., Michael Reese Hosp. & Med., Ctr., Chicago
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APS PUBLICATIONS

MID-YEAR REPORT

It appears that 1979 will be a vintage year for the publications of the American Physiological Society. The reorganized journals are maturing. The specialty journals are developing very individual characteristics in response to the needs of each field, the contributors to each journal, and the editors. The *American Journal of Physiology: Endocrinology, Metabolism and Gastrointestinal Physiology* reached sufficient size and strength to warrant its separation into two monthly publications. Therefore, in January 1980 the Society will begin to publish the *American Journal of Physiology: Endocrinology and Metabolism* edited by Ernst Knobil and the *American Journal of Physiology: Gastrointestinal and Liver Physiology* edited by Leonard R. Johnson. Also beginning in January 1980, the *Journal of Neurophysiology* will be issued at monthly intervals, rather than bimonthly as in the past. Continued increases in the number of manuscripts submitted to the journal, and the potential room for continued growth, more varied articles, and more rapid publication stimulated this change in publication frequency.

It is anticipated that about 10% more pages will be published in the journals in 1979 compared to last year. The phenomenal growth of the journals since they were reorganized continues.

Plans were laid for an expansive book publishing program for the next five years. The plans include the revision of the first three sections of the *Handbook of Physiology,* i.e., neurophysiology, circulation, and respiration, plus the publication of a new section on skeletal muscle. The Clinical Physiology Series is to be continued as the first three volumes are meeting the aim of providing an important medium for the communication of clinical and research physiology on topics of mutual concern.

Two important books were published in 1979. *The Heart,* R.M. Berne, Editor and N. Sperelakis, Associate Editor was published in June. This volume is the first in the revision of the *Handbook of Physiology* section on circulation, now entitled *The Cardiovascular System. Pulmonary Edema,* edited by A.P. Fishman and E.M. Renkin was published in February. This is the third volume in the Clinical Physiology Series. The intitial reception of each volume has been excellent.

REPORT OF THE FINANCE COMMITTEE

September 21, 1979

Present:

Committee Members:

Arthur C. Guyton, Chairman
Robert Forster
Jack Kostyo

Ex officio Members:

Earl H. Wood, President-Elect
Orr E. Reynolds, Executive Secretary-Treasurer
Walter Sonnenberg, Business Manager
A.P. Fishman, Chairman, Publications Committee
(Mr. Steve Geiger attended in Dr. Fishman's absence)

General Considerations

In general, the total proposed expenditure budget for 1980 is approximately 10% above that for 1979, which is about 3% less than the national inflation rate.

However, there has been a deficit in the Society Operating Fund budget for each of the past several years, and next year's budget, as it now stands, is no exception. The funds to cover this deficit have come from interest income earned on investments

belonging to the Publications Fund. In addition, the audiovisual production program, though considered a capital project rather than an ordinary expense item, has been in a deficit posture steadily since its inception and represents a total deficit through all the years of its existence totaling approximately $120,000 at the present time. It is probable that some of this will be recouped during the next few years from sale of slide tape programs that have already been produced. The cost of this program has also been underwritten from interest income earned on the investments belonging to the Publications Fund.

The Publications General Fund

The Publications General Fund supports publication of the Society's journals with the exception of *The Physiologist.* Despite the fact that the journal prices have not been increased during the past three years, this fund has steadily been in the black. For the 1980 year, the proposed budget will be approximately 10% above the 1979 budget. This increase will be offset by increased income generated by increasing the prices of some, but not all, of the journals. The increase in the budget is caused by general inflationary tendencies, including especially major increases in costs of printing and engraving and an increase in the amount published. It is anticiapted that expenses and income will approximately break even in the 1980 year.

Publications Special Projects Fund

This is the fund that supports publication of the *Handbook* series and the new monograph series. Both income and expenses in this fund increase and decrease greatly year by year depending upon the timing of each new *Handbook.* However, in general, income and expenses operate on a break even basis year after year. This is still true for the present year and also for the 1980 proposed budget. Over the 20 some odd years of this program, the total excess cost of *Handbook* production over and above income has been approximately $230,000, but this is offset by a present inventory of unsold *Handbooks* valued at cost, which is considerably less than sale price, approximately $630,000.

Also, the results from sale of the first three clinical physiology monographs indicate that the monograph series will continue to be at least a break even program. Thus far, the cost above income is approximately $14,000, but the inventory value is considerably greater than this, and the sales are brisk enough that it is certain that these costs would be recovered within a year or so should the project be abandoned. Thus far, only one monograph is being published per year. The Finance Committee discussed the possibility of increasing the productivity of this series as a possible financially viable program.

Society Operating Fund

The Society Operating Fund supports all the operations of the Society headquarters besides those related to publications and to the audiovisual program. The proposed increase in budget for the following year is approximately 12%, which is slightly less than the national inflation rate. Approximately one half of this increase results from a necessary budgetary increase in dues to FASEB. This is caused by the fact that the Spring FASEB Meeting has not been earning as much income in the past few years as it had previously. In the past, we had been receiving a net return each year from FASEB. During the 1980 proposed budgetary year, our net payment to FASEB will be approximately $15,000 greater than we will receive from the Spring Meeting earnings. The $15,000 represents approximately $3 per American Physiological Society member.

For the past few years, the expenses of the Education Office, which are included in Society Operating Fund Expenses have been "sub-budgeted" separately from the other expenses of the Society. However, since we no longer have a separate Education Office, the separation is now mainly an artificial accounting exercise. Therefore, it was unanimously decided by the Finance Committee to combine the accounting of these expenses with those of the remainder of the Society in future years until such time that a distinct Education Office might be recreated. This will be a saving in time and effort in the Society headquarters.

Business Office Expenses

The Business Office provides the accounting, billing, and general financial services for all programs of the Society. The expenses incurred by the Business Office are then allocated on a pro rata basis (in relation to the respective budgetary expenses) to the different budgeted funds of the Society. Because most of these expenses relate to publications, approximately four-fifths of the expenses are charged to the Publications Funds and the other one-fifth to the Society Operating Fund.

Audiovisual Production Fund

Audiovisual production was originally begun under government auspices, but the cost of this program was picked up by the Society beginning approximately five years ago. The concept of the program was to produce slide tape programs and to repay the costs from earnings generated by sale of the programs. The earnings have been considerably less than originally projected and are now approximately $120,000 less than the costs to date. However, after completion of the Peripheral Circulation slide tape programs, which are already underway, no further programs are to be produced, at least for a few years, until it is determined whether or not the utimate sale of the programs will justify the cost. Therefore, beginning in 1981, the income from the already produced slide tape programs should recoup a considerable amount of the money that has been invested in this program.

It was remarked by the Finance Committee that the actual cost to date has been greater than $120,000, because we have also lost the interest and possible capital appreciation of these funds during the intervening years, making an actual cost probably somewhat in excess of $150,000.

Society Investment Funds

The American Physiological Society has four separate investment funds. Two of these are two separate Publication Funds called the Operating Reserve Fund consisting of advance subscription funds which are used, as needed, to meet day to day operating expenses, and the Contingency Reserve Fund. The other two are the IUPS Fund and the Perkins Fund, each of which has a present market value of slightly over $100,000.

The total market value of the four investment funds has increased approximately 8% since January lst of this year, and the interest income from all the funds combined is slightly over $120,000 per year. The returns on the investments appear to be as good as could be expected, and perhaps a little better, considering the restraint imposed on our financial advisors to invest only in very sound securities.

Dues, Budgetary Deficit in the Society Operating Fund, and Possible Ways to Balance the Budget

At two previous points in this report, we have already stated that there has been a persistent deficit for the past several years in the Society Operating Fund expenses over income. In the budget proposed for 1980, without a dues increase, the deficit will be approximately $31,000. The Finance Committee sees three possible options for covering this deficit as follows:

1. Continue as we have been doing to charge this deficit to interest income from our Publications Investment Funds. This has the disadvantage that our total Publications Investment Funds in ratio to the total cost of producing the journals has been steadily decreasing for the past ten years, going from a ratio of over 1.5 to a ratio of approximately 1.0 when considering total Publications Investment Funds and a ratio of only about .6 when considering the Publications Contingency Reserve Fund, which is the only fund that does not have encumbrances against it. Therefore, the trend has been away from long-term stability of the publications financial program.

2. The second option would be to increase the dues. This would require a dues increase of approximately $6 per member for the coming year.

3. The third option is to reduce the Society Operating Fund expenses. The Finance Committee has identified the expense items that Council could eliminate as possible ways to reduce the expense of Society operation.

Two major items of expenses have been identified that should especially be considered. These are: Program Development, that is budgeted for 1980 at $24,600 for the Spring Meeting only. In addition to this, as much as $10,000 might be budgeted for the Fall Meeting but charged to the Fall Meeting costs. Elimination of the costs for program development, which means mainly support of symposia, would come near to wiping out the deficit for 1980.

The second major item that should be considered is the cost of *The Physiologist,* which is budgeted at $50,000 for 1980. Several different schemes could be used to reduce this. Discussion occurred within the Finance Committee regarding the possibility of reducing this to a small Society news bulletin which could save as much as $50,000 per year. Perhaps an appropriate plan could be worked out for the Society's scientific portions of *The Physiologist.*

Thus, the Finance Committee offers Council a number of different ways to balance the budget. Its suggestion is to consider as first priority the reduction of Society operating expense, second priority the continued use of interest income to cover the deficit and as third priority a dues increase for the coming year (though the Chairman of the Committee, as a dissenting voice, would have been more in favor of use of interest income as the last priority.)

NOTE: The Council at its Fall Meeting decided to accept the first suggestion; that is, to work on the reduction of Society operating expenses, specifically the reduction of the Federation assessment expense.

CURRENT ACTIVITIES OF THE APS EDUCATION COMMITTEE

This report summarizes current activities and plans of the Education Committee and includes business conducted at its most recent meeting held August 16 and 17, 1979, in Bethesda.

I. The Audiovisual Project (Table 1)

In 1972, the Society embarked upon a major effort to evaluate existing audiovisual materials in the field of physiology and to prepare new materials. Contracts from the National Medical Audiovisual Center (NMAC) funded the initial review of existing materials and the production of the first slide-tape presentations in the areas of renal, cardiac, and acid-base physiology. When the contract was given for the last of these series (that dealing with acid-base), NMAC indicated that no further contracts would be given to the Society for the preparation of additional materials as it was their policy to give financial support and guidance to professional groups only during the initial stages of program development. By this point (Spring 1975) the Education Committee felt that the Society had developed an effective mechanism and staff for developing and producing new materials. Accordingly, it felt it would be extremely unfortunate if all activity had to cease at the termination of the NMAC contracts. Accordingly, the Committee recommended to Council that financial support be provided from Society sources for the continuation of the audiovisual program, the assumption being that these funds would, in all probability, be recovered through sales of the materials. Council voted a maximum financial support of $150,000 until September 1978 with the expectation that the program would be self-supporting by then. As a consequence of Council's action, extensive plans were made by the Education Committee to provide an "in-house" mechanism for the preparation and quality control of the slide-tape materials. New series on renal pathophysiology and cardiac electrophysiology were begun, to be followed later by a series on peripheral circulation.

At the end of 1977, the accumulated deficit of the program to the Society was $59,942, and the Education Committee projected that this deficit would increase to $68,000 by the end of 1978 and would then begin to decrease in 1978. Given the fact that the total deficit was less than half of that approved by Council in 1975, the Committee requested that Council extend support beyond the original affixed date of September 1978, and Council so acted, in Spring 1978.

Unfortunately, these projections were overly optimistic and the deficit has continued to increase. It was approximately $98,000 at the end of 1978 and is projected to reach approximately $114,000 at the end of 1979 and $143,000 by the end of 1980, if full production continues until then. The major reason for the discrepancy between the early estimate and the actual present state is the low production rate of slide-tapes for the past few years, since sales of existing tapes have been reasonably close to original predictions. There are many reasons that the system set up for developing the materials did not function as efficiently as originally predicted, but several inter-related common denominators are apparent. First was the absence of a single full-time individual to act as manager or editor of all aspects of the entire series, both intellectual and financial. Second, and related to this, was too little early decision-making prior to major production-staff involvement; this led to costly delays and reworking of material. This latter problem was discussed in great detail by the Education Committee at its most recent meeting, and a more efficient system has been set up for the production of the materials to be recommended below.

At its August 1979 meeting, the Education Committee decided to recommend to Council that a moratorium should be set for the production of new slide-tapes, beginning, at the latest, at the end of 1980. This date was chosen for several reasons. First, the program will have come close to the maximal financial commitment authorized by Council. Even should it break even with continued production beyond 1980, it would almost certainly remain very close to this maximum value for several years. In contrast, continued sales with no production costs to the Society for several years should cut the deficit by an estimated $75,000-$100,000.

Second, the period from now (August 1979) to September 1980 should permit the orderly completion of those materials now in production. The four slide-tapes on cardiac electrophysiology and the first seven of those dealing with peripheral circulation are in varying states of completion and, because of the intellectual and financial resources already committed to them, should definitely be completed. One or two others on peripheral circulation have only just been begun but are considered necessary to complete that package. A new slide-tape for the renal series (one dealing with the kidneys' handling of calcium, magnesium, and

phosphate) and a revision of the older slide-tape dealing with sodium are also in the very early stages, and the staff believes these, too, can be finished by Fall 1980. The revision is felt to be particularly important because it will be the first one to be tackled, and should provide information of considerable value for the consideration of future revisions of other slide-tapes.

To reiterate, both financial considerations and the volume of material presently being produced establish late 1980 (December 31 as an absolute deadline) as logical time for the Society to pause in its production of slide-tape materials. This moratorium of at least two years (1981 and 1982) will provide a period for greatly reducing the accrued financial debt to the Society and, very importantly, provide an opportunity for the Committee to evaluate all aspects of the program. This information should make it possible to determine whether the program should be restarted at all, what form it should take, what reasonable financial considerations can be predicted, and whether supplementary outside funds can be obtained for its support. By that time, also, the Society may have found it possible to maintain a full-time education officer to oversee such projects. At some future time, therefore, the Education Committee would bring to Council recommendations for the program beyond the period of the moratorium.

II. Accreditation for Category I, Continuing Medical Education

For the past few years, communications have been held with the AMA and its liaison committee concerning the possible accrediting of the Society's various educational programs for category I in continuing medical education for physicians. This would include not only the slide-tape materials but the refresher course, tutorial lectures, and publications, as well. An application is being submitted, and we are to be evaluated by a visiting team at the Fall meetings in New Orleans.

III. Fall 1980 Refresher Course

The topic for the Fall 1980 refresher course has not yet been established for certain. The two topics presently being considered are "Physiology of Calcium, Phosphorus, and Bone" and "Fuel Homeostasis in the Pancreas."

IV. Learning Resource Center at Meetings

As one means of facilitating the exchange of information concerning educational matters at the Society's meetings, the Education Committee has sponsored, since 1978, a "Learning Resource Center" at both the Fall and Spring meetings. Many favorable comments have been received concerning this "Center" and it will be continued in 1980.

The following facilities are available for use:

1. Poster boards set up in the exhibit hall area assigned to the "Center."
2. Table space for books, models, or special projection equipment.
3. Telephonic connections for a computer terminal.
4. Video cassette players.

Members wishing to avail themselves of an opportunity to present educational materials should specify the "Teaching Materials and Methods" topic in the topic category list, provide an abstract on the regular abstract form for publication, and write an accompanying letter describing their equipment requirements. Presentation of an abstract in this category does not constitute use of a franchise for a research slide presentation or poster session.

In the Fall 1980 meeting, a new mechanism for facilitating exchange of educational information will be tried. At scheduled times and places, several experts in a particular area of physiology will present descriptions of how they teach their particular area -the approach, numbers of lectures and labs, topics covered, texts used, exams, etc. They will also be available at these times for informal discussions with interested persons. The areas tentatively selected for the Fall 1980 meeting are Respiratory Physiology (organized by John West), Ageing and Development (organized by Paula Timiras), and The Teaching of Physiology to Undergraduate Students (organizer to be named). The Committee welcomes suggestions concerning other areas to be covered in the future.

V. Educational Objectives

Several years ago the Education Committee was responsible for the translation and publication in the Physiology Teacher of the University of Aarhus "Objectives in Physiology." These objectives differed from the previous ones published by the Education Office in that they were written in behavioral terms rather than just being a list of topics. The Education Committee emphasized that these Danish objectives were not uniform in quality, were incomplete, and were the views of only one institution.

The Education Committee is now attempting to set up a mechanism for compiling a comprehensive set of objectives for medical physiology, representing the consensus of opinion of many physiologists. We believe that this compilation will provide valuable information for physiology departments and an essential foundation on which to base future Society educational endeavors such as the slide-tape materials.

VI. Educational Materials Review Board

Approximately 100 APS members continue to serve as an Educational Materials Review Board, which provides continuing reviews of audiovisual productions as well as reviews of articles, textbooks, laboratory experiments, etc. Each year the Board abstracts material from published papers that may be useful in teaching physiology, and these abstracts are published in the Spring issue of the Physiologist.

VII. Physiology Textbooks for Grade Schools

Throughout its existence, the Education Committee has felt that one of its major goals should be to devise a program that can contribute to the education of the general public in the areas of human physiology and health. A principal feature of this program would be the development of educational materials for the grade-school level. Mainly through the efforts of Orr Reynolds, the Education Committee has been in contact with the Biological Sciences Curriculum Study (BSCS) and has identified Society members to function as consultants for the book presently being developed by BSCS for grade-school students and dealing with the human body and hygiene. However, on the basis of past experience, it is likely that, if we desire a high-quality book dealing with physiology for high school students, we will have to initiate the project ourselves. Accordingly, the Education Committee is presently contacting several major publishers to determine whether they might be interested in an appropriate textbook to be authored by members of the society, most likely in concert with professional science writers and educators. After all relevant information has been obtained, a proposal, if warranted, will be submitted to Council.

VIII. Publication of Texts in Serialized Form

The Education Committee proposes to define circumscribed areas in physiology that are particularly in need of new teaching

materials and for which small "teaching" books would be the desirable format. These would emphasize the use of many line-drawing pictures and graphs (but would not require the extensive approach utilized by slide-tapes), and would emphasize "core" material. The Education Committee would commission these books from Society members and provide scientific review and assistance. The chapters of each book would appear first in serial form in the Physiologist and would then be bound together as a complete small book. In this manner, the Physiology Teacher would be assured a continuous supply of high quality material, the dissemination of the material would be maximized, and the costs minimized. Obviously, this endeavor also ties in nicely with the proposed accreditation for Category I credit described earler in this report.

TABLE 1

Slide/Tapes Produced and Under Development

Series 500 Acid/Base Physiology

501 Buffer Chemistry: Physiological Applications
502 The Role of Respiration in Hydrogen Ion Metabolism
503 The Role of Hemoglobin in Hydrogen Ion Metabolism
504 Renal Regulation of Hydrogen Ion Metabolism
505 Disturbances of Hydrogen Ion Regulation

Series 600 Cardiac Physiology

601 The Cardiac Pump: Structure and Mechanism
602 Regulation of Myocardial Performance
603 Heart Muscle Mechanics
604 Mechanics of the Intact Heart
605 Cardiac Contractility: The Ventricular Function Curve
606 Indices of Performance: Clinical Application

Series 800 Renal Physiology

801 Body Fluids I; Fluid Compartments and the Countercurrent Multiplier
802 Body Fluids II: Urinary Concentration and Dilution
803 Body Fluids III: Urea Excretion, Antidiuretic Hormone and Thirst
804 The Kidney and Sodium Balance (Revision in Production)
805 Understanding Renal Hemodynamics I
806 Understanding Renal Hemodynamics II
807 Renal Clearance I
808 Renal Clearance II
809 Regulation of Renal Potassium Excretion
810 Renal Handling of Calcium, Magnesium, and Phosphate (In Production)

Series 900 Renal Pathophysiology

901 Metabolic Acidosis
902 Hyponatremia
903 Edema
904 Disorders of Potassium Balance

Series 1100 Cardiac Electrophysiology

1101 Basic Membrane Physiology Part 1
1102 Basic Membrane Physiology Part 2
1103 Cardiac Cellular Electrophysiology
1104 Electrical Anatomy of the Heart Part 1
1105 Electrical Anatomy of the Heart Part 2
1106 Disorders of Cardiac Rhythm Part 1
1107 Disorders of Cardiac Rhythm Part 2
1108 Electrocardiography: Fundamental Theory Part 1
1109 Electrocardiography: Fundamental Theory Part 2
1110 Electrocardiography: Applied Theory Part 1
1111 Electrocardiography: Applied Theory Part 2

Series 1200 Peripheral Circulation (All in Production)

Hemodynmics
Arterial and Venous Systems
Capillary Exchange
Local Control
Neural Control
Hormonal Control
Integration of Cardiovascular Function

1979 FALL MEETING REPORT OF THE PROGRAM COMMITTEE

For this meeting in New Orleans we have programmed 827 contributed abstracts compared to 810 received for last year's meeting in St. Louis. That total includes 18 submitted by members of the Biosciences Section of the Gerontological Society and 17 submitted by persons identified with the IUPS Commission on Gravitational Physiology.

Seventeen Tutorial Lectures were programmed. However, one lecture was cancelled in September since the lecturer (B.A. Hills) moved to Scotland after accepting the assignment and could not obtain travel funds.

Eleven symposia sessions were programmed including one cosponsored by the Council on Cardiopulmonary Diseases of the American Heart Association. Each guest society organized and cosponsored one symposia session.

A Teaching of Physiology session of six demonstrations was programmed and, the National Aeronautics and Space Administration cosponsored with the Commission on Gravitational Physiology a mini seminar series titled Space Environment Workshop for Life Scientists.

For the first time at a Hotel based Fall Meeting, the Refresher Course has been scheduled for the first day rather than Wednesday. This provides for greater concentration of activity since it avoids a free day in the middle of the meeting.

The Program Advisory Committee is currently composed of 14 members representing the various special interests of the APS membership (list attached). Brian Duling, the current representative of the Circulatory Physiology (Peripheral) group has advised us that he can no longer serve on the Committee. Since our last meeting, Thomas B. Miller, Jr. accepted appointment to the Committee representing Physiological Chemistry and James A. Schafer was selected to replace Lawrence P. Sullivan representing Renal Physiology.

At our Committee meeting in Dallas during last year's Spring Meeting, at the request of Council, we discussed the policy of financial support for symposia participants. As a result a revised policy will become effective with the 1980 Spring Meeting. The new policy is as follows:

1. If necessary, support may be provided to nonmember speakers.
2. Reimbursement for travel expenses are not to exceed economy airfare.
3. $50 per diem, in lieu of expenses for each day of participation.
4. Complimentary registration fee.

In this connection, expenditures in support of the 1979 Spring Meeting symposia were $27,550. Since organizers raised contributions of $6,500, cost to the Society was $21,050.

For the 1980 Spring Meeting in Anaheim, the Program Committee has approved 18 APS sponsored symposia. In addition one other APS symposia will be conducted as a satellite, sponsored by the Cardiac Mechanics Section, at no cost to the Society. Karl Weber raised sufficient contributions last year to proceed in this fashion. The guest societies at the meeting will also sponsor one symposium each. The APS guest societies are:

Reticuloendothelial Society
Society for Experimental Biology and Medicine
Society for Mathematical Biology
Biomedical Engineering Society

By agreement of the Federation Executive Committee and with the cooperation of the American Society of Biological Chemists, their members will be invited to submit abstracts for the 1980

Spring Federation Meeting. This Program Committee proposal was approved by the Council at its meeting last Spring. ASBC members will submit their abstracts to APS for membership verification. Since we will have unified programming for that meeting, abstracts will be forwarded to the appropriate programming society.

Planning continues for the joint meeting with the Canadian Physiological Society in Toronto next Fall. Guest societies for that meeting are the Section of Comparative Physiology and Biochemistry of the Canadian Society of Zoology and the Division of Comparative Physiology and Biolchemistry of the American Society of Zoologists.

In addition to symposia for the joint APS-CPS Fall Meeting, a refresher course and a series of Tutorial lectures suggested by the Education Committee are being reviewed by the Program Executive Committee.

This current meeting represents a break-through of sorts. For the first time the Federation computer was used to schedule the contributed papers. The computer generated Program copy for the printer and produced the author index. The computer also prepared the confirmation cards that are mailed to first authors to advise them of the schedule for their presentation. In this connection, we designed a new abstract form that proved to be a significant improvement over the previous version. As a result of these APS actions, the Federation adopted the new form for the Spring Meeting and is investigating computerization of programming Spring Meeting abstracts.

SPECIAL INTEREST REPRESENTATIVES ON
PROGRAM ADVISORY COMMITTEE (1979-80)

Circulatory Physiology (Peripheral), Brian Duling
Circulatory Physiology (Heart), Eugene Morkin
Clinical Physiology, Francois M. Abboud
Comparative Physiology, Bruce L. Umminger
Environmental Physiology (ETEP), X. J. Musacchia
G.I. Physiology, Michael J. Jackson
Membrane and Transport, S.I. Helman
Muscle Physiology, M.J. Kushmerick
Neural Control of Circulation, J.W. Manning
Neuroendocrinology, Joseph Meites
Neurophysiology, David Carpenter
Physiological Chemistry, Thomas B. Miller, Jr.
Renal Physiology, James A. Schafer
Respiratory Physiology, N.C. Staub

PROGRAM EXECUTIVE COMMITTEE

H. Maurice Goodman, Chairman (1981)
Melvin J. Fregly (1980) Education Committee Liaison
Franklyn G. Knox (1979)
Harvey V. Sparks, non-voting - F.P. Editorial Board Liaison

REPORT OF APS COMMITTEE ON PUBLIC POLICY AND PUBLIC INFORMATION

October, 1979

Last spring the outlook for the funding of new and competing renewal grants at NIH in 79-80 looked grim. The President's budget, if passed, would result in 20-25% of the approved grants being funded. At the spring business meeting and in a mailing, your Public Affairs Committee urged the membership to write their congressional delegation; I received quite a few carbon copies and hope these were the tip of the iceberg.

I later testified before the House Appropriations subcommittee on Labor-HEW and spoke to many Congressional Staff members. Cris Schate, FASEB fellow and APS member helped to pass the word in the Senate.

At this moment a House-Senate conference report gives substantial increases across the Institutes and will allow funding of 40-40% approved grants. This year it was the Senate which resisted increasing funds for NIH research.

In preparation for the fall meeting, the Committee chose over 50 abstracts as "newsworthy" and these will be expanded into press releases and available in the Press room at New Orleans.

A Bill, HR 4805, to establish a National Center for Alternative Research has been introduced. Its major goal is to reduce, or eliminate research on mammals. This committee, in conjunction with the Animal Care Committee is drafting an APS position paper and will testify if the bill comes to hearings.

Brian A. Curtis, Chairman

REPORT OF SENIOR PHYSIOLOGIST COMMITTEE

The Committee continued its activities, as in the past, without holding any formal meetings. Form letters were sent to all members over 65 as well as birthdays. A reasonable number of replies were received and published in appropriate numbers of *The Physiologist.*

Since at least four members of the Committee plan to attend the Fall Meeting in New Orleans next month, a meeting is planned on Wednesday, October 17, for discussion of the following items:

Should form letters be sent every other year rather than annually?

Should age be raised to 70 and over rather than 65 years?

Should birthday cards be sent only every 5 years?

In all probability, the usual form letter will also be revised to contain various suggestions that have been made in the past.

The Committee is unanimous in its feelings that its activities are very much worthwhile as gleaned from comments received by members contacted as well as younger members who are interested in hearing about their elders. The members of the Committee derive personal pleasure from the contacts.

A report of the October meeting will be furnished to Council at the appropriate time.

Respectfully submitted,
Hymen S. Mayerson

REPORT TO COUNCIL

PERKINS FUND COMMITTEE

During the period July 1, 1978 - June 30th, 1979 the Perkins Memorial Fund provided partial support for four visiting physiologists and their families, including ten children. Recipients of the awards came from England, Israel and Japan to work in laboratories at Yale, UCLA, Buffalo and Emory.

Two of the above families have now returned home and they have written glowing reports of their stay in the United States.

There seem to be no reasons, at this time, to alter either the goals or the mode of operation of the Perkins Memorial Committee.

John R. Pappenheimer, Chairman

REPORT TO COUNCIL

PORTER DEVELOPMENT COMMITTEE

Dr. Eleanor Ison-Franklin
Dr. Charles E. McCormack
Dr. Barbara Rennick
Dr. Clem Russ
Dr. Wendell N. Stainsby
Dr. Sidney Solomon
Chairmen
Dr. A.C. Barger
Dr. Edward Hawthorne

We should like to take this opportunity to thank Drs. Jack L. Kostyo and Edward P. Radford, whose term on the Committee has ended, for their contributions to the program, and to welcome Drs. Wendell N. Stainsby and Charles E. McCormack.

For the new members of the Society, a brief sketch of the Porter Development Committee may be appropriate. The Committee was organized in 1966 to help the American Physiological Society attract more minority students into physiology. Funds for the program have come entirely from the Harvard Apparatus Foundation which was founded by Professor William Townsend Porter of the Department of Physiology at Harvard Medical School to "assist more young men and women of promise in the study of physiology." These grants have enabled the Society to provide predoctral fellowships and tuitions for minority students, postdoctoral fellowships, and sabbatical leave aid for faculty members of predominantly black schools who wished to update their expertise in physiology. In addition, funds have been made available for lectureships and laboratory equipment to develop teaching consortia linking predominantly black colleges with medical schools in the same area. The first program was started in 1968 under the leadership of Professor William B. LeFlore of the Department of Biology at Spelman College in Atlanta, Georgia. The grant from the Society for laboratory teaching equipment was matched by the college with renovations. An honors course in mammalian physiology was established for students in the entire Atlanta Complex, - Spelman, Morehouse, Atlanta University, Clark and Morris Brown, and the enrollment has grown from 5 students in 1968 to 42. We should like to acknowledge the assistance made to the course this past year by the members of the Department of Physiology at Emory University School of Medicine: Drs. Jack Kostyo, Chairman, Charles Reagan, Denis Valenzeno, Yorimi Matsumoto, Gilbert Renard, Dojin Poppovic, John Pooler, Stephen Frawley, Donald Humphrey, Jessica Schwartz and Mr. Rex Pritchard. The first Porter Development doctoral candidate to come through this program is Dr. Pamela Gunter-Smith, who received her Ph.D. in June 1979 from the Department of Physiology at Emory University School of Medicine. Her thesis was entitled "The effect of theophylline on the transepithelial electrical parameters of Amphiuma small intestine." She is currently a Postdoctoral Fellow in the laboratory of Dr. Stanley Schultz in Texas.

The Consortium in New Orleans was established by Drs. Joyce Verrett and Marva E. Smith of Dillard University, and Drs. Mohinder Ogra and Dr. Mack Felton of Southern University of New Orleans with the assistance of the Physiology faculty at Louisiana State University School of Medicine and Tulane Medical School. Again, we are most appreciative of the help of the following members of the two departments in the past year: Louisiana State - Drs. John Spitzer, Chairman, Theodore Schilb, Leo Happel and John Cullen. Tulane - Drs. Nicholas DiLuzio, Chairman, Lester Wade, Larry Feigen, Robert Lowe, Myron Evanich and Mr. Tom Sich. In addition, Dr. George Littleton of the Department of Physiology at Howard University School of Medicine was a Porter Visiting Professor.

Over the past year much effort was made by the Co-Chairmen of the Porter Development Committee, with the assistance of Dr. Orr E. Reynolds and Mr. Herbert Brownstein, to secure additional funding from the National Institutes of Health to expand the program. Although considerable interest in the program was expressed by the administration of the NIH, our application has not been approved. We are now turning to the National Science Foundation and to private foundations for support.

Edward W. Hawthorne
A. Clifford Barger

ANIMAL CARE AND EXPERIMENTATION COMMITTEE

Present: H. Cecil, C. Cornelius, D. Donald, M. Hast, R. Hazelwood, S. Geiger, O. Reynolds, T. Grafton, B. Orlans, A. Rowan

The Animal Care and Experimentation Committee met on Tuesday, June 19, beginning at 9:00 a.m., at the FASEB Headquarters, Bethesda, Maryland.

The main purpose of the meeting was to review the issues of animal rights in physiological research, to recommend to the Council approaches the APS could use to inform its membership of these issues, and to review the Guidelines for Animal Care. Before considering the APS role, the group spent the morning discussing the animal rights movement, the organizations involved, symposia on bioethics of animal use in research, and alternatives to animal research. The Committee invited representatives from the National Society for Medical Research (NSMR), Scientists' Center for Animal Welfare, and the Institute for the Study of Animal Problems to discuss the role of their organizations in animal issues.

Dr. Thurman Grafton (NSMR) stressed the need for animal research, the importance of the veterinarian in supervising animal care facilities and reviewing research protocol, and the respect the scientific community has for humane care of animals. The NSMR has been an active proponent of animal research and stresses humane care and treatment of animals in research and teaching, endorses well planned animal research supplemented with alternative means to reduce the number of live animals required. Dr. Grafton also reviewed three recent symposia on bioethics of animal use. His review appears in the July issue of NSMR Bulletin.

Dr. F. Barbara Orlans (Scientists' Center for Animal Welfare) Stated the Scientists' Center was in favor of animal research, but stressed the need to reduce animal suffering and to limit the numbers of animals used in experimentation. The Scientists' Center is surveying various issues of animal welfare (research use, as well as factory-farming and endangered species) and wishes to stimulate research to find idealized conditions for animal welfare. She recommended a course for undergraduates on "Bioethics of Animal Experimentation."

Dr. Andrew Rowan (Institute for the Study of Animal Problems) discussed the philosophical background for animal rights. He acknowledged the need for animal experimentation because modeling could not give adequate answers, but urged the use of alternative means. Dr. Rowan defined an alternative as a substitution which would (a) replace the animal entirely, or (b) reduce the number of animals required, or (c) reduce animal suffering

or stress; the alternative would reach the same conclusion with the same degree of confidence as the original experiment.

After lunch the Committee considered recomendations to present to the Society.

1. *Guiding Principles in the Care and Use of Animals*

   The Committee considered revisions suggested by guests and members; although the preset document is quite good, it could be strengthened by some minor modifications. Three changes are recommended:

   a. An introductory statement of appropriatenss of experimental procedures.
   b. A reference to the NIH Guide.
   c. A modification of the paragraph on muscle relaxants and anesthesia.

2. *Symposia or Workshop on "Bioethics"*

   After discussion of the avenues the APS could use to inform its membership of the bioethical issues of animal use in research, two possibilities were endorsed:

   a. Tutorial or Refresher Course
   b. Symposia

   The Animal Care Committee will submit an outline for a program on "Bioethics" to both the Education and Program Committees to be considered for presentation at a future APS Meeting, possibly Fall 1980 in Toronto. Dr. Reynolds will contact the Canadian Physiological Society to determine their activities in this area. Committee members are to send suggestions for the program to H. Cecil. No future meetings are scheduled; all additional Committee work will be done by phone or letter.

The meeting adjourned at 3:00 p.m.

Helene Cecil, Chairman

FINANCIAL DEVELOPMENT COMMITTEE
REPORT TO COUNCIL
OCTOBER 1979

Current members of the Committee are:

Edward L. Alpen
Edward H. Blaine
A. Clifford Barger
Walter Garey
C.R. Park
David F. Bohr - Chairman

This marks the Committee's second year of existence. Last year the Committee reported on its efforts to develop a list of potential Sustaining Associate members and Council approved that list. After additional review by the Committee and the APS office, a number of changes were found necessary to reflect the changing nature of corporate affiliations and their operating officials. Invitations to these potential Sustaining Associates were mailed early in October 1979.

Letters have also been sent to about 45 Foundations requesting support for the Society's activities. In this connection a brochure has been developed to describe the Society's history, organization and programs. A copy of the brochure was included in each of the letters to industrial and foundation addresses. The brochure will now also be available for other purposes such as membership recruitment and to provide members with a better understanding of the Society, its services and programs.

Senior members of the Society were sent letters in September 1979 asking them to consider the possibility of providing bequests to the Society.

In an effort to obtain annual voluntary contributions from the membership, in addition to dues, the dues notices for the 1979-80 dues year provided for the identification of a contribution to any of six purposes. To date, (Sept. 14, 1979) of the 4,064 members (Regular, Associate and Corresponding) who had paid their 1979-80 dues, 517 elected to make contributions totaling $5,683.00. Distribution of these donations were as follows:

1. General Purpose	$4,464.00
2. Educational Activities	609.00
3. Program Development	106.00
4. Porter Development	112.00
5. Perkins Fund	159.00
6. Centennial Program	233.00

(In addition, 2,735 members contributed $5,470.00 to the voluntary assessment for travel grants to the XXVIII International Congress in Budapest.)

Our future plans include a repeat of our solicitation of contributions from our Retired Members. (In the 1978-79 dues year $4,194 were contributed by Retired Members). Additionally, we will seek to stimulate greater involvement of the Sustaining Associates by asking that they identify official representatives who would be invited to meet annually with Society officers and staff to learn more about their interests and needs.

REPORT OF THE U.S. NATIONAL COMMITTEE FOR IUPS CURRENT ACTIVITIES RELATED TO THE 1980 CONGRESS

Activities of the APS in relation to the IUPS have been, in large part, related to the USNC for IUPS. Dr. Ganong was replaced as Chairman of the Committee by Dr. Reynolds on July 1, 1979.

Prior to that date, Dr. Ganong appointed an Administrative Sub-committee, chaired by Dr. Reynolds, to work on general administrative relations with the NAS/NRC and manage a travel grant program for the 1980 Congress.

APS agreed to handle the funds for the travel grant program, and therefore, formally submitted proposals to potentially interested Federal agencies.

The total budget for the travel award program was established at $264,000. This included $30,000 from funds already available in APS (about equally contributed from voluntary assessments and from interest on the USNC investment fund). Of the $234,000 requested from Federal agencies, $24,000 was set aside for administrative costs and $210,000 for travel awards. This budget is based on a plan for providing travel awards to 300 scientists. Awards are limited to lowest available cost air travel.

At the present time, no solid information is in hand on which to base a prediction of the total funds available.

An announcement of the availability of the Awards Program was published in the newsletters of each member society of USNC. At present, the number of requests for application forms exceeds twice the number of grants that the budget contemplates.

On encouragement of Council, Dr. Reynolds visited Budapest during July 1979, (air travel to Budapest and living expenses were borne by sources other than APS). This offered a good opportunity to work with representatives of the local committee in establishing plans for housing, transporation and circulation of

announcements that should enhance the benefits and enjoyment of the Congress by American participants.*

One specific result of this visit was the acquisition by APS of 500 copies of the various forms required for registration and submission of abstracts. In the August issue of *The Physiologist,* the second announcement of the Congress was reprinted, with a return form to obtain the required forms. As of this writing, approximately 150 requests have been received.

The second announcement, including all forms, had been sent previously to those who preregistered. About 1,300 individuals from North America submitted the card provided in the August 1978 *Physiologist.* (It appears that *The Physiologist* is a good medium for distributing IUPS material in North America. Between 1,000 and 1,300 people respond to items of general interest published.)

By agreement with the IUPS Executive Committee, the next issue (and perhaps the last) of the *IUPS Newsletter* will be printed in *The Physiologist.* Reprints will be provided to the IUPS Secretariat to distribute to other member societies.

A Review Subcommittee to evaluate applications for travel awards, chaired by Dr. John Cook, will meet on November 26, 1979, in Washington, D.C. The following day, November 27, the USNC will meet to approve the Subcommittee's recommendations and take up other USNC business.

Future International Congresses of Physiological Sciences

The next Congress in 1983 is tentatively scheduled for Australia. A letter has been written to the IUPS Secretariat asking for more explicit information.

The 1986 Congress has been discussed as appropriate for North America and as the initiation of the APS Centennial Celebration. APS should make its wishes known to the U.S. National Committee.

Orr E. Reynolds, Chairman

* A sightseer's view of Budapest, and other points of interest in Hungary is provided by "At the Crossroads" by Marjorie Reynolds on p. 13 of this issue.

A Change in Submission Procedures

The editors of the journals of the American Physiological Society have asked that *three* copies of manuscripts and illustrations be submitted instead of two. The third copy will be kept in the editor's office and will be sent to a third reviewer if one of the reviewers is delinquent in returning a manuscript to the editor. The Publications Committee endorses this simple change, which will shorten the time between submission and publicaton of many manuscripts.

Publications Committee
A.P. Fishman, *Chairman*
R.M. Berne
H.E. Morgan

HANDBOOK OF PHYSIOLOGY, THE RESPIRATORY SYSTEM

Revision in Preparation

The Publications Committee is pleased to report that the revision of the *Handbook of Physiology* section on respiration is progressing well. The editors have met and outlined the material to be covered, a "mission" statement for the section has been prepared and distributed, and authors are being invited to participate. The section will be organized as follows:

SECTION: THE RESPIRATORY SYSTEM
Section Editor: Alfred P. Fishman

Volume I. *Regulation of Ventilation*
Volume Editors: Neil S. Cherniack
John C. Widdicombe

Volume II. *Mechanics of Breathing*
Volume Editors: Peter T. Macklem
Jere Mead

Volume III. *Gas Exchange*
Volume Editors: Leon E. Farhi
S. Marsh Tenney

Volume IV. *Pulmonary Circulation and Metabolism*
Volume Editors: Alfred P. Fishman
Aron B. Fisher

REPORT FROM THE STEERING COMMITTEE ON THE SECTION OF THE NERVOUS SYSTEM

Three new members have been elected to the Steering Committee on the Section of the Nervous System for three year terms. They Are Richard Orkand, George Somjen and Douglas Stuart. They will replace Donald Humphrey and Dennis Poulos who have completed their term.

Six symposia have been organized for the spring FASEB meeting in Anaheim to be held 13-18 April 1980. The symposia, organizers and participants are as follows:

"Biophysical Aspects of Transmitter Actions"
Organizer, Paul Adams, Galveston, Texas
Other Participants:
V. Dionne, San Diego, California
H. Lester, Pasadena, California
T. Pellmar, Bethesda, Maryland
W. Giles, Galveston, Texas and R. Zucker, Berkley, California

'Ionic Calcium Currents in Nerve and Muscle"
Organizer, D. McAfee, Durate, California
Other Participants:
R. Llinas, New York, New York
S. Hagiwara, Los Angeles, California
R. Eckert, Los Angeles, California and A. Gorman, Boston, Massachusetts

"Brain Monoamine Mechanisms"
Organizer, B. Hoffer, Denver, Colorado
Other Participants:
T. Dunwiddie, Denver, Colorado
R. Wise, Montreal, Canada
B. Bunney, New Haven, Connecticut
R. Wyatt, Washington, D.C.
G. Siggins, San Diego, California

"Acute and Sustained Changes in Reflex Amplitude"
Organizer, J. Wolpaw, Bethesda Maryland
Other Participants:
C. Woody, Los Angeles, California
J. Bryne, Pittsburgh, Pennsylvania and D. Robinson, Baltimore, Maryland

Neuronal Activity and Energy Metabolism"
Organizers, P. Yarowsky, Bethesda, Maryland and D. Ingvar, Lund, Sweden
Other Participants:
J.M. Ritchie, New Haven, Connecticut
M. Rosenthal, Miami, Florida
L. Sokolove, Bethesda, Maryland and D. Kuhl, Los Angeles, California

"New Advances in Cerebellar Physiology"
Organizer, C. Woolsey, Madison, Wisconsin
Other Participants:
T. Thach, St. Louis, Missouri
W. Welker, Madison, Wisconsin
R. Llinas, New York, New York
M. Ito, Tokyo, Japan (Invited)

We hope that the symposia will provide the basis for an exciting meeting and encourage interested APS members to submit abstracts. Unlike the past year, we will be meeting simultaneously with the pharmacologists and they will also be sponsoring several symposia related to nervous system function.

David O. Carpenter, M.D.
Chairman
The Section of the Nervous System

1980
HARWOOD S. BELDING AWARD IN ENVIRONMENTAL PHYSIOLOGY

The Environmental, Thermal and Exercise Physiology section of the American Physiological Society will present the Annual Award to a graduate student at the Temperature Regulation Dinner during the Federation Meetings, April 13-18, 1980. The Award includes a prize of $150.

REQUIREMENTS

1) The graduate student applicant must plan to give the paper at either the 1979 Fall or 1980 Spring meeting of the APS. He or she must be first author on the abstract which is published in the *Physiologist* or the *Federation Proceedings.*
2) A requirement for receiving the Award is the attendance of the student at the Temperature Regulation Banquet. In case of illness he or she could still receive the Award by a vote of the Award Committee.
3) The typewritten copy of the presentation with illustrations should be submitted. Alternatively, a manuscript which is ready for publication may be submitted. Manuscripts must be received by *March 10,* 1980.

Manuscripts for the Belding Award should be mailed to:

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

AT THE CROSSROADS

A Visit to Budapest

Marjorie J. Reynolds

In July this year, Orr and I visted Budapest. It may be of interest to those planning to attend the International Congress of Physiological Sciences next year to hear of the experiences of a nonscientist spouse of a physiologist.

We stayed at the Budapest Hilton, which is located in the historic center of Buda and built around the ruins of a Dominican monastery next door to the Mathias Coronation church, which dates back to the 13th century. The Dominican monastery was the site of the first Hungarian university in Budapest and was founded in the 14th century. This is perhaps the main tourist attraction in this city, with the Fishermen's Bastion and Royal Palace within walking distance. The Royal Palace is now the home of the National Gallery and other museums. The present Royal Palace is built on the site of two earlier palaces, one built in the 14th century for the Hungarian king Carl Robert, and the other for the Renaissance king Mathias. During the last decade, some of the ruins of the earlier palaces have been excavated and can be visited as a museum. There is a lovely view of the Danube and the Parliament from the Fishermen's Bastion.

Budapest: Fishermen's Bastion

There are shops, coffee houses, and many restaurants nearby. Coffee houses are called Cukrászda in Hungarian; the Korona Cukrászda, Ruswurm, and Behram were recommended to us. Among the fine restaurants here are the Halászbástya, Fortuna, Régi Oszaghás, Alabárdos, Pest-Buda, Fehér Galamb, Fekete Halló, Aranyhordó, Muscketás, Vörös sün, and Old Firense.

If you look into the vestibules of the old houses or palaces, you can see that the stone benches on the two sides of the entry were built in different centuries and in different styles (Romanesque, Gothic, Baroque). I spent almost a full day seeing everything in this beautiful old area.

On another day I took a bus tour of the city, stopping at Hero's Square and ending up at the Mathias Coronation church, which is a beautiful Gothic church on the outside and whose inside walls are painted with old Hungarian text writings. On a previous occasion (Sunday at 10 a.m.), we had attended a musical Mass at the church -- a wonderful experience.

In the afternoon I went shopping in downtown Budapest, on the Pest side of the Danube. It is exciting walking in the streets because in Váci Street there is a variety of handmade items to buy, such as hand-embroidered blouses, table cloths, tapestries, and the peasant (Kalocsa) china. There is also a Herend china shop in Higyó Street and many stores featuring modern ceramics.

Public transportation is excellent in Budapest, with trams, buses, electric buses, and a new modern Metro. Tickets for single bus and tram rides are purchased at tobacco shops. A weekly ticket for an unlimited number of rides on trams, buses, and Metro is also available.

Mathias church, Budapest

On another day I went to Szentendre, which is about 22 km (a one-hour trip) up the Danube, north of Budapest. Just outside this small city is a country village representing life 200 years ago. The buildings were brought to the present site from the Plains, which are in the eastern part of Hungary; the village has been reconstructed so that you can see how people lived then. There are a number of white, thatched-roof, furnished houses that you can go into, stables, a very picturesque little church with the bell tower built to one side, and a horse-drawn mill. It is absolutely charming.

Szentendre itself was built mostly by Serbians and Greeks who were merchants and had no interest in gardening. The houses are built adjoining, like our row houses, but there is no monotony because they are all painted in bright colors. Street vendors, one with handmade ceramics and another with the most colorful and artistic pastries I have ever seen aroused interest. Walking through the city streets is fascinating because they are narrow, winding, and hilly. The central court area is set up as a theater where plays are performed at night. There are many museums (Ferenczy Family, Barcsay, Crobel, etc.) in Szentendre, but the only one we had time for was the Margit Kovacs Museum. She is world famous for her work in ceramics. Walking though the small rooms, seeing at close hand her mosaics and statues, was one of the most thrilling experiences I have ever had. Her work is absolutely beautiful.

Our last day for sightseeing was spent driving through the country on the way to Lake Balaton. On the way we stopped at Gorsium, where Roman ruins are being excavated. It is the junction of eight Roman roads and the ruins are interesting to see, particularly the theater. There was a rehearsal of a Roman play going on during our visit. Also on the way to Lake Balaton we took a short side trip to Székesfehérrás, the first capital of Hungary between the 10th and 13th centuries, and to the Herend china factory, 130 km from Budapest. We were permitted to see artisans creating the various pieces and two ladies handpainting the fired products. We talked to the workers, and I found it fascinating to see how they actually handcraft some of the 15,000 patterns. We went through the museum wearing slippers over our shoes, so that you sort of slide through the rooms. There are beautiful, lovely, even spectacular, pieces of Herend to be seen.

We had lunch that day in Veszprem, which is a very old city and the site of the coronation of Hungarian queens, among them Maria Theresa, queen of Hungary and empress of Austria. Surviving buildings date back to the 10th century. We walked through the streets after lunch and went into a chapel, first used in the 10th century, where Queen Gisella, wife of the first Hungarian king, St. Stephan, 998-1038, went to her own private chapel and bishop for absolution. Also we visited a 12th century church and the ruins of the St. George chapel, which is still being excavated and dates back even before the 10th century.

Finally we arrived at Lake Balaton, which is the largest lake of Central and Western Europe. It covers an area of about 600 square kilometers and is perfect for relaxation, with swimming, boating, and walking through the park. In the vicinity is a water-powered grain mill in operation ever since it was built in the 12th century. We visited the Benedictine monastery of Tihany and the beautiful church founded in the 11th century by King Endre I, whose grave was still covered by flowers. Tihány is historically interesting because the first constituion of Hungary was signed there in the 11th century, and the last Hungarian king, Karoly IV, and his wife Zita spent their last night there before they lost the crown.

There are many other interesting places to visit and things to experience, including the restaurants with their varieties of goulash, strolling gypsy violinists, and the cimbalom. After three visits, I still feel that I am inexperienced in my knowledge of Budapest. I only want to express to you my delight and wonder over such a beautiful country that is so filled with history and with happy, warm people.

MEDICAL GROUP SYMPOSIUM

A national symposium involving independent, academic and hospital-affiliated group practice will be held in New York City, April 14-16, 1980.

The conference will feature Robert H. Ebert, M.D., president of the Milbank Memorial Foundation, and a number of prominent medical and management executives. The 2½-day working meeting is sponsored by Chesapeake Education/Research Trust, an affiliate of Chesapeake Physicians, P.A., the largest nonprofit group practice in Maryland and associated with the Johns Hopkins University School of Medicine.

According to Joseph L. LaAsmar, coordinator, the symposium will emphasize the organizational, financial, academic and marketing effects of legally independent medical groups upon the success of the teaching hospital.

The sessions will cover alternative solutions for problems involving reimbursement and program financing; bed occupancy, case-mix and hospital marketing maintaining an excellent medical staff; benefits and taxation; effects on teaching and research programs; and serving needs in the institution's service community.

Distinctions will be drawn between closed and open staff hospitals. In addition to formal presentations by national leaders in these areas, panels and workshops will be woven into a unified learning and sharing experience.

Early registration is $295 through Feb. 29, 1980. Regular registration is $325. Persons interested in attending should call collect or write for a registration brochure and enrollment forms to CE/RT, 4940 Eastern Avenue, Baltimore, Md. 21224, tel: (301) 396-9129.

PAST PRESIDENT'S ADDRESS

The Health Market and Physiologists

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Elmer McCrutchin had had trouble for a couple of weeks slopping his pigs and shoveling out the chicken coop. It seemed to him he just didn't have enough pep and energy. Finally his wife Gertrude talked him into accompanying her into Centerville to Dr. Talbot to find out what was troubling him. They waited an hour and a half in Dr. Talbot's posh office before the receptionist escorted Elmer into an examing room. Ten minutes later when Elmer came out Gertrude asked: "Did he find out what you had?"

"No," said Elmer, "he didn't. He charged me only $100, and I *had* $125."

This incident characterizes a situation and attitude that I have watched develop over 40 years since I finished medical school. The cost of health care delivery and the public concern about the physician's attitude have now reached such levels that changes *are going to occur.*

This kind of subject may seem a bit off-beat for the annual physiology lecture. Let me tell you why you're getting it:

First, the subject is relevant for physiologists. As physiologists we are involved with the research for, and teaching of the health care professionals. Many of us work within medical schools; we train future clinical doctors and nurses and dentists. We may even be models for their behavior. Moreover we have the advantage of an objective viewpoint; we are not ourselves so caught up within the clinical system that our perspective is biased. Yet we hold a measure of responsibility for the caliber, the quality, the integrity of health care in America that we cannot disown. We have a responsibility to be informed, to consider and examine and weigh the facts, - and, I hope, to act.

Second, as part of my function as President-Elect of the American Physiological Society I got to poke around Cuba. The purpose of this tour was to look at Physiology, education and health care delivery behind the sugar cane curtain. I saw a quite different approach to health care delivery that's well worth telling about.

Third, physiologists, as everyone else in this country, are hurting because of the unreasonably high cost of health care delivery and the attitude of health care professionals. My own personal ranking of global problems for this country in 1979 goes like this: #1: Energy; #2: Inflation; #3 Health Care Delivery; #4 World Peace; #5: Crime.

I'll tackle #3 because I don't know anything about the other 4.

I will first describe the problem as I see it in our country, then how it has been dealt with in Cuba, and finally I will tell you how I think we can solve our problems within our own system.

The problem of health delivery has two parts: One is attiude; the other is the economy; they are certainly related. Recently I have had first-hand experience with each. These I will submit as anecdotal evidence:

My daughter phoned me from Chicago to say she had flu or something. The day before she had gone to see a private doctor. His nurse had found her temperature to be 102.5 but he refused to treat her because she didn't have cash on the barrelhead to pay him for his services. I phoned the guy immediately to let him know my attitude about his attitude. He explained that it was my daughter's fault-she didn't tell him that her father was a doctor.

The other personal experience gave me insight into *cost of current medical sophistication.* A physiologist from Belgium visiting me in Ann Arbor developed a chest pain. He was admitted to the coronary intensive care unit on Friday evening. I visited him early Saturday morning and he had not slept well because of the intrigue of his own EKG playing continuously on his T-V set. He was discharged less than 12 hours after admittance with a diagnosis of a pulled intercostal muscle from carrying a heavy suitcase - and a bill for over a thousand dollars.

This anecdotal evidence is substantiated by data describing the overall cost of health care in the United States, and its growth rate. In the past ten years the annual national health care expenditure has risen from 65 billion to over 200 billion dollars. These numbers are too big to have any meaning to nonmolecular physiologists, but when the numbers are reduced to the bite that this expense puts on each of us we should more exquisitely feel the pain. The typical family of four now contributes more than $3,500 per year to health care expenses.

The major problem is that we are kept from becoming aware of the size of this bite. We are protected by the procaine of having our medical bills paid by Government programs or by employer-paid private insurance. Today patients pay directly only 6% of hospital bills, private insurers pick up 37% and the government pays for 55% of hospitalization in this country. We have no easy way to see how much tax we pay for Medicare and Medicaid, how much our salaries are lowered because our employers have to pay health insurance premiums or that we have to pay Ford Motor Company an additional $130 for each car they sell in order to cover the cost of the health insurance that they have to buy for their employees.

In obstetrics the average hospital and delivery cost for a baby ten years ago was $350. Now a seven pound baby costs over $450 per pound. This rate of increase is far greater than inflation. This example of cost increase is reflected in data that demonstrates that ten years ago medical care expenditure comprised about 7% of the Gross National Product. Now it is over 9%.

As proper physiologists who are interested in mechanisms, let's analyze why this situation is getting out of hand. I will give you four reasons:

1. *Pay-for-service insurance systems.* A young man who had had a belly-ache for the past two weeks went to his doctor for help. The doctor could have investigated the problem with three office calls and appropriate X-ray and laboratory tests on an outpatient basis. That would have cost $400. However, since the young man's insurance covered only costs incurred during hospitalization, the only pragmatic decision was to have the studies done as an *in-patient.* The total bill for three days in the hospital was $1,600. This insurance practice operates directly to drive up costs.

2. *Technology:* Many advanced technologies are being employed in our hospitals. Although these improve diagnosis and treatment, it is hard to justify their increase in cost. Coronary by-

pass surgery was introduced in 1967 and last year more than 80,000 of these operations were carried out at an average cost of $12,000 each. The patient who is operated on must have had diagnostic cardiac catheterization and expensive radiology. The funds must support the surgical team, the anaesthologist, the extra-corporeal pump team, the blood bank. After surgery the patient is monitored continuously for five days in an intensive care unit.

Another recent invention is the equipment for computerized axial tomography which costs $700,000. This is the CAT scanner. Although this is a valuable diagnostic tool under circumscribed conditions, it is reasonable that after making this type of investment a hospital will be eager to extend the uses of the machine into questionable applications in order to help amortize the cost of it. In addition to the initial outlay for new equipment the use of technically advanced equipment requires highly trained, high-priced personnel.

3. *Hospitals* are by their nature expensive places. They need 2.6 employees for each hospital bed, most of these union members, so that wages now take 70% of the hospital budget in contrast to 35% 20 years ago. They must be staffed 24 hours a day and standby personnel paid for, to cover emergencies.

Hospitals must buy modern sophisticated equipment. Their prestige is judged by the quality of the doctors; and talented doctors gravitate to hospitals that have the most advanced facilities. Hospitals are also expensive because doctors order extensive laboratory tests to reassure the patients and to protect themselves against malpractice suits.

4. *Doctors:* The average annual income of the practising physician is $65,000. Differences in income among physicians is not made on a rational basis. In general the doctor who *does* something to the patient-cuts him open, sticks something in one end or the other, or takes his picture-gets more money.

With the present system it is difficult for the doctor to keep his income down. For instance I know a psychiatrist who did not like medico-legal work; so he doubled his fee per hour. Instead of discouraging his customers, this change increased his demand. I suppose this was because customers thought that the more he charged the better he was. There are no real constraints on the income of the physician.

In economic terms when an item is in short supply the price will rise and continue to rise until the number of consumers who can afford the item is less than the number of the available items. Supply exceeds demand and the price will fall until a new equilibrium of supply and demand has been reached. The free enterprise of medicine in our country today violates this basic law of supply and demand-just as weightlessness violates the law of gravity. What goes up keeps going up.

It is a seller's market. The only decision made by the buyer is the one he makes that he is going to see the doctor. After that the decisions are all in the hands of the seller.

There is another complex matter that must be considered in adding up the growing costs of modern medicine. Everybody dies sometime. Each time modern medicine has a therapeutic success of an otherwise fatal disease, it adds another candidate to the list of those who will be a cost of health care in the future. A man with a cancer of the prostate at age 40 if he has successful surgery may live to develop severe hypertension at the age of 50. With energetic and continued thereapy he can keep his blood pressure down and prevent the fatal complications of high blood pressure. At the age of 60 he could very well develop an arrhythmia for which he could benefit from the use of a pacemaker....and so on. Each costly therapy adds to the future cost of medical care. I am not arguing that we should allow only one lethal disease to a person, but this is the way things are.

These are the cold hard financial facts. They have ignored the ethical or moral aspects of the practice of medicine. I have known premedical and medical students well enough over the past 30 years to be convinced that they are motivated primarily by high ideals of improving the quality of human life. I am also convinced that their experiences in medical school and the years that follow have an enormous disenchanting influence. With the overwhelming load that the student or young doctor carries he is confronted with a steady series of accommodations and rationalizations and inevitable errors in judgment. Normal sensitivity gets blunted in accommodating to the real situations of the everyday life of the doctor. It is easy for him to succumb to the very insensitivity that he started out to fight.

To hit the issue of his own income he would have to ask: how much money is too much money? It would be extremely difficult for him to convince himself that he is earning too much money.

Let's go to Cuba. Delivery of health care there is worth describing because it is so different. Twenty years ago, when Cuba became Castro's Island, Committees for the Defense of the Revolution (CDR) were created throughout the island to protect Castro's health. They did this by ferreting out counter-revolutionaries before they could bomb Cuba's new leader. Today Castro's health is quite secure, but these Committees play a major role as a grass roots machine for carrying out the government policies, including health care delivery.

About 100 families living near each other join together into one CDR. They decide where the school bus should stop, collect paper for recycling, are alert to health problems and monitor all kinds of human behavior including who tossed his beer can on the lawn. In the summer of 1978 one CDR president arranged with the police to have three men held in detention camps during the two week long International Youth Festival. The reason was that they had a tendency to get drunk and make lewd comments to women.

Each CDR has a health director who pushes immunization, gets volunteers for helping in hospitals and blood doning, encourages people with hypertension to stay on treatment. The health director can do this by asking the patient at a CDR meeting if he is complying with therapy-everyone knows who has what health problem. As we perceive the system, Cuba does not get prizes for civil liberty.

There were many things wrong with the Batista regime that preceded Castro, so it was not hard for Castro to make changes that would improve the lot of most Cubans and at the same time show them what a good guy he was. He chose to push education and health care. One of the slogans that is operative in Cuba is "every worker a student and every student a worker." Castro started business in 1959 and by 1961 he had reduced illiteracy from 30% to less than 5%.

Upgrading health care delivery was a slower process. Of the 6000 physicians in Cuba when it became Castro's, 3000 left for a cooler climate. Castro's ministry of health decided to correct the deficit with fully qualified doctors rather than the China barefoot doctor approach. Cuba developed an excellent system for medical education. There are now 11,000 doctors in Cuba and over 1000 per year are coming off the production line. To accomplish this they have sent faculty abroad for basic science and clinical training. They have built new schools and teaching hospitals and they even use a Spanish translation of Arthur Guyton's physiology text.

Medical school takes six years plus three years of community services. The doctor then may have specialty training for an additional two to four years. Medical education is not only free but

the students are subsidized. Admission to medical school is at least as competitive as it is in our country and it depends primarily on academic performance, but also on the socio-political attitude of the applicant. The basic instrument for health care delivery is the outpatient polyclinic. Each polyclinic serves a population of approximately 30,000 and they are appropriately distributed throughout the island. The 10,000,000 people in Cuba make 40,000,000 visits to the polyclinics per year.

Public helath results are impressive. Tuberculosis is nearly eradicated; malaria is eradicated; and infant mortality is lower than in any other Latin American country.

I was impressed with this health care delivery system and commented to my host, the Director of International Relations of the Ministry of Health: "Your taxes sure must be high."

He answered of course: "What taxes?"

Cuba doesn't work that way. If more money is needed they just increase the price of rum, tobacco or sugar, all of which are owned by the government. Physician's salaries range from $715 to $1000 per month with professors receiving top pay. This is low by our standards but in Cuba it is near top income in the country and besides, it's sufficient because there is virtually nothing in Cuba to buy.

Health care in Cuba is clearly not a sellers' market. It's Just there. It is a non-market.

In the United States we are not about to give up the free enterprise and the many other goodies that we would necessarily forfeit to operate as the Cubans do. We do have open to us *a better way.*

This is the free enterprise Health Maintenance Organization. You or your employer pays in advance for your complete health coverage for one year. Doctors are salary-paid and may receive a bonus that depends on the net annual profits of the organization. Motivation in this system will be toward outpatient rather than hospital care, toward short rather than long hospital stays, toward essential rather than luxury laboratory tests. Quality is kept high through free enterprise competition between systems. Kaiser Permanente Foundation has now operated successfully with this system for over thirty years. In the past five years many smaller organizations have developed and within the past few months General Motors, Ford, and Chrysler and the UAW have combined forces to set up its new *Health Alliance Plan* which is an HMO. Eight million people in this country now belong to HMO's.

The HMO system is not yet perfected but it certainly is to be supported to improve the economic balance of health care delivery. Both buyer and seller profit from its sound economic practices.

We are left then with my other concern about our health care delivery system. *This is the physician's attitude.* How can the sensitive ethical dedication of the beginning student be maintained throughout medical school and subsequent years of medical practice?

It has been the tradition in our medical schools to emphasize the teaching of normal structure and function and the processes that result in disease. The physician thinks and speaks of "the peptic ulcer" rather than "John Doe who has the peptic ulcer." The practice of medicine is now dehumanizing.

This deficit in medical education is currently being dealt with in some schools by special courses in medical humanities, given at both undergraduate and post-graduate levels. Moral and ethical issues are considered that deal with decisions that the physician must make that are not primarily related to the specific disease process. For instance, which professional requirements morally command the physician's time and which do not? What extra-medical factors enter into the decision to hospitalize or not to hospitalize? What are the legal and ethical factors involved in decisions related to abortion or to pulling the plug? How much money is too much money for a physician to receive?

Expansion of courses in the area of medical humanity will be important in correcting the dehumanizing effects of medical practice.

This country's best-known doctor today does not have a medical degree. He is actor Alan Alda, known to the country's televiewers as "Hawkeye" in MASH. In his commencement address last May to the graduates of Columbia University's College of Physicians and Surgeons he had the following to say: "In some ways you and I are alike. We both study human beings. We both try to reduce suffering. We've both dedicated ourselves to years of hard work *and we both charge a lot."*

He closed his address by saying: . . ."There is one more thing that only a non-doctor would tell you - and I hope you will always remember this: The head-bone is connected to the heart bone. Don't let them come apart."

This sensitivity and feeling that Hawkeye is talking about and that he has for his sick patients in MASH adds nothing to the cost of health care delivery.

Physiologists, without access to a national T-V audience, can also contribute importantly to our system for health care deliver. 1)We can be aware of the severe problem that is developing, 2)we can encourage the formation of health maintenance organizations and 3)we can support courses in medical humanity.

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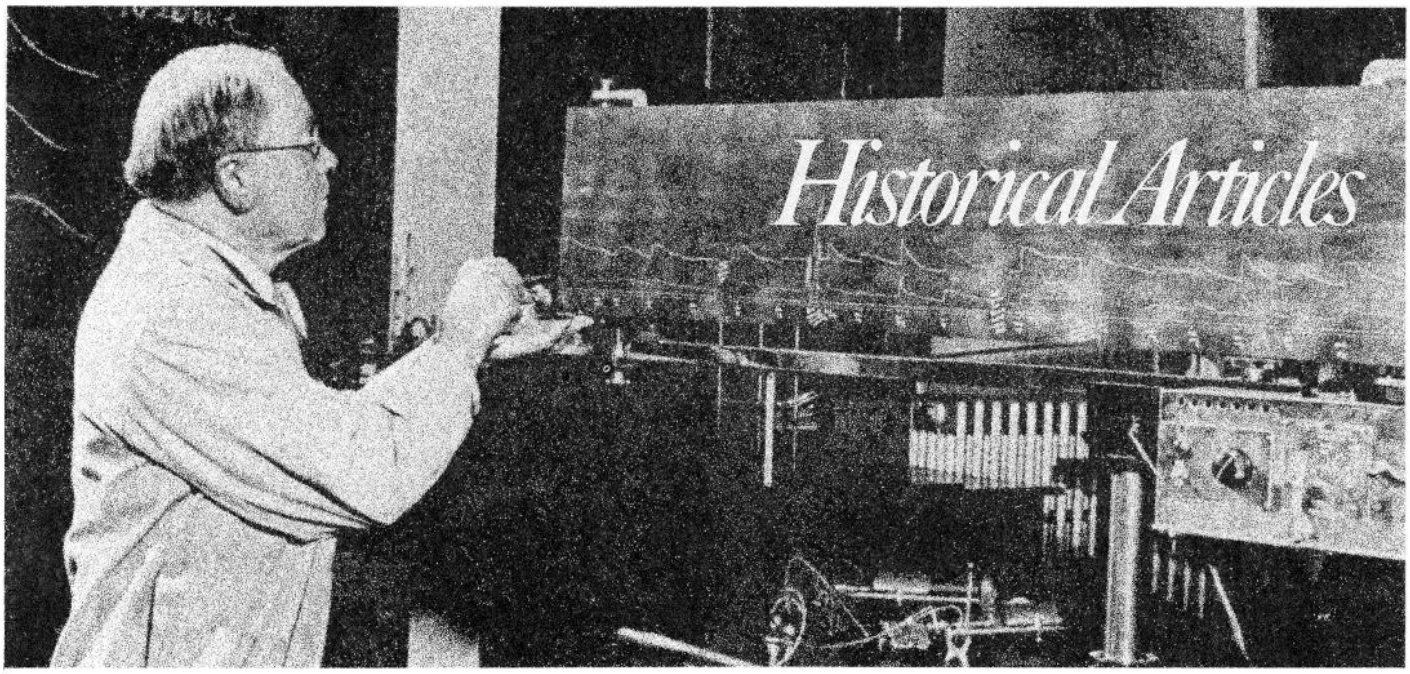

ECHOES OF THE PAST

Reflections on the Early History of the Concept of "Active Transport"

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1. INTRODUCTION

Some of the most challenging problems in cellular physiology are those which bear upon a particular coupling of the flow of ions across cell membranes to the release of free energy from metabolic reactions. This association is called "active ion transport." It is at once clear that the problems which present themselves in this field are directly related to questions which touch upon cellular homeostasis and modes of its physiological control. Among the ions of principal interest are sodium, potassium, and chloride. The association of the physiological and biochemical processes mentioned above are observed in many, if not most types of animal cells, and in plant cells as well. Some of the important literature which antedates the concept of "active transport" is cited in one of the papers listed below (17). Certain epithelial cells are unique because they are able to move ions transcellulary and thermo-dynamically "uphill." This means that ions, e.g., Na^+, are taken up at one boundary of the cell and discharged at the opposite boundary. This implies that the supportive chemical reactions in some domain of the cell set up vectorial forces which can drive the ion uphill across the cell. This property of epithelial cells is observed in the epithelia of many organs. Examples are, the kidney, the gastrointestinal tract, the salivary and sweat glands; also urinary bladders, and the gills of marine *teleosts* and last but not least, the amphibian skin in which the occurrence of "active salt transport" was discovered (15, 17). Parenthetically, to the best of my knowledge, the term "ion pump" was coined in 1941 by Robert B. Dean (7) in a publication which deals with ion equilibra in muscle.

The following article decribes in some detail the early history of the concept of "active transport" which emerged from studies on frog skin and which now pervades so much of the biological, biophysical, and biomedical literature. This early history is in the vivid memory of this author who has witnessed the development of this branch of knowledge during the period from 1935-1940. Accordingly, this communication narrates a moderately updated sequence of some personal experiences in the exploration of new frontiers in the realm of electrolyte metabolism in epithelial membranes.

The early studies on the permeability and active transport characteristics of isolated frog skin (15-25) had a remarkable renaissance at the Laboratory of Zoophysiology at the University of Copenhagen (31,47,48), and the Physiological Institute at the University of Uppsala (33). It soon turned out that the ability of active transepithelial ion transport resides also in other epithelial membranes. The discovery of the occurrence of active ion transport across the epithelium of toad bladders (32) marked the beginning of an impressive succession of publications which have greatly enriched our knowledge about active and passive transport of electrolytes, and non-electrolytes as well, within and across epithelial membranes. However, our understanding of the molecular mechanism of an "ion pump" is still rather incomplete.

Another matter which remains unclear concerns the physicochemical properties of the ion barriers which are located in front of and behind the ion pumps. There is great interest in all of these problems as a vast worldwide literature shows. Substantial progress has already been made in untangling the problems pertaining to transcellular "active ion transport" from associated problems related to cellular homeostasis and its regulation. The literature in this area is of overwhelming magnitude and because of this avalanche of new publications it appears timely to carve out the early history of the discovery of "active salt transport" in frog skin. This is done for the benefit of students entering this field of research, but I hope that the research scientists who have learned from experience that knowledge of the history of science facilitates the journey of discovery are also beneficiaries.

2. REID'S EXPERIMENT

In 1890, and more extensively in 1892 E. Waymouth Reid described a startling discovery (43,44). It is the foundation on which our current sophisticated knowledge of "epithelial transport" rests. Reid observed "the passage of fluid across living skin by virtue of its own unaided activity." [(44), p.323]. Figure 1 shows the apparatus used in his studies. Since then, numerous modifications of Reid's double flux chamber have been devised for studies on "membrane transport" in frog skin and other epithelial membranes. The open ends of the cylinders were closed with "an inert animal membrane" (baudruche[1]) which was soaked for 24 hours in normal saline solution. Pieces of fresh skin (4.5 cm^2) were placed between the two chambers which were then clamped together. Both cylinders were filled with identical normal saline solution. Great care was taken in proper leveling of the horizontal observation tubes. Fluid transport occurred in the inward direction, i.e., from the epidermal to the dermal (corium) side of the skin. Reid recorded the advance of the meniscus in millimeters in one tube, and the nearly identical retreat of fluid in the other tube. Net fluid transport must have been of the order of a few $\mu l \times cm^{-2} \times h^{-1}$, if one applies the value for volume calibration of the observation tubes given elsewhere (45).

In the mid thirties it appeared to me that isolated frog skin would be a good "model" to use in studies which I then had in mind. There was a snag to this plan: between 1913 and 1936 "Reid's experiment" came into total disrepute. Six scientists, working in the USA, Yugoslavia, Switzerland, and Russia concluded from new studies that Reid must have observed experimental artifacts. The relevant references are (16,18,19). Three additional observations, however, made me wonder whether the harsh criticism was justified.

The first of these observations is found in the paper by Reid (43) dealing with osmotic fluid transport across skin. Paired skins were extended in recording "discharging osmometers." They were filled with normal saline solution on the epidermal side, and 5% glucose in saline solution on the dermal side of the skin. A record of the osmotic fluid movement is shown in Figure 2, upper graph. When the solutions on the two sides of the skin contained 0.1% digitaline, osmosis occurred in a fashion as shown in the lower graph of Figure 2. During the first hours, the rate of osmosis in the inward direction is decreased, later it increased, compared to the rate of osmosis in the control skin. Reid interpreted this observation as follows (p. 347).

"By rapidly killing the tissues of the exsected skin with such a drug as digitaline, the passage from the state of diminished permeability from without inwards, due to the depressant action of the drug, to the state of increased permeability due to death of the tissues and commencing disintegration, may be easily observed."

In our "modern time" of trying to comprehend the rather complex transport phenomena by "modeling" the events, it is quite interesting to look at the model proposed by Reid (in 1890!). He drew this model to present his views on the effects of digitaline on osmosis in frog skin. Figure 2 is the forerunner of the "three compartment model" of the very heterogeneous frog skin to which in our modern era so many investigators tenaciously resort to in their interpretation of their kinetic studies. It is also interesting to note that sixty-seven years later Koefoed-Johnsen (30) used another cardiac glycoside, ouabain, to depress active inward sodium transport in frog skin.

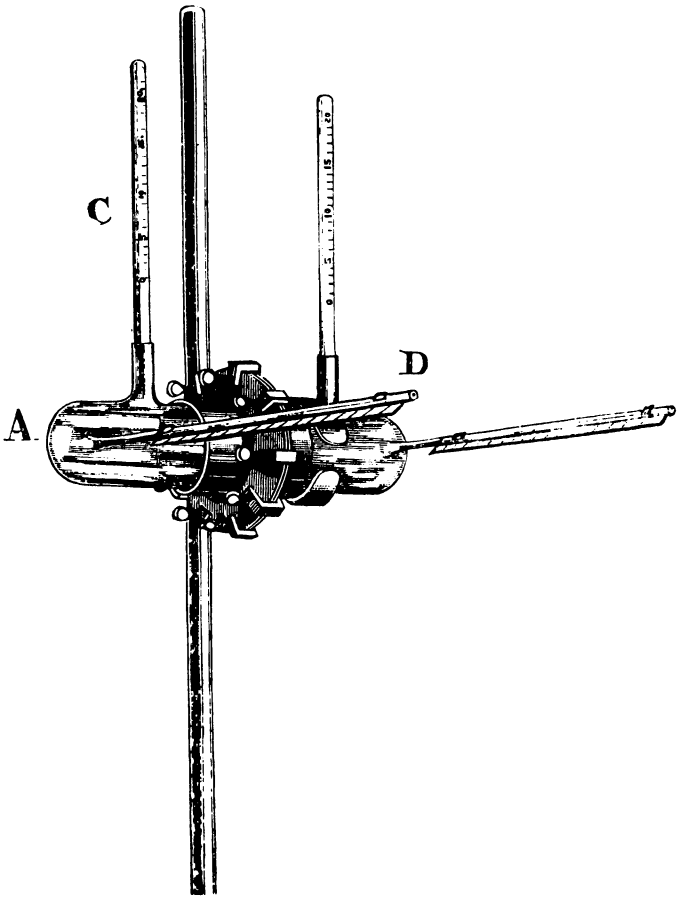
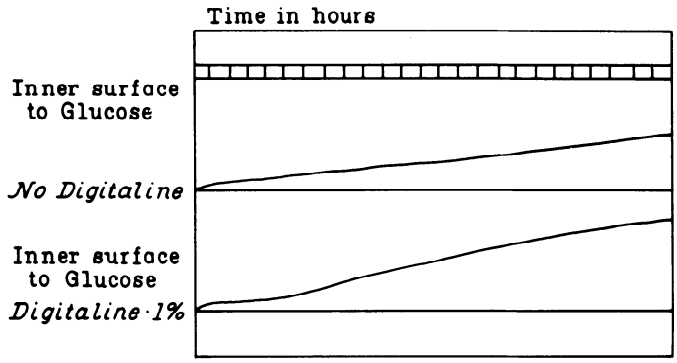


Fig. 1. Apparatus used by Reid to demonstrate net movement of saline solution across frog skin between two identical saline solutions. *Brit. Med. J.* 1892, Vol. 1, 323-326.

The second of the three relevant observations is described in another little known paper by Reid (45). He noted that net fluid movement across the skin in normal saline was reversed when skins of frogs in the breeding season were used. Fluid transport occurred in the direction from the dermal to the epidermal side. He attributed this to the known hyperactivity of the glands in the skin. In the same publication he also described experiments with the *gastric* mucosa of the toad, stripped from its musculature, and the ileum of the rabbit in varying physiological and pharmacological situations. When reading these reports in the early and mid thrities, it appeared to me, that with his apparatus (Figure 1) Reid did indeed measure "fluid transport of physiological origin" (p. 442), and not artifacts.

1) Baudruche, or goldbeater's skin, is made of the outer coat of the caecum or the blindgut of the ox.



Tracing 10.

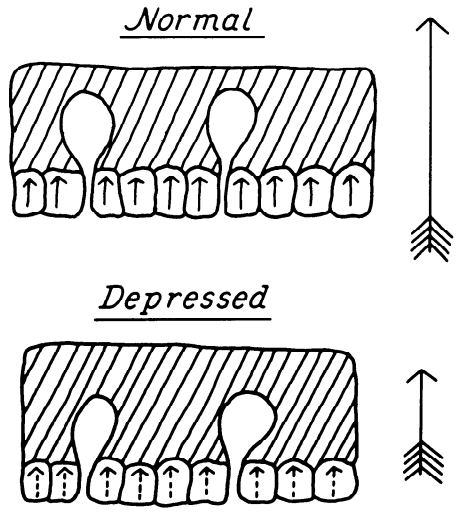


Fig. 2. Osmotic water flow across frog skin. Control skin and skin poisoned with digitaline. Normal saline at the epidermal side. 5% glucose in saline at the dermal side. Below the records are the "skin models" used to explain the effect of digitaline. Reid, *Journal of Physiology* 11, 312-351, 1890.

The third of the three observations alluded to above is found in the brief communication in 1933 by Francis (9). He showed that the isolated electrically (partially) "short-circutied" skin produced, for many hours, approximately 0.5 microwatts/cm^2 electrical energy. This suggested that perhaps electrical energy is utilized in the "true absorptive process...without the aid of ordinary osmotic action:[Reid (44), p. 326]. Much later during 1941-1947 Stapp (46), and Lund and Stapp (36) used an iodine coulometer to obtain a value for the "coulomb-efficiency" in skin. Briefly, this was the controversial state of affairs concerning the matter of physiological fluid absorption in isolated frog skin.

In the 1930's, I attempted to resolve the controversy about "Reid's experiment." My results (16, 18, 19) confirmed the correctness of Reid's observation and conclusion. These new findings led to renewed interest about Reid's views and experiments on the possible role of electroosmosis in frog skin. Electroosmosis, the process of fluid transfer across certain membranes situated in an electric field, is a phenomenon which was well known to physiologists of the late nineteenth century. Furthermore, it was well known to Reid that frog skin in normal saline is an electrically polarized tissue membrane. The dermal side carried positive charge relative to the epidermal side. Reid, therefore, considered the possibility that electrical current loops (Ringströme," in German) drive fluid in the inward direction across frog skin in normal saline solution. Here is what he wrote in 1892 [(44), p. 326]:

> "The idea that this fluid transfer may be of electro-osmotic origin has naturally occurred to me. The frog skin current which Engelmann[1] attempted to make serve the purpose of a motor of secretion, might be called in, upon the return journey of its circuit, to do the work of absorption. Indeed, with electrical currents circulating as they do in the skin[2] the question of outward or inward transfer of fluid would have become one of relative "porosity" in the two directions. With equal resistance to fluid transfer in the two directions, theoretically, there need be no passage of fluid across the skin; with unequal "porosity" there might be movement of fluid along current lines coinciding with lines of lesser filtration resistance. Unfortunately, the skin offers a greater filtration resistance from without inwards than in the reverse direction. Again, if what I have observed be of electro-osmotic origin, the coupling up by a good conductor of the fluids on the two sides of the skin should increase the rapidity of the fluid transfer from without inwards, by diminishing the amount of current flowing in the skin against the direction of the absorption stream. When I have done this I have failed to find any effect, though an included galvanometer gave evidence of the normal skin current. I do not, therefore, see how the electrical hypothesis can be made to suit the case."

From our vantage point we can understand why Reid "failed to find any effect" on fluid transport in the (partially) short-circuited skin. Reid did not know that the primary event in skin is inward active salt transport, and that water follows the osmotic gradient which is generated by the ion transport. We also know now that active salt transport in skin is not abolished by shortcircuiting the skin (49).

3. SALT TRANSPORT

Throughout his work Reid assumed that when the skin is extended between "normal saline solutions," the fluid which moves from epidermal to the dermal side is "normal saline." In the mid thirties, I set out to answer the following important questions:

1) What are the effects of specific metabolic inhibitors (cyanide; bromoacetic acid) alone, and in combination with specific metabolites (lactic acid; pyruvic acid; hexosediphosphate; glucose), on the net flow of solution across the skin? The aim was to establish a more secure metabolic basis on which the energetics of the net fluid transport could be understood.

It is perhaps interesting that the choice of bromoacetic acid in studies on fluid transport across poisoned skins was suggested to me by my participation in 1931 in studies, both in Bethe's laboratory and across the hall in Embden's laboratory, on the role of lactic acid in muscle contraction[1]. At this time the muscle physiologists and biochemists took great interest in observations made by Lundsgaard (37, 38). He found that the injection of monoiodo-, or monobromoacetate into rabbits or frogs resulted in rigor mortis of the striated musculature with total suppression of lactic acid formation.

The rational of employing in membrane transport studies chemical agents whose biochemical mode of action is generally known, is today still very much with us. To the extent that such

1) Pflüger's Archiv. Bd. VI, 1872

2) V. Rosenthal, Reichert v. du Bois-Reymond's Archiv. 1865, p. 311

chemical probes act specifically, they are valuable tools in the pursuit of establishing definite links between "cellular metabolism" and "transepithelial ion transport" in epithelial tissue membranes (26, 51, 10). This approach is equally useful when a particular agent fails to establish a direct link between transport and cellular metabolism. Ouabain and Amiloride are good examples to illustrate these points. The former acts primarily on the Na^+-pump, the latter does not.

2) What is the chemical composition of the fluid which is transported in Reid's experiment?

The discovery in 1935-1936 (15, 17) that the isolated, surviving frog skin when placed between two identical saline solutions transports hypertonic salt solution from the epidermal to the dermal side was most startling to me. The transport of hypertonic saline solution across the isolated skin could be blocked by cyanide, or by bromoacetic acid. In bromoacetic acid poisoned skins lactate, or pyruvate, but not hexosediphosphate and glucose, enhanced the inward transport of hypertonic saline solution; these metabolites also increased the O_2-consumption of frog skin (15-18, 20-22).

I set out to do studies on isolated frog skin because I thought that these studies may shed new light on problems of osmoregulation in invertebrates (2,12,13,14). Two recent Symposia dealing with active transport of salt and water in many types of living tissues, and especially in epithelia, give testimony of the merits of transport studies on frog skin (29,50). They are, rightfully, a good meeting ground for biomedical workers in the realm of water and salt metabolism in living organisms.

Once transmembrane salt transport in isolated, surviving frog skin was firmly established (17), I considered the possibility (as an alternative to electroosmosis) that in Reid's experiment, the primary event was salt transport, the secondary event a concomitant osmotic water movement in the direction of salt transport, i.e., movement of hypertonic salt solution in the inward direction [(17), p. 151]. All that was needed to make this possible was structural characteristics of the skin such that the salt gradient generated by the skin is not rapidly dissipated again. In my first experiments on frog skin (15) I had addressed myself to this problem:

A[1]. "Zweifellos wird aber auch die Struktur und die funktionelle Eigenart der Körperoberfläche (Haut, Kiemen) die Erscheinung der Aufrechterhaltung des relativ hohen Salzgehaltes mitbedingen" [(15) p. 669].

In support of this view I showed that the permeability of the isolated skin for net outward diffusion of salt (Cl^-) increased when the skins were poisoned with cyanide [(15), p. 669]. This decrease in the "reflection coefficient" for NaCl (to use a modern term) was associated with a long lasting decrease in transmembrane osmotic water flow (23). House (11) made similar observations on the effects of cyanide on osmotic water flow across isolated skins. Those observations supported the notion mentioned above, that in Reid's experiment, water movement might be secondary to salt transport.

B. "Fast könnte man jetzt schon zu der Ansicht geführt werden, der "active." Vorgang bestehe in einem Transport salzreicher und wasserarmer Flüssigkeit und schaffe somit die Bedingungen für einen osmotischen Wasserstrom in derselben Richtung. Dieser Prozess wäre dem ersten gegenüber als "passiv" zu bezeichnen, da er nicht direct vom Zellstoffwechsel abhängig ist." [(17), p. 151). Some three decades later there appeared a notable revival of this concept in the work of Curran et al. (4,5) dealing with the problem of solute-solvent interactions in fluid transport across epithelial membranes.

In all of my early work I had measured changes in the Cl^- concentrations in the solutions on the two sides of the skin. However, to make sure that the observed increase in Cl^- on the dermal side, and the observed decrease in Cl^- on the epidermal side was the result of net "salt" transport, I also measured changes in the freezing point depression of the salt solutions adjacent to the skin membranes (21, 24). An increase in Cl^- in the solution on the dermal side was associated with an increase in the freezing point depression. Similar correlations were found when the solutions on the epidermal side were studied. In those days one could have estimated sodium by microgravimetric analysis, but it was a very tedious process. By contrast, Cl^- was rapidly and very accurately measurable by iodometric titration.

Two important events, one in 1939-1940, the other in 1951 then ushered in a truly explosive rate of progress in studies on ion transport in frog skin, and in other types of epithelial membranes as well.

Katzin (27, 28) was the first to make use of radioisotopically labeled ions to measure the ionic permeability of isolated frog skin. He found that the rate of Na^+ influx (epidermis→dermis) always exceeded the rate of Na^+ back flux (dermis→epidermis). We may wonder today why the ratio of (rate of influx)/(rate of backflux) in the skins never exceeded the value of 3. But the great step forward taken here was the clear recognition of the fact that thus far "the phenomenon of irreciprocal permeability has been hampered by the low permeability of the skin, and the necessity of using similar solutions on both sides of the membrane. By the use of radioactive tagged ions (Na^{24}, K^{42}) it has been possible to make quantitative measurements.....using chemically similar solutions on both sides of the skin" (28). It is proper from time to time to be reminded of the fundamental premise which is made here when isotopes are used to trace the flow of an unlabeled species for the purpose of calculating the permeability characteristics of a "membrane," such as frog skin. Specifically, Dawson (6) is quite correct when he states: "The properties of the membrane which are reflected in the tracer rate coefficient may be a strong function of the total concentration of the abundant isotope. We assume, however, that the tracer may be added to the system in such a minute quantity on a molar basis that the properties of the membrane remains virtually unchanged." (p. 353).

Ussing and Zerahn (49) and, shortly afterwards, Linderholm (33) confirmed the observations of Katzin. But they took an additional important step forward. They measured ionic fluxes across the skin by the isotope technique and compared the calculated net flow of electrical charge with the electrical current which can be drawn from the skin membrane. Their device was similar to the one used earlier by Rehm (42) to control the gastric membrane potential. These studies revealed, among other facts, that in "short-circuited skin," the electrical current is predominantly a Na^+- current, except for a few situations where net flux of Cl^- in the shorted skins may also contribute to the current flow in the membrane (52, 40).

3) Returning to Reid's experiment, there was a third question which, in 1935, I wished to clarify: Is there a close correlation between the inward transport of hypertonic salt solution and the electrical skin potential? Are transport and skin potential affected in the same manner by metabolic inhibitors, and by the supply of nutrients? Some affirmative answers are found in my papers of 1935-1938 (15, 21), and in the thesis work of Eckstein (8). It must

[1] Translation of this paragraph A, and those which follows (B through I) are given at the end of this article.

also be said that in the early and mid thirties, studies on the dependence of the skin potential on skin metabolism was a much favored research topic. References are given in the papers just cited.

4. ACTIVE TRANSPORT

In dealing with these membrane phenomena in isolated frog skin I found it useful to introduce in 1935 the concept of "active transport," defined thermodynamically as follows: (16,17,19); see also Eckstein (8).

In "active transport," the "driving forces (Triebkräfte)" are generated within the skin membrane. They drive certain molecules against the partial pressure gradient which exists for the substance in question. Hence, in order to demonstrate active transport one must experimentally eliminate all unsymmetrical external solution conditions. But one must stop short of eliminating the energy gradient within the skin along which the material is driven. Because of this intrinsically generated energy gradient, "active transport" is different from accelerated (facilitated) diffusion across a membrane. The intrinsic driving forces are sustained by the free energy of biochemical reactions, such as in frog skin the combustion of lactic acid, or pyruvic acid.

C. "Aktive" order "vitale Triebkraft" soll hier nur heissen: dass unbekannte chemische Vorgänge einen unbekannten physikalischen Mechanismus in Gang halten. Aus der vorliegenden Untersuchung hat sich immerhin ergeben, dass die "vitale Triebkraft" an einen Verbrennungsvorgang geknüpft ist"....."Der Aufklärung der anderen Unbekannten, der Lösung der Frage, welcher physikalische Mechanismus freie chemische Energie in Resorptionsarbeit umsetzt, werden sich vermutlich grössere Schwierigkeiten entgegenstellen. Die Annahme eines elektrischen Mechanismus ist zur Zeit die einzige, zu deren Gunsten uberhaupt etwas gesagt werden kann." [(16), p. 14-15].

I could have written this near the end of my academic career in 1978. Likewise, the following which was a good prediction of things to come:

D. "Als eine irreziprok arbeitend Maschine muss man aber auch z.B. ein kurzgeschlossenes galvanisches Element bezeichnen. Hier wird chemische Energie in elektrische verwandelt, die sich als Elektronenstrom in *einer* bestimmten Richtung ausgleicht" [(15), p. 16].

The term "irreziprok arbeitende Maschine" used here is an old expression for "active transport mechanism," or simply, "pump."

E. "Die Erklärung des Stofftransportes mit Hilfe ringförmiger Membranströme könnte wesentlich gestützt werden durch den Nachweiss, dass die in der Membran enstehende und ungesetzte elektrische Energie, ein ausreichendes Äquivalent für die von der Membran geleistete Resorptionsarbeit ist." [(15), p. 14].

F. "Der aktive Mechanismus einer Membran ist einem galvanischen Element vergleichbar, das in einen anderen (Haupt)-Stromkreis eingeschaltet, den darin fliessenden Strom abschwächt oder verstärkt, je nachdem, ob es parallel oder hintereinander zur Stromquelle des Haupstromkreises eingeschaltet ist." [(15), p. 17].

This encompasses the principle of "voltage clamping" the skin. Assuming the existence in skin of Ringströme (current loops), the above is a verbal expression of an electrical equivalent circuit.

In the older electrophysiological literature, electrical Ringströme were frequently discussed. In trying to close a conceptual gap in the electrical skin model, I assumed the existence of such currents. My views were especially swayed in this direction by the publication in 1919 by Nathansohn (41). He put forth the idea that in secretory processes in which salts move against a concentration gradient, the cations and the anions may move along separate pathways. Based on several classical papers (e.g. by Freundlich, Höber, Bethe and Toropoff, and others) he theorized that in NaCl secreting cells the Na^+ - most likely -moves via the particular matter of the membrane, whereas Cl^- travels via pervading capillary spaces. Nathansohn illustrated his views by considering a renal tubular cell[1].

It is most illuminating to follow excerpts from his paper:

G. "Haben wir es aber z.B mit einer Nierenzelle zu tun, deren Funktion darin besteht, NaCl von der verdünnteren Lösung im Blut zu der konzentrierteren im Harn zu transportieren, so müssen in erster Linie die Plasmamembranen an dieser Stelle für die Ionen des Chlornatriums durchlässig sein. Für den positiven Stromtransport in den Kapillaren könnten also ausser den positiven Wasserteilchen und den H^+-Ionen noch das Na^+-Ion zur stehen .... Was geschieht aber in diesem Falle mit dem zugehörigen Cl'-Ion? Da es mit sezerniert wird, muss es gleichfalls durch die Membran treten; beruht die Sekretion auf elektrischer Grundlage, dann muss es einen anderen Weg gehen als das Na^+-Ion.[2]. Es wird dann vom negativen Strom getragen und wenn das Na^+-Ion[2] den Weg durch die Kapillaren nähme, so müsste das Cl'-Ion durch die Membranteilchen wandern. Unter diessen Verhältnissen wird das Chlornatrium durch den Strom von der negativen Membranseite nach der positiven Seite transportiert werden. Im umgekehrten und wahrscheinlicheren Fall, müssten aber umgekehrt die negativen Cl'-Ionen durch die Kapillaren, die positiven Na^+-Ionen[1] im positiven Strom durch die Membranteilchen getragen werden." (p. 297-298)

The extraordinary clarity with which Nathansohn visualized the salt secreting process is also documented in the following passage, which shows that he was aware of the fact that, in modern terminology, Na^+ backflux must be much smaller than Na^+ influx:

H. "Wenn wir aber die Sekretions - Erscheinungen, wie es versucht wurde, durch ringförmige Membranströme erklären, so ist hierzu noch eine zweite Annahme nötig. Die Kationen müssen nicht nur durch die Membransubstanz wandern können, es muss vielmehr ausserdem unter deren Einfluss ihre Wanderungsgeschwindigkeit in dem Kapillarenwasser stark herabgestzt sein; sonst würden sie nämlich durch den in den kapillaren zurückkehrenden Strom wieder an ihre ursprüngliche Stelle zurückbefördert werden, und es könnte keine einseitige Anhäufung erfolgen: (p. 299).

Nathansohn concludes the section on NaCl-secretion as follows:

I. "Die Annahmen, die wir zur elektroosmotischen Erklärung der Sekretion gemacht haben, sind also gar nicht neu, sie stellen vielmehr nur eine Erweiterung der Schlussfolgerungen dar, die Bethe und Toropoff aus ihren Beobachtungen gezogen haben. Die Fortsetzung dieser Untersuchungen an geeigneten Membranen wird zweifellos noch weitere Aufschlüsse liefern." (p. 299-300).

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1) It will be noted that Nathansohn adopted for his discussion the theory of urine formation proposed in 1874 by Heidenhain according to which solutes, including salts are secreted from the blood into the tubular fluid. As we know now, just the opposite is correct. However, regardless of the direction of the movement of NaCl across the "renal cells," Nathansohn's arguments remain of interest.

2) The original text says "K^+-Ion." This is a misprint. Nathansohn considers NaCl, not KCl.

By the mid thirties, I had data on isolated frog skin which showed that it actively transports NaC1 from the negatively charged epidermal side to the positively charged dermal side. The question arose therefore: Are there in frog skin Ringströme which account for the active inward NaC1 transport? It was at this point that I temporarily left this field of research. But I was certain that isolated frog skin, used in a fashion as described in Reid's experiment, is one of the "geeigneten Membranen" (suitable membranes) of which Nathansohn spoke, which would prove useful to elucidate the fundamental mechanism of active salt transport in and across epithelia. Progress would have been impossible, however, without the use of tagged ions, which became soon available for biological studies.

In 1939-1940 Katzin introduced isotopes into frog skin research (27,28). He showed that the rate of Na^+ influx (epidermis→dermis) exceeds the rate of Na^+ backflux across skins placed in normal saline solutions. In 1951 Ussing and co-workers (48,49) combined isotope flux measurement with measurements of the electrical currents which flow in the "short-circuited" skins, and in the electrically "open" skin as well. These important experiments can reveal which ion species is "actively" transported. In frog skin it is predominantly, but not exclusively, the Na^+ ion. During the period from 1952-1954 Linderholm (33,34,35) extended these experiments by also taking direct electrical measurements on total skin conductance. He found that the sum of the partial ion conductances, obtained from the isotope flux measurements, is equal to the measured total skin conductance. Thus the question of the existence of Ringströme in salt transporting frog skin found an affirmative answer. Simple electrical equivalent circuits were drawn up to summarize the experimental results. Much remains to be done to portray the finer details of the electrical network in skin. Unresolved remains also the question, how the skin generates its "Na^+-battery" or its "$C1^+$-battery," as the case may be, which forces cations and anions to flow also passively in tissue fluid channels (Nathansohn's "capillaries") in accordance with the laws of electrochemistry. The mode of transfer of chemical energy at the ion-pump sites is unclear at this time. Na^+-K^+-ATP-ase, linked to an electrontransport chain, seems to be an essential part of the energy transducer. On the basis of several observations made on frog skin (26), I thought that transmembrane active Na^+ transport from the outside to the inside of the skin may be conceived as a metabolically supported, triggered Na^+/K^+ exchange reaction involving a rotating carrier complex, existing in two states, such as RK_mNa_n and $R'K_{m+1}Na_{n-1}$ with cycling participtionof intracellular K^+ at the transport site. What is also needed is a detailed kinetic theory of the flows of ions within and across the skin membrane, based on the molecular structure of its anatomical and functional components, and their topological relationship to each other (3,10). Very little is known about these matters. All things considered, it would be a bit presumptuous to claim that we have today a detailed understanding of Reid's experiment which was published in 1892.

5. TRANSLATIONS FROM THE GERMAN

A. Undoubtedly, the structural and functional characteristics of the body surfaces (skin, gills) play a role in the phenomenon of maintenance of the relatively high salt contents.

B. Already now one could be led to the notion that the "active" process consists in the transport of solution rich in salt and poor in water. This would set up the condition for osmotic flow of water in the same direction. As compared to the primary process, the latter process should be regarded as "passive" since it does not directly depend on cellular metabolism.

C. Here, "active" or "vital driving force" should only mean: that unknown chemical reactions maintain an unknown physical mechanism. The present investigations have at least shown that the "vital driving force" is coupled to an oxidative process.....The elucidation of the other unknown, i.e., the answer to the question which physical mechanism converts chemical free energy into work of resorption, probably, will encounter greater difficulties. At present, the hypothesis of an electrical mechanism is the only one which has some merit.

D. A short-circuited electrical battery is an irreciprocally working engine. Here chemical energy is converted into electrical energy which gives rise to a flow of electrons in *one* direction.

E. The explanation of mass transport by means of electrical current loops in the membrane could be greatly strengthened by the proof that the electrical energy conversion within the membrane is a sufficient equivalent for the work of resorption done by the membrane.

F. The active mechanism in a membrane is equivalent to a galvanic battery which, if hooked up to an external main circuit, can attenuate, or augment the current in the electrical circuit. This depends on whether the membrane battery is in parallel, or in series to the current source of the external circuit.

G. Let us consider a renal cell whose function is to move NaC1 from the diluted blood to the concentrated urine. First of all, the plasma membrane of this cell must be permeable for the ions of NaC1. For transport of positive charge (current) in the capillaries, Na^+ - besides the positively charged water molecules, and H^+ - may be available.....But what happens in this case to the associated Cl^- ion? Since it is also secreted, it must also pass through the membrane; if secretion has an electrical basis, then $C1^-$ must travel via another route than Na^+ ion. It will be carried with the negative current. If the Na^+ ion passes through the capillaries, the $C1^-$ ion must move through the membrane particles. Under these circumstances, NaC1 would be carried from the negative to the positive side of the membrane. In the opposite, and more likely case, $C1^-$ ions would move via the capillaries, the Na^+, in the direction of the positive current, via the membrane particles.

H. Our attempts to explain secretory processes by electrical current loops in the membrane requires a second assumption. The cations must not only be able to move through the membrane matrix but in addition, under their influence, their mobility in the capillary water must be severely reduced; otherwise they would be carried in the capillaries by the returning current back to their place of origin, and no accumulation on one side of the membrane would occur.

I. The assumptions which we have made for the electrosmotic explanation of secretion are not new at all. They are only an extension of the conclusions which Bethe and Toropoff have drawn from their observations. There can be no doubt that the continuation of these studies on suitable membranes will uncover additional information.

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INSTRUCTIONS FOR APPLYING FOR APS MEMBERSHIP

CURRENT APPLICATION FORMS

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

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

GENERAL INSTRUCTIONS

FOR ALL CATEGORIES:

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

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

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

Send no reprints.

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

QUALIFICATIONS (Except Students):

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

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

SPONSORS:

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

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

CHECK LIST:

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

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

SPECIAL INFORMATION AND INSTRUCTIONS

FOR REGULAR MEMBERSHIP

Bylaws of the Society:

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

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

Duties and Privileges:

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

FOR CORRESPONDING MEMBERSHIP

Bylaws of the Society:

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

Duties and Privileges:

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

FOR ASSOCIATE MEMBERSHIP

Bylaws of the Society:

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

Duties and Privileges:

Same as for Regular Members except for the privilege of:

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

FOR STUDENT MEMBERSHIP

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

Bylaws of the Society:

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

Duties and Privileges:

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

Submit original and 7 copies of application and supporting documents.

APPLICANT'S LAST NAME _____

Date _____

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

MEMBERSHIP APPLICATION FOR:

- REGULAR ☐
- CORRESPONDING ☐
- ASSOCIATE ☐
- STUDENT ☐

CURRENT MEMBERSHIP CATEGORY; YEAR ELECTED _____

See Instructions

Name of Applicant: _____
First Middle Last

Mailing Address _____ Birth Date: _____

Citizenship: _____

Country of Permanent Residence:* _____

Telephone No.: _____

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

1. EDUCATIONAL HISTORY

Dates	Degree	Institution	Major Field	Advisor

Doctoral Dissertation Title: (if any)

Postdoctoral Research Topic:

2. OCCUPATIONAL HISTORY

Present Position:

Prior Positions:

Dates	Title	Institution	Department	Supervisor

SPONSORS

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

Mailing Address: _____ Mailing Address: _____

Telephone No. Zip Code Telephone No. Zip Code

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

#1 Signature _____ #2 Signature _____

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

APPLICANT'S LAST NAME _____

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

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

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

SPRING (FASEB)

Date	Presented	Coauthor
_____	☐	☐
_____	☐	☐
_____	☐	☐
_____	☐	☐
_____	☐	☐

FALL (APS)

Date	Presented	Coauthor
_____	☐	☐
_____	☐	☐
_____	☐	☐
_____	☐	☐
_____	☐	☐

List other scientific societies of which candidate is a member:

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

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

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

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

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

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

THE PHYSIOLOGY TEACHER

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A COMPUTER MODEL OF THE CARDIOVASCULAR SYSTEM FOR EFFECTIVE LEARNING

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Indianapolis, Indiana 46223

The following model and its description is presented as a useful teaching tool and also as an example of the ease of developing the differntial equations of a physiological system and then solving them through simple numercal integration on a digital computer. The physiological model itself is well-established (1-5, 8). Unlike models using a series of algebraic equations, this implementation, like more complex system simulations solves a set of interacting, possibly non-linear, differential equations. Using the same approach, all sorts of relationships (respiration, neural action potentials, drug dynamics, compartmental mixing) can be handled without developing an analytic solution for the set of equations. Implementation is not restricted to a dedicated computer, a large time-sharing system or the availability of a specialized simulation language. Futhermore, the implementation presented here is interactive; responses from the computer come before the student loses interest.

(The model used is simlar to that used by M. N. Levy in a recent review of cardiovascular fundamentals: "The cardiac and vascular factors that determine systemic blood flow." *Circ. Res.* 44:739-747, June 1979).

The interaction between the heart and the peripheral parts of the cardiovascular system must be understood to be able to distinguish between normal and abnormal function. A key variable is the central venous pressure, because this is a major (but not the only) determinant of: (a) the rate of blood flow from the periphery, and (b) the filling of the heart and so rate of flow from the heart. Under steady state conditions, when the venous return equals the cardiac output, the resulting central venous pressure is the "operating point" for the system. The concept of such operating points — in contrast to set-points — is crucial for our understanding of homeostasis. The ultrasimple cardiovascular model described here was designed to aid the development of such understanding and to simulate the effect of various distubances on the cardiovascular system. The cardiovascular response to exercise (reduce arterial resistance) and the compensations needed to provide adequate homeostasis may be simulated, as well as the effect of cardiac weakening (reduced contractitlity) on central venous pressure and cardiac output. The effect on "cardia output" and "blood pressure" of changing other parameters, such as "blood volume," "venous compliance" and "cardiac compliance," may also be studied. To think only in terms of final steady state responses, rather than considering also the transient pattern of change and its quantitative characteristics, limits functional understanding. The model was designed to give this potentially valuable information for study and contemplation. Finally, the model demonstrates the ease and power of digital simulation of complex physiological systems using easily learned BASIC and a microcomputer. A differenct kind of information is available from such mathematical models than from mechanical models (6), for although the computer model is less direct and seemingly less real, it is much more precise and flexible.

The model is simple in that only one "heart" is used, and the cardiac output is a linear function of illing volume. Only one vascular pathway is present, and the vasculature is lumped into only one arterial bed and on venous bed. There are no reflexes. However, the basic phenomena are graphically and validly demonstrated. A much more complex model (two non-linear hearts, a pulmonary bed, two parallel vasculatures, and provision for fluid shifts across the capillaries) is valuable for exploring research ideas and concepts in my laboratory, but such a model is cumbersome to use and requires either a very high speed computer or long computing time. On a small microcomputer (Processor Technology SOL with a North Star disk system) this model operates at about real time, is quickly set up, and can be easily "revived" if "killed."

The model is presented in schematic form in Figure 1. The 9 interacting equations used to describe this dynamic system are described in the Appendix, as is the computer approach to provide an iterative solution to the set of equations.

In Figure 2, control conditions and the initial printout are presented. If a printer is available, hard copy of the results can be printed for later study. In the table of "Current Values of Variables and Parameters," note that the total distending blood volume is much less than the total blood volume. The veins, especially at zero transmural pressure, contain a large volume of

blood. At the bottom of Figure 2, a plot of the Gutonian relationship between venous retrn and cardiac output is presented.

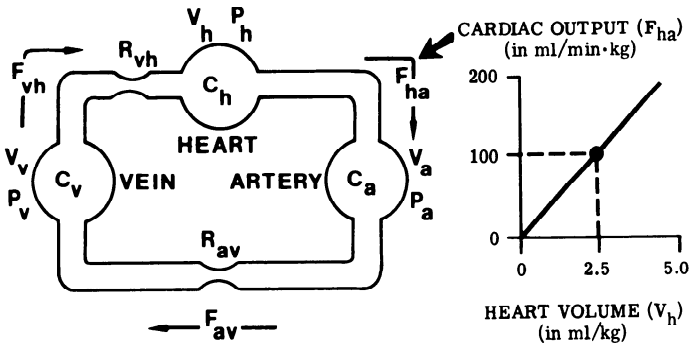

Fig. 1 Schematic diagram of the model.

Fig. 2 Start-up and Normal Conditions.

```
RUN

For hard copy output type 1, for video 0 ? 0
Simple Cardiovascular Model  -  CVMDL  -  1978
  C.F.Rothe - Physiology - Indiana Univ., Indianapolis
Integration step size (in minutes) is  .005
Printout is set for 0.1 min intervals.
After changing parameters, continue runs until
  the flows in all 3 segments are equal.
Venous Pressure = ca. Mean Circulatory(capacity vessel) Pres.
Heart  Pressure = Central venous pressure
Distended vasc vol(ml/kg) + unstressed(55) = Total bld volume.
The MODEL has NO REFLEXES or transcapillary fluid compensation
Explore effect of the following - Try various compensations.
 1) EXERCISE - Arterial resistance (Res #1) 40% of normal.
 2) HEART FAILURE - Cardiac Contractility 30% of normal.
 3) HEMORRHAGE - Blood volume decreased 10 ml/kg
                              Press RETURN to continue
You will be given choices:
  1 - To CONTINUE computing
  2 - To CHANGE parameter values
  3 - To list as PERCENT of control values
  4 - To start over with original control values
  5 - To PLOT cardiac output & venous return vs. R. Atrial Pres
  6 - To QUIT
Use RETURN to ENTER each of your responses.
                              Press RETURN to continue
T=  0   CURRENT VALUES OF VARIABLES  &     PARAMETERS
SEGMENT       PRESSURE     OUTFLOW    VOLUME   COMPL RESISTANCE
             (mm Hg)    (ml/min-kg) (ml/kg)
-------      -------      -------     ------   ----- -------
01 ARTERIAL    100.00     100.00      4.00      .04       .92
02 VENOUS        8.00     100.00     14.00     1.75       .05
03 HEART         3.00     100.00      2.50      .83       .00
Heart contractile ability = 100.00 % normal
Total blood volume (ml/kg)=  75.50
Vasc distending blood vol.=  20.50 or 100.00% normal
Mean Circ Filling Pressure=   7.8 mmHg

Cont:1,Chng param:2,% of control:3,Plot:5,Quit:6? 5
Flow    Venous Return,R           Cardiac output,O
 240 I                                          *
 220 I                                       O
 200 I                                    O
 180 I                                 O
 160 IR                             O
 140 I      R                    O
 120 I            R          O
 100 I                 N - normal operating point
  80 I              O       R
  60 I          O                R
  40 I       O                        R
  20 I    O                                R
   0 I*-----I-----I-----I-----I-----I-----I-----I-----*-----I
R Atrial Pressure 2     3     4     5     6     7     8     9
Cont:1,Chng param:2,% of control:3,Plot:5,Quit:6?  2
```

An example of changing parameters to mimic exercise is presented in Figure 3. Arterial resistance (Segment 1) is reduced to about 40% of normal; venous compliance (Segment 2) is reduced to about 2/3 of normal to provide Venoconstriction, and cardiac contractility is increased to 250% of normal. A steady state is reached by the next printout (0.1 min) with arterial pressure somewhat less than normal. By choosing option 3, the variables and parameters are presented as percent of control. Even though venous compliance is 2/3 of control, the doubling of blood flow increased the transmural pressure enough to increase the venous (capacity vessel) pressure and volume to a value greater than normal. The central venous pressure operating point is at a value less than control, even with an increase in mean circulatory pressure, because cardiac contractility was greatly increased.

Fig. 3. Simulation of exercise with cardiovascular compensation.

```
T=  0   CURRENT VALUES OF VARIABLES  &     PARAMETERS
SEGMENT       PRESSURE     OUTFLOW    VOLUME   COMPL RESISTANCE
             (mm Hg)    (ml/min-kg) (ml/kg)
-------      -------      -------     ------   ----- -------
01 ARTERIAL    100.00     100.00      4.00      .04       .92
02 VENOUS        8.00     100.00     14.00     1.75       .05
03 HEART         3.00     100.00      2.50      .83       .00
Heart contractile ability = 100.00 % normal
Total blood volume (ml/kg)=  75.50
Vasc distending blood vol.=  20.50 or 100.00% normal
Mean Circ Filling Pressure=   7.8 mmHg

To make no change type: 0 then RETURN
Change resistance? Type SEGMENT number: 1
New value of RESISTANCE is? .40
Change compliance? Type #: 2
New value of COMPLIANCE is? 1.2
Change CARDIAC CONTRACILITY? (Yes=1,No=0) 1
New value of contractility in % of normal: 250
Change BLOOD VOLUME? (Yes=1,No=0) 0
Shorten print interval to <0.1 min? Yes=1: 0
                Patience please, computing.
CONTinue computing until outflows about equal.

Time is  .1 minutes                        I # =  20
 SITE          PRESSURE  OUTFLOW  VOLUME
01 ARTERIAL      92.06    199.26     3.68
02 VENOUS        12.35    199.26    14.83
03 HEART          2.39    199.26     1.99
         Total distending volume =  20.50

Cont:1,Chng param:2,% of control:3,Plot:5,Quit:6? 3
T=  .1   CURRENT VALUES OF VARIABLES  &     PARAMETERS
SEGMENT       PRESSURE     OUTFLOW    VOLUME   COMPL RESISTANCE
             (mm Hg)    (ml/min-kg) (ml/kg)
-------      -------      -------     ------   ----- -------
 :* * * Values as percent of control * * *
01 ARTERIAL     92.06    199.26     92.06    100.00    43.48
02 VENOUS      154.43    199.26    105.89     68.57   100.00
03 HEART        79.71    199.26     79.70    100.00   100.00
Heart contractile ability = 250.00 % normal
Total blood volume (ml/kg)=  75.50
Vasc distending blood vol.=  20.50 or 100.00% normal
Mean Circ Filling Pressure=   9.9 mmHg

Cont:1,Chng param:2,% of control:3,Plot:5,Quit:6?  5

Flow    Venous Return,R           Cardiac output,O
 240 I                                          *
 220 I        R       O
 200 I              X - CURRENT VALUE
 180 I            O     R
 160 I          O             R
 140 I        O                     R
 120 I       O                           R
 100 I                N - normal operating point
  80 I     O                                        R
  60 I   O                                                R
  40 I  O
  20 I O
   0 I*-----I-----I-----I-----I-----I-----I-----I-----*-----I
R Atrial Pressure 2     3     4     5     6     7     8     9
Cont:1,Chng param:2,% of control:3,Plot:5,Quit:6? 4
```

The effect of hemorrhage is shown in Figure 4. The model, just as a living animal, cannot be hemorrhaged instantly. We chose a hemorrhage or transfusion rate to complete the volume change in 0.2 min. Even when the hemorrhage is completed, flows out of the various segments are not equal; about 10 sec is required for the transients to die out. Please remember that the model incorporates no reflexes nor any provision for fluid shifts from the interstitial space into the vasculature. We defined "hypotension" as a blood pressure less than 50 mmHg and "shock" as a cardia output less than 60 ml/min•Kg. A separate plot of hemorrhaged volume, cardiac output, central venous pressure, and venous retrun as a function of time will provide clues as to the transient pattern of response of the cardiovascular system. Compensatory mechanisms should be tried and enough information copied to provide a report.

Fig. 4. The effect of hemorrhage.

```
To make no change type: 0 then RETURN
Change resistance? Type SEGMENT number: 0
Change compliance? Type #: 0
Change CARDIAC CONTRACILITY? (Yes=1,No=0) 0
Change BLOOD VOLUME? (Yes=1,No=0) 1
Current TOTAL blood vol=  75.50 DISTENDING vol=  20.50
                        Normal  DISTENDING vol=  20.50
Desired (+ or -) change in volume (ml/kg) is? -10
Shorten print interval to <0.1 min? Yes=1: 1
What interval (in multiples of .005 min)? .020
                  Patience please, computing.
CONTinue computing until outflows about equal.

Time is  .02 minutes                        I # =  4
 SITE          PRESSURE  OUTFLOW  VOLUME
01 ARTERIAL     96.82     96.59     3.78
02 VENOUS        7.95    111.92    13.84
03 HEART         2.36     78.51     1.88
         Total distending volume =  19.50

Cont:1,Chng param:2,% of control:3,Plot:5,Quit:6? 1

Time is  .04 minutes                        I # =  8
 SITE          PRESSURE  OUTFLOW  VOLUME
01 ARTERIAL     87.54     86.75     3.41
02 VENOUS        7.72    112.83    13.38
03 HEART         2.08     69.37     1.70
         Total distending volume =  18.50

Cont:1,Chng param:2,% of control:3,Plot:5,Quit:6? 2
      [Changed print interval & skipped some prints]

Time is  .24 minutes                        I # =  48
 SITE          PRESSURE  OUTFLOW  VOLUME
01 ARTERIAL     45.40     44.77     1.85
02 VENOUS        4.21     52.84     7.33
03 HEART         1.57     52.39     1.31
         Total distending volume =  10.50
**** DANGER ***** PATIENT HYPOTENSIVE
**** HURRY *****  PATIENT IN SHOCK !!!!

Cont:1,Chng param:2,% of control:3,Plot:5,Quit:6? 1

Time is  .34 minutes                        I # =  68
 SITE          PRESSURE  OUTFLOW  VOLUME
01 ARTERIAL     51.14     51.13     2.05
02 VENOUS        4.10     51.22     7.17
03 HEART         1.54     51.26     1.28
         Total distending volume =  10.50
**** HURRY *****  PATIENT IN SHOCK !!!!

              [ Skipped a printout & chose option 3 ]

T=  .44   CURRENT VALUES OF VARIABLES  &     PARAMETERS
SEGMENT      PRESSURE    OUTFLOW   VOLUME  COMPL RESISTANCE
            (mm Hg)    (ml/min-kg) (ml/kg)
-------      -------     -------   ------  ----- -------
 :* * * Values as percent of control * * *
01 ARTERIAL    51.22     51.22     51.22   100.00   100.00
02 VENOUS      51.22     51.22     51.22   100.00   100.00
03 HEART       51.22     51.22     51.22   100.00   100.00
Heart contractile ability = 100.00 % normal
Total blood volume (ml/kg)=  65.50
Vasc distending blood vol.=  10.50 or  51.22% normal
Mean Circ Filling Pressure=   4.0 mmHg

Cont:1,Chng param:2,% of control:3,Plot:5,Quit:6? 5
Flow    Venous Return,R          Cardiac output,O
 240 I                                        *
 220 I                                    O
 200 I                                 O
 180 I                              O
 160 I                           O
 140 I                        O
 120 I                     O
 100 I                  N - normal operating point
  80 I R             O
  60 I       R   O
  40 I       O     R
  20 I    O             R
   0 I*-----I-----I-----I-----I-----I-----I-----I-----*-----I
R Atrial Pressure 2     3     4     5     6     7     8     9
Cont:1,Chng param:2,% of control:3,Plot:5,Quit:6?  4
```

In contrast to hemorrhage, which causes a marked reduction in the venous return curve, cardiac failure causes the cardiac output curve to decrease to low values, even if the central venous (heart filling) pressure is high. Cardiac contractility reduction to 30% of normal with compensatory vasoconstriction, venoconstriction, and transfusion to mimic fluid shifts into the vasculature gave the results shown in Figure 5.

The sensitivity of the cardiovascular system model to changes in various parameters can be explored by plotting cardiac output (as percent of control) against the parameters (as percent of control). an adequate plot will be obtained if 25, 50, 100, 150 and 200% of control parameter values are used. How close are these values to reality, i.e., experimental values? What would be the effect of reflexes and fluid shifts? In many cases, reliable data are not available to test critically even this ultra-simple model.

Fig. 5. Reduced contractility; with compensation by increased arterial resistance and increased blood volume.

```
Cont:1,Chng param:2,% of control:3,Plot:5,Quit:6? 2
T=  0   CURRENT VALUES OF VARIABLES  &     PARAMETERS
SEGMENT      PRESSURE    OUTFLOW   VOLUME  COMPL RESISTANCE
            (mm Hg)    (ml/min-kg) (ml/kg)
-------      -------     -------   ------  ----- -------
01 ARTERIAL   100.00    100.00      4.00     .04      .92
02 VENOUS       8.00    100.00     14.00    1.75      .05
03 HEART        3.00    100.00      2.50     .83      .00
Heart contractile ability = 100.00 % normal
Total blood volume (ml/kg)=  75.50
Vasc distending blood vol.=  20.50 or 100.00% normal
Mean Circ Filling Pressure=   7.8 mmHg

To make no change type: 0 then RETURN
Change resistance? Type SEGMENT number: 1
New value of RESISTANCE is? 1.38
Change compliance? Type #: 0
Change CARDIAC CONTRACILITY? (Yes=1,No=0) 1
New value of contractility in % of normal: 30
Change BLOOD VOLUME? (Yes=1,No=0) 1
Current TOTAL blood vol=  75.50 DISTENDING vol=  20.50
                        Normal  DISTENDING vol=  20.50
Desired (+ or -) change in volume (ml/kg) is? 5
Shorten print interval to <0.1 min? Yes=1: 0
                  Patience please, computing.
CONTinue computing until outflows about equal.

Time is  .1 minutes                         I # =  20
 SITE          PRESSURE  OUTFLOW  VOLUME
01 ARTERIAL     87.07     57.17     3.50
02 VENOUS        8.18     41.85    14.39
03 HEART         6.09     60.89     5.10
         Total distending volume =  23.00
**** HURRY *****  PATIENT IN SHOCK !!!!

Cont:1,Chng param:2,% of control:3,Plot:5,Quit:6? 1

Time is  .2 minutes                         I # =  40
Time is  .3 minutes                         I # =  60
 SITE          PRESSURE  OUTFLOW  VOLUME
01 ARTERIAL     96.49     63.12     3.86
02 VENOUS        9.39     62.62    16.43
03 HEART         6.26     62.56     5.21
         Total distending volume =  25.50

Cont:1,Chng param:2,% of control:3,Plot:5,Quit:6? 3
T=  .3   CURRENT VALUES OF VARIABLES  &     PARAMETERS
SEGMENT      PRESSURE    OUTFLOW   VOLUME  COMPL RESISTANCE
            (mm Hg)    (ml/min-kg) (ml/kg)
-------      -------     -------   ------  ----- -------
 :* * * Values as percent of control * * *
01 ARTERIAL    96.49     63.12     96.42   100.00   150.00
02 VENOUS     117.34     62.62    117.36   100.00   100.00
03 HEART      208.53     62.56    208.54   100.00   100.00
Heart contractile ability =  30.00 % normal
Total blood volume (ml/kg)=  80.50
Vasc distending blood vol.=  25.50 or 124.39% normal
Mean Circ Filling Pressure=   9.7 mmHg

Cont:1,Chng param:2,% of control:3,Plot:5,Quit:6? 5
Flow    Venous Return,R          Cardiac output,O
 240 I                                        *
 220
 200
 180 I  R
 160 I        R
 140 I              R
 120 I                   R
 100 I                N - normal operating point
  80 I                                  R              O
  60 I                                       O R
  40 I                              O                R
  20 I           O                                        R
   0 I*-----I-----I-----I-----I-----I-----I-----I-----*-----I
R Atrial Pressure 2     3     4     5     6     7     8     9
Cont:1,Chng param:2,% of control:3,Plot:5,Quit:6? 6
CONTROL IS AT VIDEO TERMINAL
```

APPENDIX

The model in schematic form is presented in Figure 1. At the right, the assumed Starling or ventricular performance relationship of cardiac output (Fha = Flow from heart to arteries) at various end diastolic volumes (Vh = Volume of heart at end of filling) is presented.

1) Fha = Kh * Vhfilled

The slope of this linear curve with the intercept at zero filling volumes is the "contractility," Kh. Just as the left heart normally buffers the right heart from changes in systemic arterial pressure, the model cardiac output is not directly influenced by arterial pressure. If the "contractility," Kh, is doubled, then twice the outflow occurs at the same filling volume. Note that heart rate is not included. In this areflexic model we assume that the product of heart rate and stroke volume is constant. In real life, compensatory mechanisms tend to maintain the stroke volume with an increased heart rate.

FLOWS through the arterial (Fav) and venous (Fvh) beds are assumed to follow "Ohm's Law," and so are directly proportional to the pressure gradients and inversely proportional to the arterial-to-venous resistance (Rav) and venous-to-heart resistance (Rvh), respectively.

2) Fav = (Pa-Pv)/Rav

3) Fvh = (Pv-Ph)/Rvh

The mean pressure in the heart during diastole (filling) is Ph. In real life there are, of course, many more segments and a pulsatile flow.

PRESSURES at each segment are computed from the definition of compliance (C = Δv/Δ/P). A linear compliance is assumed. The volume is the volume causing the vasculature to be distended and does *not* include the volume present if the transmural pressure is zero.

4) Pa = Va/Ca (Arterial)

5) Pv = Vv/Cv (Venous)

6) Ph = Vh/Ch (Heart)

The venous pressure (Pv) is the peripheral microvenous pressure and is about the same as the mean circulatory filling pressure. The heart pressure (Ph)is the central venous pressure. A simplifying assumption is that the intrathoracic pressure is zero and so Ph is also the transmural filling pressure of the heart. The "heart" diastolic distensibility (Ch) is assumed to be linear with no limit. "The heart is overdistended" is printed if the diastolic heart volume (both ventricles) exceeds 10 ml/kg.

VOLUMES of each segment, at a given instant, are then computed as the volume at a previous instant plus the integral of inflow minus outflow. Numerically, this integral is merely the difference between inflow and outflow (Fin-fout), at a given iteration, times the time interval (Δt) represented by the iteration.

7) $Va_{(t+\Delta t)} = Va_{(t)} + (Fha-Fav) \cdot \Delta t$

8) $Vv_{(t+\Delta t)} = Vv_{(t)} + (Fav-Fvh) \cdot \Delta t$

9) $Vh_{(t+\Delta t)} = Vh_{(t)} + (Fvh-Fha) \cdot \Delta t$

The logic of these equations is based on the differential equation for conservation of material:

a) $\frac{dV}{dt} = f_{in} - f_{out}$

By definition, dV/dt can be approximated at very small time intervals as:

b) $\frac{dV}{dt} = \frac{\Delta V}{\Delta t} = \frac{V_{n+1} - V_n}{t_{n+1} - t_n}$

Thus, letting $\Delta t = t_{n+1} - t_n$ and converting iteration number to time:

c) $\frac{V_{t+\Delta t} - V_t}{\Delta t} = f_{in} - f_{out}$

And so, at the next iteration:

d) $V_{t+\Delta t} = V_t + (f_{in} - f_{out}) \cdot \Delta t$

By making the time interval (Δt) short (e.g., 0.005min), variables do not change appreciably during each iteration. A much longer integration step size (Δt) leads to instability, a much shorter one extends computation time. The following is the heart of the algorithm in BASIC. Values of the variables and the volumes of "blood" in the segments are repeatedly computed by looping back from line 1140 to 970 until the end of the next print interval (T4) is reached.

```
 970  P(1) = V(1)/C(1)
 980  P(2) = V(2)/C(2)
 990  P(3) = V(3)/C(3)
1000  F)1) = (P)1)-P(2))/R(1)
1010  F(2) = (P(2)-P(3))/R)2)
1020  F(3) = K9 * V(3)
1050  V(1) = V(1) + (F(3)-F)1)) * T1
1060  V(2) = V(2) + (F(1)-F(2)) * T1
1070  V(3) = V(3) + (F(2)+F4-F(3)) T1
1080   V4 = V4 + F4 * T1
1140 IF T9<T4 THEN 970
```

Symbols are:

(1) is the arterial segment, (2) the venous, (3) the heart, P = pressure, V = volume, C = complicance, F = flow, R = resistance, K9 is the cardiac contractility (flow as a function of fiber length), T1 is the integration interval (0.005 min), T9 = the current time, V4 = hemorrhaged blood volume, F4 = hemorrhage rate, and * means multiply.

The computer we use computes with 8 digits of precision, and so truncation errors are minor. This bootstrap method works. Although more elaborate integration routines are available, the simple Euler or rectangular integratoin is simple yet satisfactory (7) for these models. From a set of differential equations describing the system (such as above), the difference differential equations can be easily developed and solved on a digital computer. Difficult analytical solutions or gross simplifications are not required. The approach works with complex or non-linear differential equations describing physiological functions.

The parameters for "normal" are given in Figure 2. The compliance and distending volumes for each segment are less well established than the values for flow and resistance.

Although the basic equations require only 9 lines of coding, the program is 214 lines long to provide for user information, plotting of the cardiac output and venous return relationships, output of variables and input of changes in parameter values. The model was designed for video (CRO) display with 16 lines of 65 characters each. It is written in BASIC and is available, with suggestions for use, on request from the author or from the ASIS auxiliary publication service. Serious users will document the magnitude and importance of the oversimplification employed and may find ways to improve the model without losing its heuristic value.

ACKNOWLEDGEMENTS

Modeling approaches and concepts from Authur Guyton, Tom Coleman and colleagues are gratefully acknowledged.

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SIMPLE AMPLIFIER FOR OXYGEN ELECTRODES

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Some of your readers may be interested in the following simple, reliable and inexpensive amplifier circuit for use with polarographic micro oxygen electrodes. I first made it for field use and for classroom teaching, but it has proved to be excellent also for general laboratory use.

The core of the circuit (Fig. 1) is the RCA operational amplifier CA3140 which has a very high input impedance (typically $1.5.10^{12}$ ohms). It costs about one dollar. Similar operational amplifiers made by other manufacturers may be tried as substitutes. The circuit essentially is a current to voltage converter. Dual supply operation was chosen in order to avoid non-linear responses and other problems. The 100 per cent negative feedback features of the circuit provides excellent stability. The value of the feedback resistor (R_1) depends on the general sensitivity of the oxygen electrode. When used with a Radiometer Model E5046 Clark-type electrode, a value of 2.10^8 ohms for R_1 gave a convenient output voltage of about 3 volts for air-equilibrated water. If special high-megohm resistors are not available, the resistance can be made up by a string of standard resistors. There should be no decrease in circuit performance with feedback resistances which are at least ten-fold higher than the present one, if electrode sensitivity should demand such values. The resistor bypass capacitor C_1 must have low leakage current, such as the mica types, but the capacitance is not critical.

A 0-50 microampere meter with series resistors (R_7-R_{10}) serve as a volt meter, the sensitivity of which is determined by the shunting switch for R_9 and the ten-turn potentiometer R_{10}. R_7 provides output for a recorder with 10 millivolts full scale sensitivity. The circuit is nulled by potentiometer R_4. In my case, the circuit was powered either by two 9 volt transistor radio batteries (B_2 and B_3) or a ± 15 volts DC power supply. The electrode polarizing voltage was obtained from a 1.5 volt penlight battery, adjusted to 0.65 volt by means of potentiometer R_3.

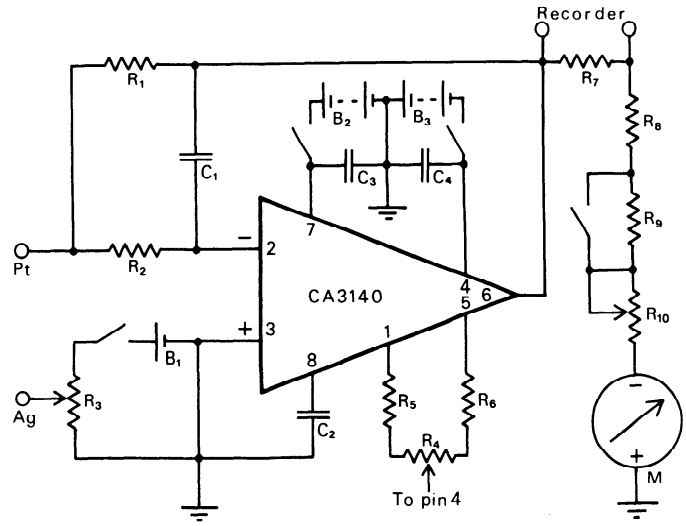

Fig. 1. Amplifier circuit. Pt and Ag indicate the inputs for the platinum cathode and the silver/silver choloride anode, respectively. B_1:1.5v; B_2, B_3:9-12v; C_1:33pf; C_2:68pf; C_3,C_4:0.1μf; R_1:2000MΩ; R_2:240KΩ; R_3, R_4:10KΩ; R_5, R_6:470Ω; R_7:200Ω; R_8:22KΩ; R_9:47KΩ; R_{10}:50KΩ.

It is advisable to mount the operational amplifier in a Teflon socket to avoid potential current leaks between the input pin and other points of the circuit. The circuit must be enclosed in a metal box for electrical shielding. If high humidity or dust may be problems, this box should be reasonably tight.

READERS' FORUM

REPORT ON THE THIRD ANNUAL SYMPOSIUM ON COMPUTER APPLICATIONS IN MEDICAL CARE

From October 14th-17th, 1979 the third annual symposium on Computer Applications in Medical Care was held at the Sheration Inn in Silver Spring, MD. In addition to the main symposium there were introductory tutorials on the first day; and the last session merged with an NIH Sponsored Consensus Development Conference on "The Use of Microprocessor-based 'Intelligent' Machines in Patient Care" which continued for another day and a half. There were a total of 38 sessions including a keynote address by Nobel Laureate Joshua Lederberg. The meeting which was directed at physicians, engineers and other interested scientists, was well attended. There were over 750 registrants. An 896 page Proceedings was available prior to the sessions. It carries document #79CH1480-3C and can be obtained from IEEE Computer Society, 5855 Naples Plaza Suite 301, Long Beach, CA 90803, or IEEE Service Center, 445 Hoes Lane, Piscataway, NJ 08854 for a fee of $37.50.

This year's symposium differed from the two previous programs in that some papers on education were scheduled. The three sessions were titled, "Influence of Computer Environment on Educational Applications," Computer Applications in Medical Education," and "Education in Medical Computing." The full text of the sixteen papers which dealt with educational computing is contained in the Proceedings referred to above.

Dr. Charles S. Tidball

GLOMERULAR PERMEABILITY AND DYNAMICS*

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Direct measurements of glomerular permeability and the dynamics underlying the formation of glomerular filtrate have led to new insights in understanding the function of the glomerulus. In this lecture, I will focus on comparisons of glomerular dynamics in rat and dog with subsequent implications for glomerular dynamics in man. Further, exciting new concepts for the mechanism of proteinuria will be discussed.

The net filtration pressure provides the driving force for the formation of glomerular filtrate. This pressure is the difference between the net hydrostatic pressure for filtration and the oncotic pressure opposing filtration (Fig. 1A, 1B). As protein-free filtrate is formed, the oncotic pressure progressively increases along the length of the glomerular capillary. In the rat, the glomerular capillary oncotic pressure opposing filtration equals the net hydrostatic pressure favoring filtration by the end of the glomerular capillary (Fig. 1C). This phenomenon, filtration pressure equilibrium, has been elegantly demonstrated by Brenner, et al (1). These investigators have micropunctured superficial glomeruli in a unique strain of rats in which the glomeruli are located directly on the surface of the kidney and have directly measured glomerular capillary pressures using a servo-null device. In these studies, the difference between the measured glomerular capillary pressure and proximal tubule pressure, the net filtration pressure, was found to equal the oncotic pressure in efferent arterioles as determined from measurements of protein concentrations in blood directly collected from efferent arterioles on the surface of the kidney.

The attainment of filtration pressure equilibrium in the rat is an important finding since this concept predicts a high degree of dependence of glomerular filtration rate on renal plasma flow. The consequence of an increase in renal plasma flow is that filtration pressure equilibrium is obtained at a point further from the origin of the glomerular capillary. Thus, increased capillary area is recruited for filtration, and filtration rate may increase without a significant change in the net hydrostatic pressure for filtration. As a result, increase in plasma flow in the rat are accompanied by proportionate increases in glomerular filtration rate. Indeed, in additional studies by Brenner et al (2), such a direct relationship was reported following infusion of Ringer's solution or plasma.

However, in studies in both dog and man, the high degree of dependency of filtration rate on renal plasma flow predicted from the filtration equilibrium concept is not observed. Significant increases in renal plasma flow in the dog following vasodilation with acetylcholine, bradykinin, prostaglandin E_2 or volume expansion have little or no effect on simultaneously measured filtration rate (3). Similar findings have been reported following vasodilation with prostaglandin A1 in man in which renal plasma flow was increased 175 ± 41 ml/min without significant changes in glomerular filtration rate (4). This independence of filtration rate and renal plasma flow may be due to a vasodilator mediated decrease in the hydraulic permeability of the glomerular capillary or due to filtration pressure disequilibrium in which the net filtration pressure remains positive throughout the entire length of the glomerular capillary.

The suggestion that glomerular dynamics in the dog are characterized by filtration pressure disequilibrium has been tested by studies in our laboratory (5). We have characterized glomerular dynamics both at normal plasma flow and at increased plasma flow following infusion of acetylcholine into the renal artery of the dog (6). At the end of the glomerular capillary, the net hydrostatic force favoring filtration, 42 ± 2.5 mmHg, was significantly higher than the oncotic force opposing filtration, 33 ± 2.6 mmHg. These findings indicate that at normal plasma flow, glomerular dynamics in the dog are charaterized by filtration pressure disequilibrium (Fig. 2A-C).

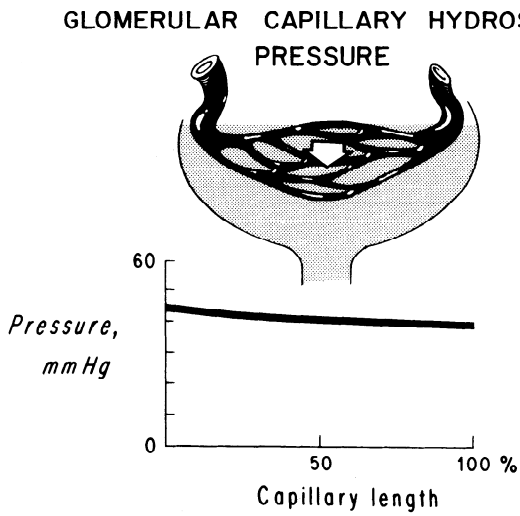
Following infusion of the vasodilator acetylcholine, 2 μg/kg/min, into the renal artery, single nephron plasma flow increased from 228 to 307 nl/min. Single nephron filtration rate was unchanged and averaged 58 ± 5 nl/min before and 60 ± 6 nl/min after vasodilation, again indicating that filtration rate is not highly plasma flow dependent in the dog. Glomerular capillary and tubule pressures both increased by 11 mmHg. Thus, net hydrostatic pressure for filtration was unchanged at 42 ± 3 mmHg. Efferent arteriolar oncotic pressure was 28 ± 2 mmHg, again indicating filtration pressure disequilibrium (Fig. 3). Thus, glomerular dynamics in the dog are characterized by filtration pressure disequilibrium both at control plasma flow and at increased plasama flow without evidence for a change in K_f. We interpret these findings to indicate that filtration rate in the dog is not plasma flow-dependent because of the failure to obtain filtration pressure equilibrium at normal renal plasma flow.

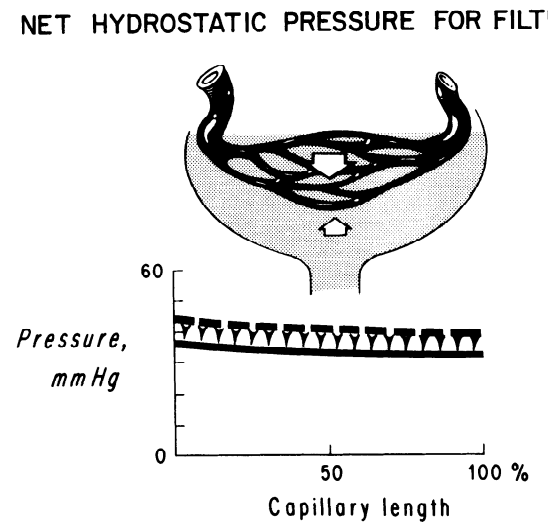
Next, we reduced single nephron glomerular plasma flows and pressures in the dog to values similar to those in the rat to evaluate whether filtration pressure equilibrium can be obtained in the dog (7). Reduction of renal artery pressure from 121 to 65 mmHg by constriction of the renal artery resulted in a decrease in single nephron filtration rate from 75 ± to 35 ± nl/min, values similar to those seen at normal pressures in rats. Glomerular capillary pressure, decreased from 60 ± 1 to 45 ± 1 mmHg, again, a value very similar to that seen in the rat at normal blood pressure. The filtration pressure at the efferent end of the glomerular capillaries, 12 ± 2 mmHg at normal pressure, decreased to a value not significantly different from 0 at reduced pressure (Fig. 4). Thus, when renal perfusion pressure was reduced so that glomerular plasma flows and pressures were similar to values found in rats, filtration pressure at the efferent end of the glomerular capillaries reached equilibrium in the dog.

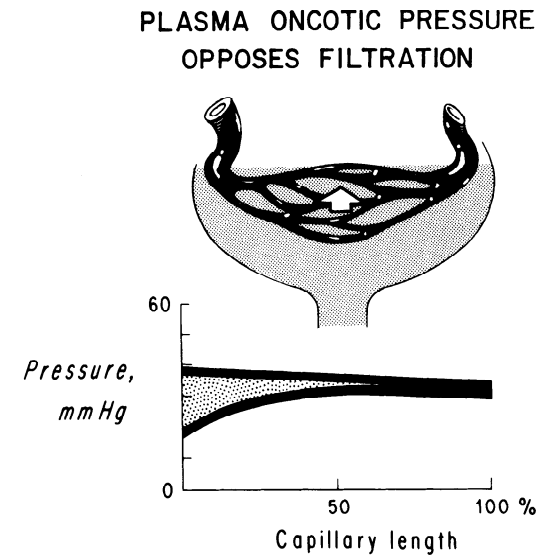
Although glomerular dynamics in dogs at a renal artery pressure of 65 mmHg are strikingly similar to most studies of rats at normal blood pressure, it is important to note that the dog glomerulus has a surface available for ultrafiltration which is approximately twice that of the rat (Table I). Thus, the hydraulic permeability, normalized for surface area in the dog is approximately half that for the rat. Extrapolation of these findings in laboratory animals to man should take into consideration that the estimates of single nephron glomerular filtration rate and glomerular plasma flow in man are very similar to those reported for dogs.

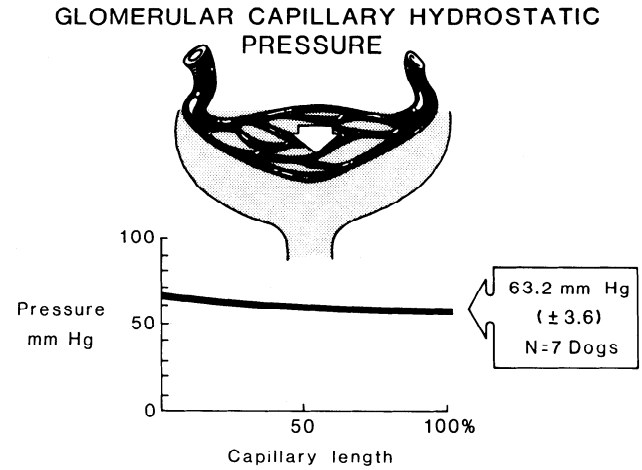
It is important to note that the studies mentioned above in the rat were conducted in Munich-Wistar rats which have glomeruli directly on the kidney surface and hence are available for direct

* Tutorial Lecture presented at the October 1978 meeting in St. Louis.









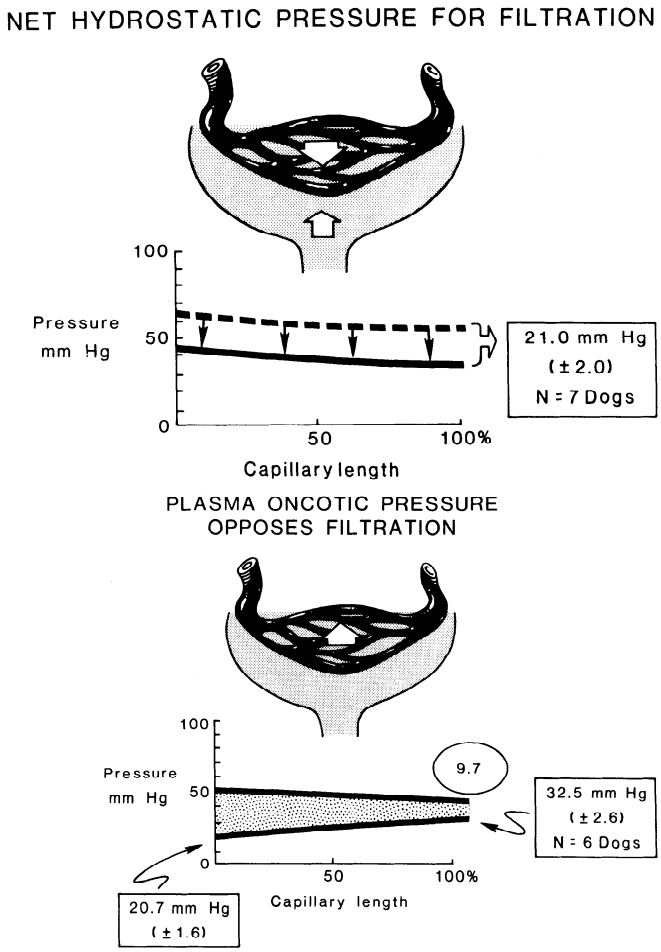


Fig. 1.A-C. *Panel A:* The forces underlying glomerular filtration in the rat glomerulus are depicted. Glomerular capillary pressure is shown as a function of capillary length. *Panel B:* The net hydrostatic pressure, solid line, is obtained by subtracting the intratubular pressure, arrows, from the glomerular capillary pressure, dotted line. *Panel C:* The effective filtration pressure, dotted area, is the difference between the net hydrostatic pressure for filtration, upper solid line, and the plasma oncotic pressure which opposes filtration, lower solid line.

Fig.2.A-C. The forces underlying glomerular filtration in the dog glomerulus are depicted. *Panel A:* Glomerular capillary pressure in the dog. *Panel B:* Net hydrostatic pressure for filtration. *Panel C:* The effective filtration pressure is depicted by the dotted area. The filtration pressure at the efferent end of the glomerular capillary was 9.7 mmHg.

micropuncture measurements of glomerular capillary pressure. Since glomeruli in the dog are not situated directly on the surface of the kidney, the method of stop-flow measurement for glomerular capillary pressure was utilized. Ott et al and Marchand have made comparisions of stop-flow and direct measurements of capillary pressures both in Munich-Wistar rats and in dogs (5, 8). The measurements in dogs were made by blind impalement of glomeruli lying below the surface of the kidney. As indicated in Table II, there were no significant differences in glomerular capillary pressures measured by these two methods indicating that the differences in the results obtained in rats and dogs regard-

ing glomerular capillary pressure and filtration pressure equilibium were not due to differences in methods used for measurement of glomerular capillary pressure.

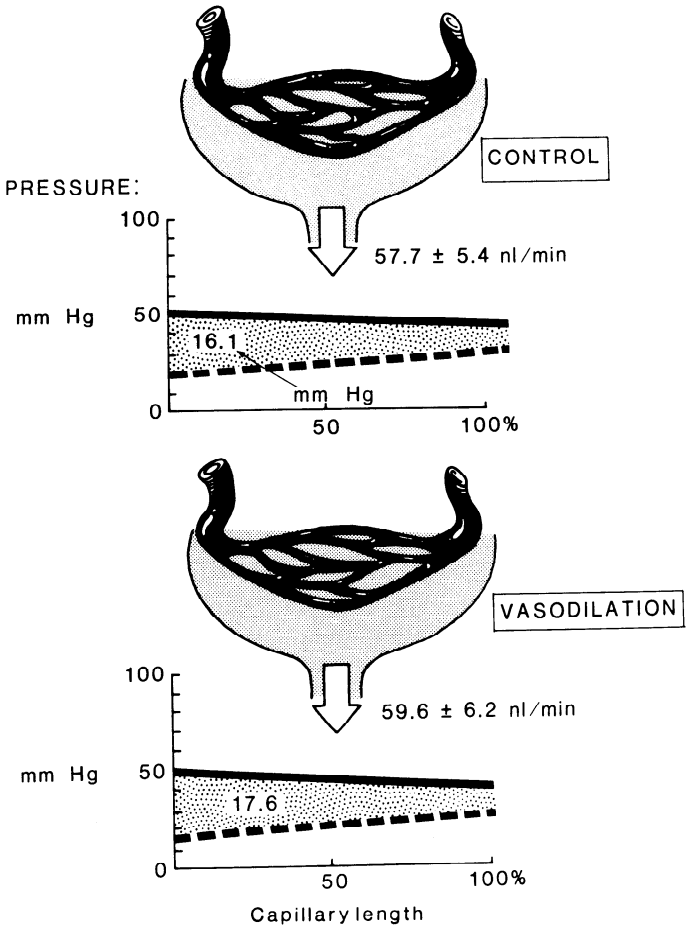


Fig. 3. The effect of vasodilation with acetylcholine on effective filtration pressure and single nephron filtration rate is shown. The effective filtration pressure is not changed because increases in glomerular capillary pressure are offset by equal increases in intratubule pressure.

TABLE I
Hydraulic Permeability of Glomerular Capillaries in Dogs and Rats

	Rats	Dogs	Dogs	Dogs
Blood Pressure, mmHg	120[c]	65[b]	87[d]	120[b]
SNGFR, nl/min	28[a],33[c]	35[b]	56[d]	70[a],69[b]
K_f, nl/min per mmHg	4.8[c]	4.2[b]	4.7[d]	3.2[a],4.3[b]
Filtration surface,[e] $cm^2 \times 10^{-3}$	1.9[c],2.3[a]	4.7[a]	4.7[a]	4.7[a]
k, $\mu l/(min \cdot mmHg \cdot cm^2)$	2.5[c]	0.9[b]	1.0[d]	0.9[b]

Abbreviations: SNGFR, single nephron glomerular filtration rate; K_f, ultrafiltration coefficient; k, hydraulic permeability. [a]From Ref. 15. [b]From Ref. 7. [c]From Ref. 16. [d]From Ref. 17. [e]Per single glomerulus.

TABLE II
GLOMERULAR CAPILLARY PRESSURE
mmHg, Mean ± 1 SE

	Micropuncture Methods	
	Stop-flow	Direct
Munich-Wistar rats (n = 5)	45 ± 0.9	47 ± 0.8
Mongrel dogs (n = 16)	58 ± 2	58 ± 3

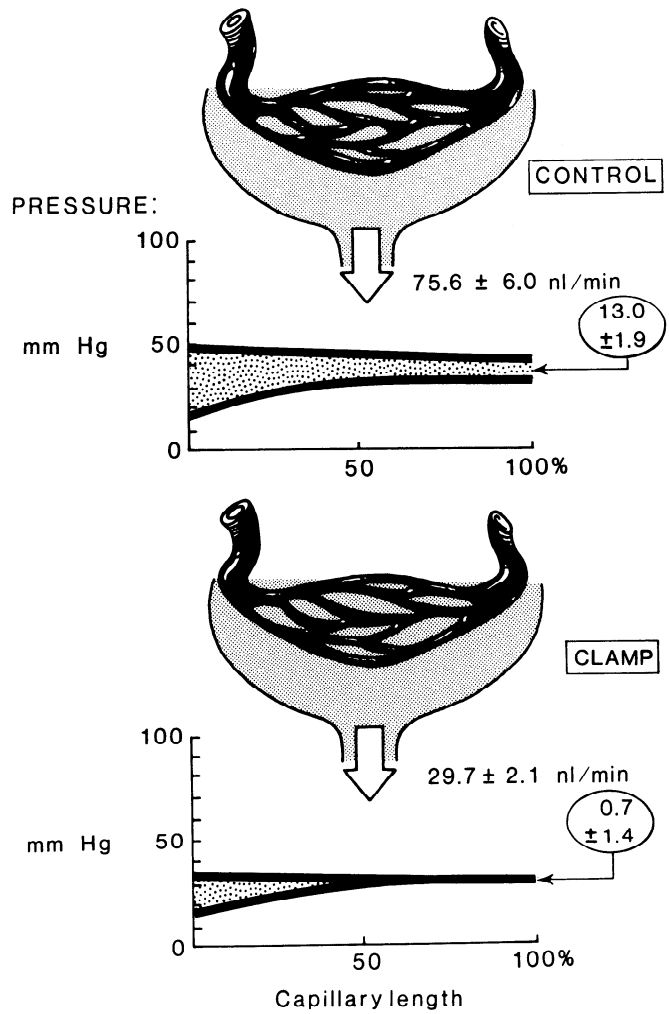


Fig. 4. The effect of reduced perfusion pressure to the kidney in the dog is shown. The filtration pressure at the efferent end of the glomerular capillary was reduced from 13 to 0.7 mmHG.

Thus, we conclude that glomerular dynamics in the dog, and perhaps in man, are characterized by filtration pressure disequilibrium. Accordingly, this may account in part for the very small effects of vasodilation on glomerular filtration rate.

I would now like to turn our attention to exciting recent findings concerning the permeability of the glomerular capillary to large molecules such as protein. Although pores in the glomerular membrane are difficult to directly visualize, it is useful to consider conceptualized pores in the glomerular capillary of approximately 20 to 30 angstroms in radius (Fig. 5). Hence, small molecules such as inulin with an effective radius of 14 angstroms can easily

penetrate the glomerular capillary and enter Bowman's space. Of course, inulin is the classic marker utilized for measurement of glomerular filtration rate. The notion that the radius of these pores lies between 20 and 30 angstroms comes from the fractional clearances of dextrans of various sizes (Fig. 6). Thus, the fractional clearances of dextrans with an effective radius of 18 angstroms is complete whereas the fractional clearance of dextrans over 40 angstroms is negligible. An important consideration is that the charge of the macromolecule and the charge lining the pores of the glomerular capillary is a very important determinant of the fractional clearance of these macromolecules (15). For example, as in Figure 7, positively charged dextrans are facilitated in their passage through the glomerular capillary through charge attraction. Conversely, as shown in Figure 8, negatively charged, anionic dextran sulphate is retarded in regard to permeation of the glomerular capillary by charge repulsion.

Since protein is also an anionic macromlecule, the normal fractional clearance for albumin is less than that for a neutral molecule of the same size. However, in glomerular disease or injury, a loss of charge on the glomerular capillary results in enhanced fractional clearances of albumin because of the loss of the charge effect (Fig. 9).

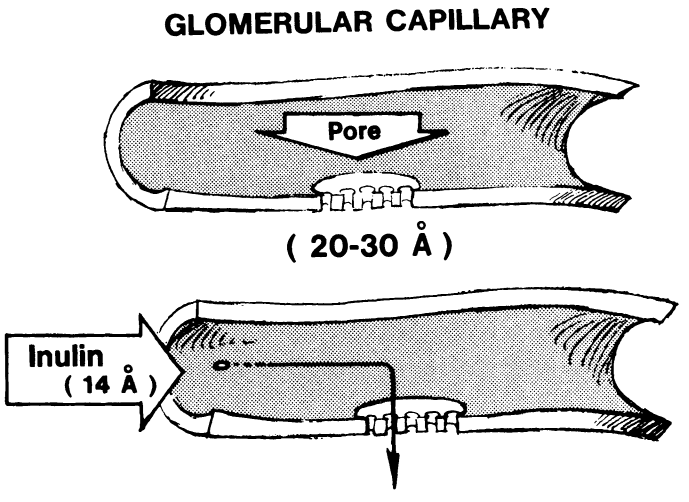


Fig. 5. A highly schematic representation of the glomerular capillary is depicted.

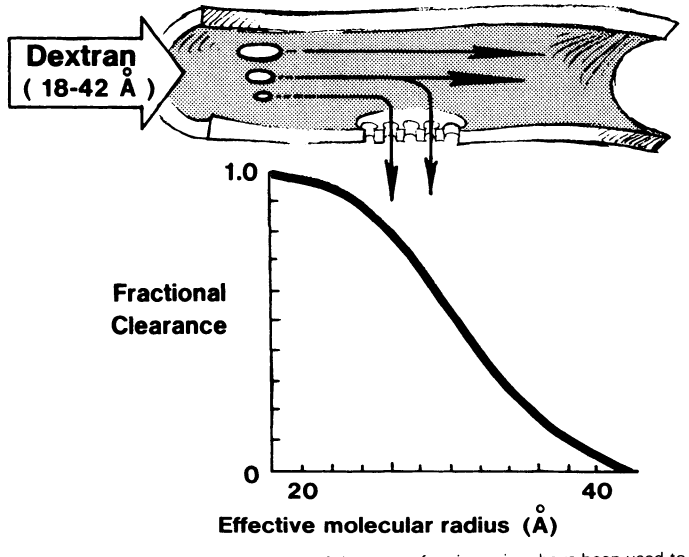


Fig. 6. The fractional clearances of dextrans of various sizes have been used to estimate effective molecualr radius.

These physiologic findings have been recently reviewed by Brenner et al (9), and correlated with structured findings by Venkatchalam and Rennke (10). In brief, these negative fixed charges on the glomerular capillary have been correlated with anionic structural components of the capillary wall utilizing morphologic studies and selective binding of cationic stains. Binding

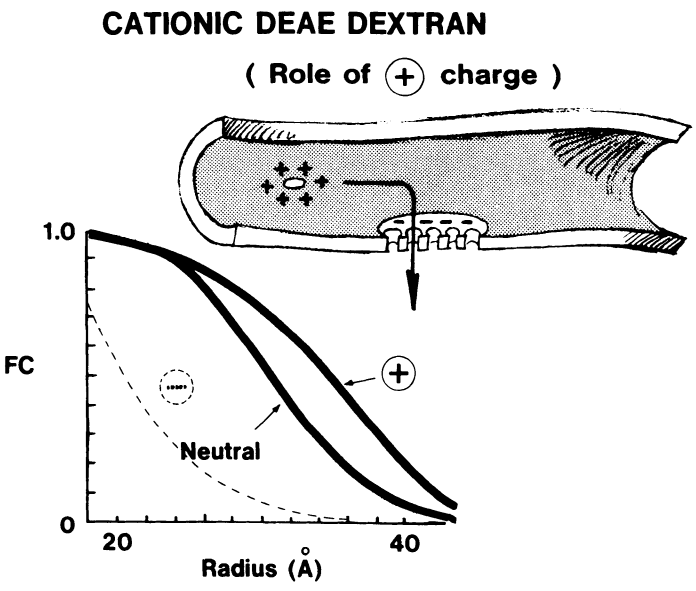


Fig. 7. The fascilitated filtration of positively charged molecules is illustrated.

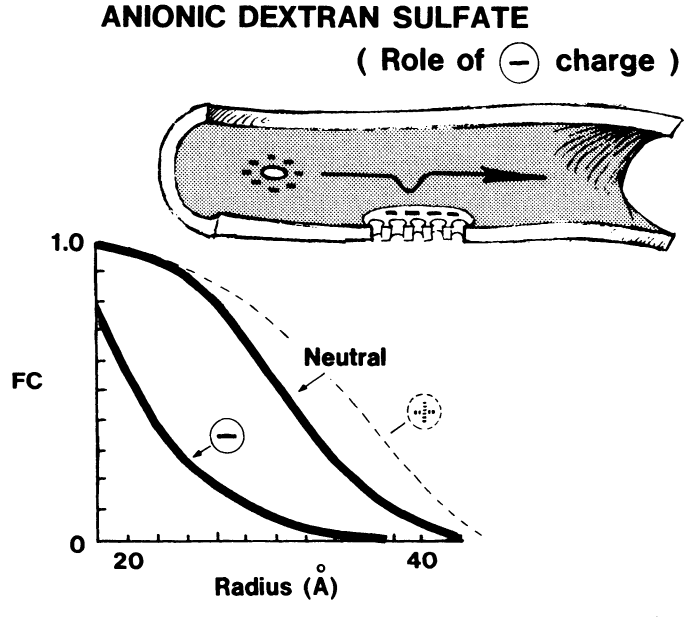


Fig. 8. The retarded filtration of negatively charged molecules is illustrated.

of cationic substances has been demonstrated for all layers of the glomerular capillary wall. In this regard, it has been known for some time that the glomerular epithelial cell and its foot processes are covered with thin layers of acid glycoprotein which are negatively charged. Michael and Blau have demonstrated that in glomerular diseases associated with proteinuria, there is a reduction in the sialic acid surface coat (11, 12,13). Recently, Andrews

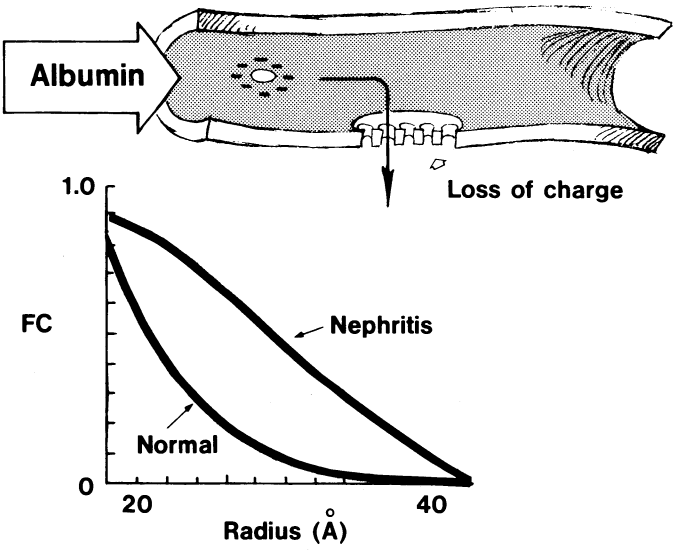


Fig. 9. The loss of charge in the glomerular capillary wall increases the fractional clearance of albumin and may contribute to the proteinuria characteristic of nephritis.

documented that the glomerular epithelial alterations of experimental nephrosis could be reproduced in vitro by removal of the sialic acid surface coat with neuromidase (14). Thus, it is widely held that a reduction in cell surface polyanionic charge may lead to reduced electrostatic repulsion between proteins and the glomerular membrane. These recent studies provide an excellent foundation for further characteriaztion of the mechanisms for proteinuria in glomerular disease.

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A.B.L.E. ANNUAL MEETING

The Association for Biology Laboratory Education, A.B.L.E., will hold its annual meeting/workshop, June 2-6, 1980 at the University of Illinois at Urbana campus. The purpose of the meeting is to exchange ideas on creative, innovative techniques used in the teaching laboratory. Scheduled workshops will accompany the meeting. For more information contact:

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NON-INVASIVE VISUALIZATION AND QUANTITATION OF CARDIOVASCULAR STRUCTURE AND FUNCTION†

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Introduction

A new approach to investigative physiology, based on computerized transaxial tomography, is currently under development. The purpose of this presentation is to demonstrate that this new approach enables the investigator to non-invasively* visualize and measure the internal structure (e.g., size and shape) of the cardiopulmonary system much like a pathologist does at postmortem and to measure dynamic structure and function (e.g., stroke volume and regional myocardial blood flow) much like a vivisectionist. Because this capability is expected to provide most of the data currently available in man and experimental animals only via highly invasive procedures such as postmortem, biopsy or vivisection, we have elected to describe this approach as "non-invasive numerical vivisection." The "numerical" description indicates that the "biopsy" and "dissection" procedures are strictly numerical in nature and are based on computer processing, display and analysis of the time-varying three-dimensional image and associated functional data with no requirement for additional x-ray exposure or patient involvement.

Method of Approach

Implementation of non-invasive vivisection has technical requirements not met by any commercially available computerized transaxial tomography scanners. A high temporal resolution "volume" imaging system, the Dynamic Spatial Reconstructor (DSR) which is currently undergoing fabrication, has been designed to provide three basic requiremets for non-invasive vivisection. This device (see Figure 1) is described in detail elsewhere (1,2).

A *volume* must be imaged so as to ensure that the region, or section, of interest in an organ is imaged even though the location of this region, or most useful orientation of a section through the organ, is not known until after the image data have been reconstructed and scrutinized. Figure 2 illustrates how this is achieved with the DSR scanner system.

The volume must be imaged *synchronously.* A "volume image" of the cardiovascular and pulmonary systems could be "synthesized" from successive ECG-synchronized ("gated") scans of many contiguous parallel cross sections. This volume image is, however, likely to be distorted. The long series of successive cardiac cycles which would be required to obtain ten to fifty contiguous cross sections encompassing the full axial extent of the heart requires that physiologic stationarity** be maintained. This is generally not possible even in the presence of cardiac pacing and breath-holding. Some of the common causes of absence of stationarity are arrhythmias, respiration, variable autonomic activity, and the transient nature of angiography. Imaging of the volume must be in *stop action* so as to reduce motion blurring to the point where it does not degrade spatial and density information within the image. As movement is a fundamental function of the heart, circulation, and lungs, the volume must be imaged *repetitively* so as to permit evaluation of dynamic changes of shape and dimensions.

The required "aperture" time and "frame" rate for adequate stop action and motion imaging is intimately dependent on the structural and functional data desired. For example, spatial resolution of cardiac images of approximately 1 mm would permit visualization of the lumen of major branches of the coronary arteries, quantitation of the size of a moderate (40 g) transmural infarct to within 5% and detection of a 5% change in left ventricular wall thickness. The image "aperture" time should be such that motion occurring in this time is less than one spatial resolution element (1 mm). As the endocardium moves at approximately 100 mm/second during systole (3), a scan time of less than 0.01 second is required. In addition, there should be the capability of rescanning the entire axial extent of the heart at a repetition rate greater than 20/second (4,5) to allow adequate description of the dynamic geometry of the heart during the systolic ejection phase and of vascular morphology during transient "first pass" angiography.

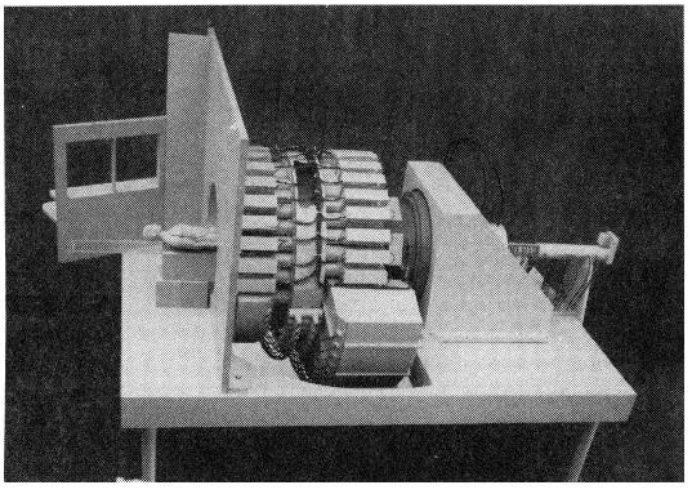


Fig. 1. Photograph of scale model of dynamic spatial reconstructor system. Patient lies on horizontal radiolucent table. Twenty-eight x-ray sources are mounted along semicircle below patient so that corresponding projection images of patient are formed on 12-inch-wide semicircular fluorescent screen suspended above patient. Mechanical rotation of entire circular structure permits scanning at many angles of view over range up to 360°. Slip rings mounted along horizontal shaft permit continuous rotation at 15 revolutions per minute. Gantry would be located in room separated from patient area by soundproof wall. Patient and clinicians would see only stationary tunnel opening in one wall of laboratory.

† Tutorial Lecture presented at the October 1978 Fall Meeting, St. Louis.

* Non-invasive is used here to indicate that measurements of anatomic structure and related biologic functions can be made without altering or controlling the static or dynamic anatomic structural and functional relationships of the heart or circulation that are being studied.

** In this context, stationarity means exact reproducibility of the position and movement of all parts of the body being imaged during successive respiratory and cardiac cycles during the period required for the scanning procedure.

NON-INVASIVE NUMERICAL DISSECTION
(DSR Based Synchronous, Stop-Action Volume Scanning)

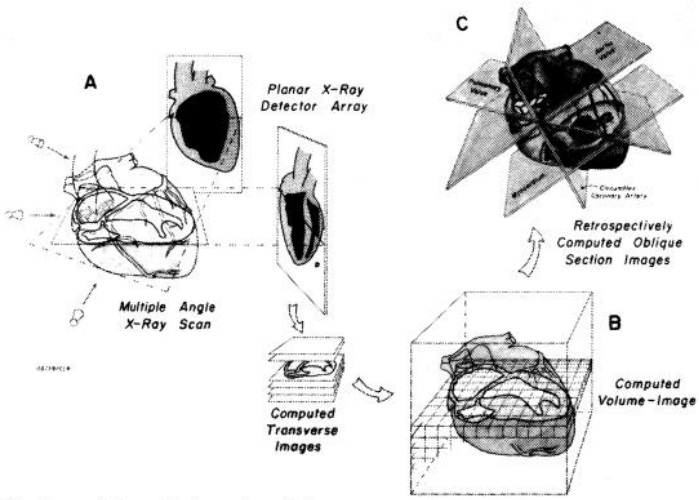


Fig. 2. Schematic flow chart of the sequence of procedures performed by the Dynamic Spatial Reconstructor system for generation of volume images (Panel A) which can be mathematically reprojected for viewing in their entirety (Panel B) and viewed following mathematical sectioning in arbitrary orientations and locations (Panel C). *Panel A*: X-ray images of the chest and its anatomic contents (e.g., heart) are recorded from many angles of view around the patient or experimetal animal. This information is used to generate the data ("stack" of images of parallel transverse sections) required for a volume image using a reconstruction algorithm. *Panel B*: Synthesis from up to 240 parallel, 1 mm thick, cross sections of the chest and its contents results in three-dimensional array of little cubic picture elements (voxels) each with a grey scale value. By appropriate mathematical transformation (reprojection), x-ray-like images of the contents of this volume image can be generated from any selected angle of view which may correspond to a true x-ray or from a vantage point which cannot be achieved by an actual x-ray projection device. *Panel C*: This illustrates the need for sectioning this volume image in arbitrary orientations and locations. Section I (myocardium) and parallel contiguous sections would be required for measurement of regional myocardial wall thickness: Section II (pulmonary valve) would be required for measurement of pulmonary valve area whereas Section III (circumflex cornary artery) is representative of many multi-orientated adjacent (and often intersecting) contiguous sections required for visualization of coronary artery cross sections along the length of tortuous multi-orientated major branches of the coronary arterial tree.

The density resolution of the reconstructed image should ideally permit detection of the time-dependent changes in the roentgen density of the myocardium which occurs, for instance, distal to stenosis or obstruction of a coronary artery at various stages of ischemic episodes or infarction processes. Detection of the 1% change in roentgen attenuation between normal and infarcted myocardium (difference in roentgen opacity of water and air being 100%) is desirable (6) but probably not necessary for detection and quantitation of infarct location and size. Data of Doherty et al. (7) show that roentgen opacity of normally perfused myocardium increases by approximately 5% following "first pass" passage of a 1 ml/kg intravenous bolus injection of roentgen contrast agent whereas myocardium deprived of blood supply does not change reoentgen opacity during the initial passage of the bolus of contrast agent. Siemer et al. (8) have demonstrated that approximately five minutes following injection of 2 ml/kg contrast agent into a peripheral vein, ischemic myocardium selectively retains the roentgen contrast agent for hours. The roentgen opacity differential between ischemic and normally perfused myocardium is approximately 2%.

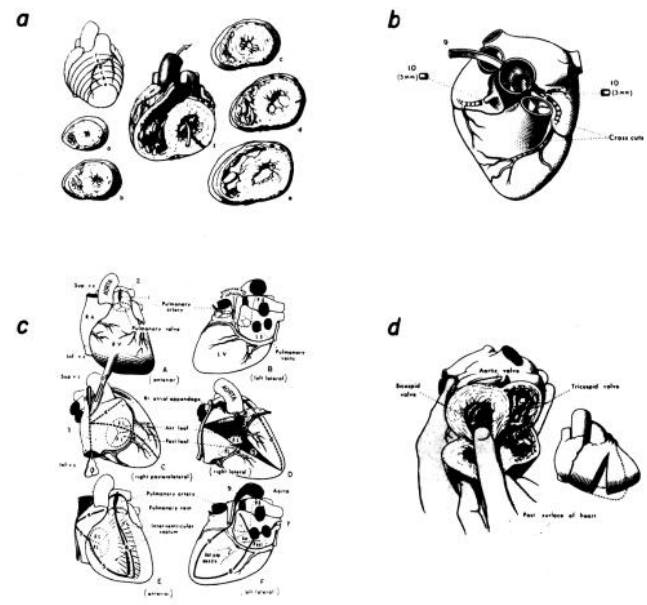
The DSR has been designed to meet these resolution requirements. The design of the DSR permits high temporal resolution,low spatial and density resolution scans (10 msec "aperture" time at a 60/sec repetition rate), medium temporal, spatial and density resolution scans (60 msec with 60/sec scans overlapping in time) and low temporal resolution, high spatial and density resolution scans (2.14 seconds). The importance of this flexibility (i.e., selectable tradeoffs between decreased temporal resolution and increased density resolution) has been indicated by computer simulations (9).

The DSR is to be installed in mid-1979 and evaluated over a period of several years. Technical feasibility of this approach has been demonstrated with a single source dynamic spatial reconstructor (SSDSR) over the past three years (10,11). This prototype system has the disadvantage that many seconds are required to obtain the image data - hence synchronization of respiration and heart beat had to be artificially induced by gated imaging.

Consequently, several applications for which the DSR will be particularly suited, such as imaging of dynamic distribution of contrast agent in the blood stream, which occurs during angiography, are impossible. In addition, lack of true physiologic stationarity in the experimental animal and spatial and grey scale non-linearities of the imaging system result in inaccuracy of the image to an unknown extent.

The main value of the SSDSR, notwithstanding these limitations, has been to indicate technical feasibility and qualitative indication of the utility of dynamic volume images. Quantitative analysis of these prototype images indicate accuracy of the estimates that is superior to that possible with conventional techniques such as cineangiography and echocardiography.

TECHNIQUES FOR
DISSECTING HEART POST-MORTEM*
(Illustration of Value of Interactive 3-D Display)



*US Armed Forces Institute of Pathology Autopsy Manual, 1960

Fig. 3. Four approaches to postmortem dissection of the heart. Selection of any one approach often eliminates the other approaches. Approaches illustrated in the four panels can be emulated in the numerical "volume" image as illustrated in Panel C of Figure 2.

Results and Discussion

The analogy between postmortem examination techniques and the DSR-based non-invasive vivisection technique is useful because many of the procedures used in postmortem examination are equally applicable to non-invasive vivisection. Numerical dissection of the DSR-generated volume image has some advantages over direct dissection, however. For instance, the problem of destroying structural relationships by dissection has resulted in a fairly rigid "ritual" of the postmortem procedure (see Figure 3). Because of the non-invasive nature of non-invasive vivisection, however, it is not necessary to restrict dissection to a preselected approach to the exclusion of other approaches.

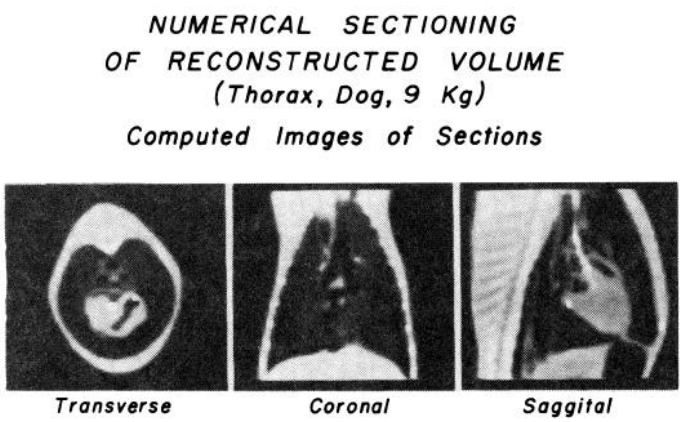


Fig. 4. Computer generated images of three sections of the chest of a dog; transverse, coronal, and sagittal. A volume image of the chest was obtained by the prototype SSDSR scanning system. Multiple transverse sections would be particularly useful for delineation of the lungs for estimates of lung volume, coronal sections through the trachea for evaluation of airway obstruction and the sagittal sections for evaluation of spinal canal continuity. (Reproduced with permisssion from Harris et al., "Computation and Display of Cylindrical Scanning Tomographic Image Data," Society of Computer Medicine (In Press)).

As the identity and location of a lesion of interest is usually not obvious at first, the capability for "scanning" the entire volume image becomes very important. This problem and a sloution is discussed in detail elsewhere (12). Briefly, overview of a volume is most readily provided by "reprojection imaging" - a numerically generated projection image analogous to a transmission x-ray projection image or radiograph (see Panel B, Figure 2). This approach allows one to numerically create an "x-ray" of the volume image and thereby look through the body from any angle of view. On the basis of this image, a suitably oriented section (or cut) can be made through the volume image. As indicated in Panel C of Figure 2, the location and orientation depends very much on the object of interest. Figure 4 illustrates three orthogonal cuts through a dog's chest. In the case of the coronal section through the entire extent of the airway, the presence, location, and to some extent severity of localized pathology of the trachea could be obvious in one image. For parameters requiring analysis of three-dimensional morphology of, for instance, the heart, the location of the heart must first be identified and then isolated (i.e., numerically "excised") to permit detailed analysis. Either operator initiated or automated identification (13) of the epicardial and endocardial borders of the heart allow convenient analysis of cardiac anatomy as illustrated in Figure 5. This type of pre-analysis image mainipulation is essential for quantitative analysis (14) such as delineation of valve rings for estimation of orifice area and of myocardium for estimates of ventricular muscle mass, etc. Figure 6 illustrates the accuracy with which left ventricular myocardial mass and left ventricular chamber volume have been estimated using the SSDSR system. Note the good correlation with stroke volume although muscle mass varied relative to the postmortem weight. In view of the good correlation of muscle mass obtained in scans of the postmortem ventricle, this variability in muscle mass in the working ventricle may be due to varying amounts of blood in the muscle depending on such variables as aortic pressure and transmural pressure.

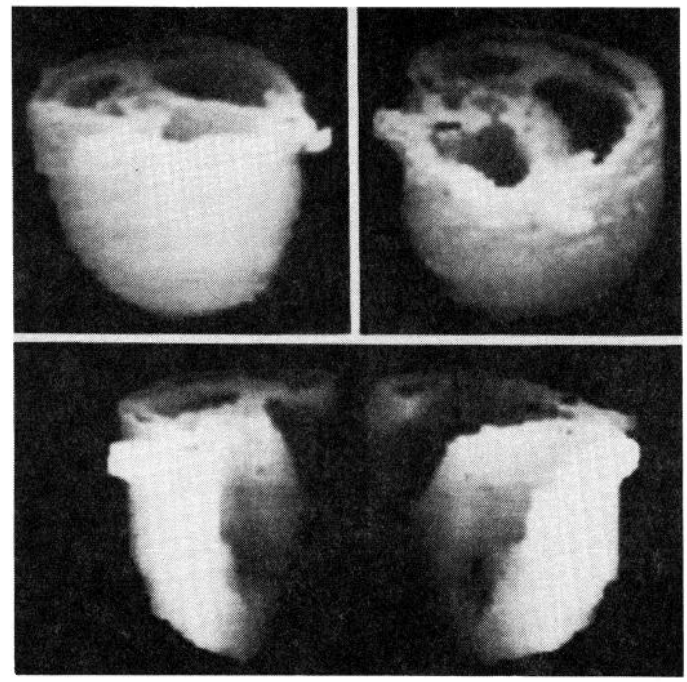


Fig. 5. Computer generated display of three-dimensional perspective display of a canine heart. The data used to generate these images was generated as follows: Injection of 1 ml/kg of roentgen contrast agent into a peripheral vein results in distinct delineation of the endocardial surfaces of the heart imaged in multiple parallel transverse section images of the heart. Automated or operator assisted outlining of the epi- and endocardial surfaces of the heart in each of the multiple parallel transaxial images encompassing the base to apex extent of the heart is performed. Computer programs developed by Liu (13) use the outline data to "reconstruct" the three-dimensional arrangement of the epi- and endocardial surfaces to produce the "hidden surface" perspective image illustrated here. This image can be rotated to allow visualization from any angle of view and the image can be "dissected" to permit visualization of internal structure. The power of this approach is that the "dissection" can be "undone" and repeated for different aspects as often as desired. (Reproduced with permission from Robb et al., "Computerized x-ray reconstruction tomography in stereometric analysis of cardiovascular dynamics," Proceedings of the Society of Photo-Optical Instrumentation Engineers 89:69-82, 1976).

Coronary artery morphology holds its own interest as shown in Figure 7. The coronary artery reprojection image can be enhanced by the use of numerical dissolution of the myocardium. Note that in this particular view, the left circumflex coronary artery obscures the septal artery. By rotating the heart in three-dimensional space - that is reprojection from different angles of view, superposition can be overcome. This does, however, involve much computer time and time spent by the viewer. A more useful method is to "numerically" slit the heart wall down the dorsal/inferior aspect of the left ventricle, and opening the wall and laying it flat. This is achieved by radial reprojection (12) as indicated in Figure 8.

In additon to providing a measurement of coronary artery stenosis, the DSR will provide a direct indication of the three-dimensional distribution of myocardial perfusion (see Figure 9) and of myocardial function (see Figure 9) in the region of the

myocardium perfused by the stenosed vessel. This information, plus simultaneously acquired myocardial function assessed in terms of regional wall dynamics (15) is likely to more directly answer the question as to the seriousness or threat of a stenosis to a patient than does knowledge of only the size and location of a stenosis.

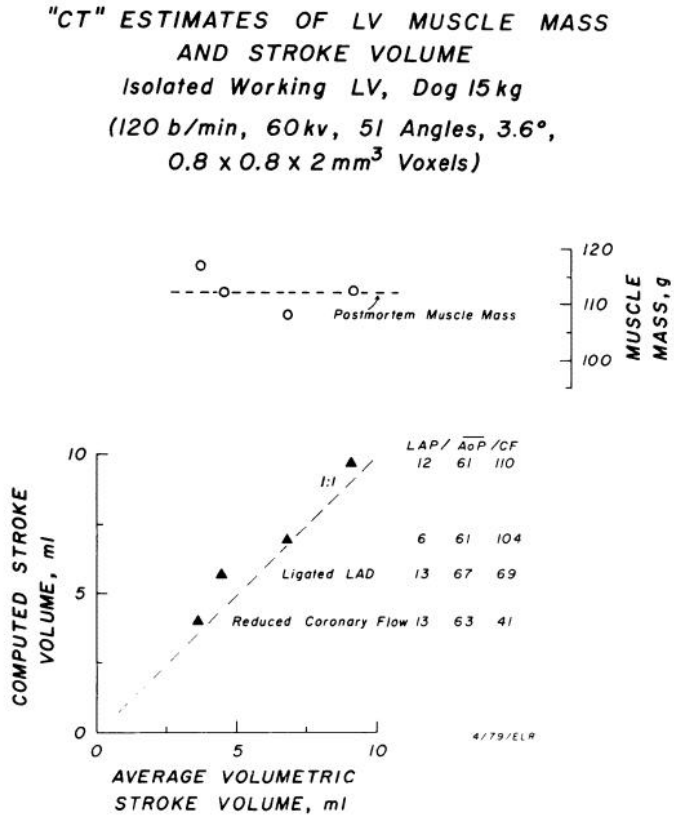


Fig. 6. Stroke volumes in four different cardiac cycles computed from cross sections (35 base to apex cross sections, 2 mm apart in each cardiac cycle) reconstructed by CT volumetric scanner, SSDSR, closely correlated with "average stroke volumes" measured during the experiment in an isolated, working canine left ventricle. A heart rate of 120 b/min was maintained by cardiac pacing throughout the experiment. An average of computed end diastolic and end systolic muscle mass was within ± 5% of directly measured muscle mass at the end of the experiment. The computed muscle mass was obtained by subtracting total endocardial volume from total epicardial volume at each instant in a cardiac cycle and then multiplying this myocardial volume by myocardial density. LAP: Mean left artrial pressure; AoP: Mean aortic pressure: CF: Coronary flow.

Conclusion

A technique for accurate measurement of dimensions, appreciation of three-dimensional morphology, and spatial distribution of perfusion can be made without resorting to the assumptions (e.g., ellipsoidal shape of left ventricular chamber) or invasive techniques (e.g., implanted flow meters, ultrasound crystals or injection of microspheres) currently necessary. These approaches can be applied also to emission tomography (16-19) and ultrasound tomography (21) and to other energy forms (22). Before full advantage is taken of the approach, however, many theoretical and practical questions as to the scanner components, geometry, and mathematical considerations need to be answered.

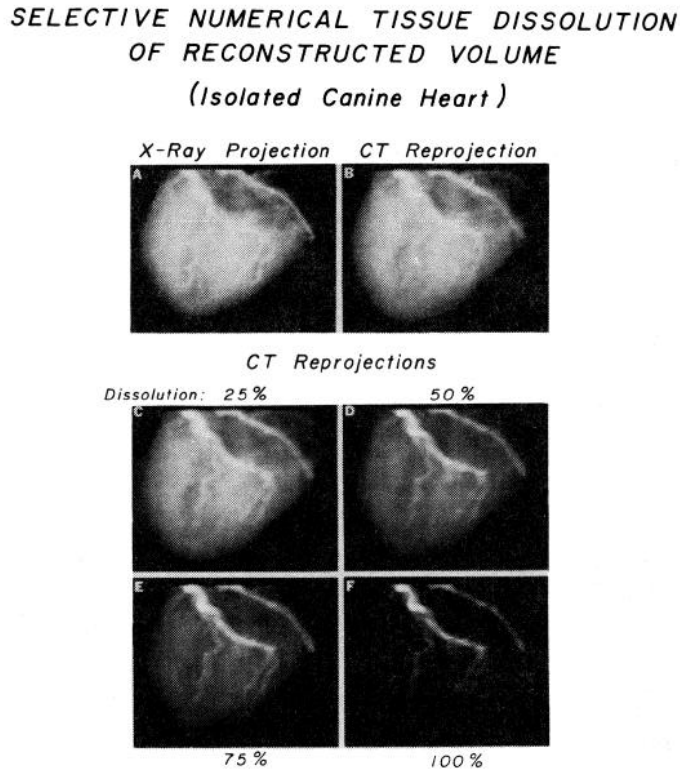


Fig. 7. Comparison of radiograph (Panel A) of isolated canine heart with x-ray contrast medium in the coronary arteries and reprojection images (Panel B-F) illustrating selective numerical "dissolution" of the myocardium. Reprojection images are shown of the reconstructed heart before "dissolution" (Panel B) and after dissolution of the myocardium by 25%, 50%, 75%, and 100% in Panels C-F. (Reproduced by permission from Harris et al. (12)).

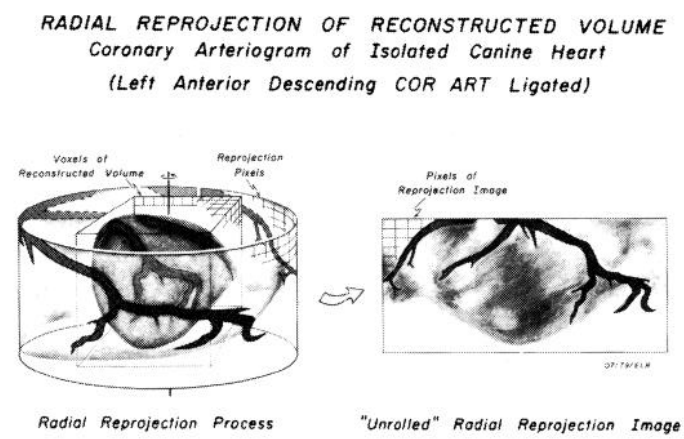


Fig. 8. Diagram of radial reprojection process. Voxels of reconstructed volume are radially projected onto pixels arranged on the surface of a cylinder which surrounds the reconstruction. Eight representative radial reprojection summation paths are shown (dark arrows). The cylindrical surface is "unrolled" mathematically and the reprojection image (right) can be displayed on a television monitor as a two-dimensional image using a digital-to-video display device. Left anterior descending coronary artery was not filled because it was ligated near its origin.

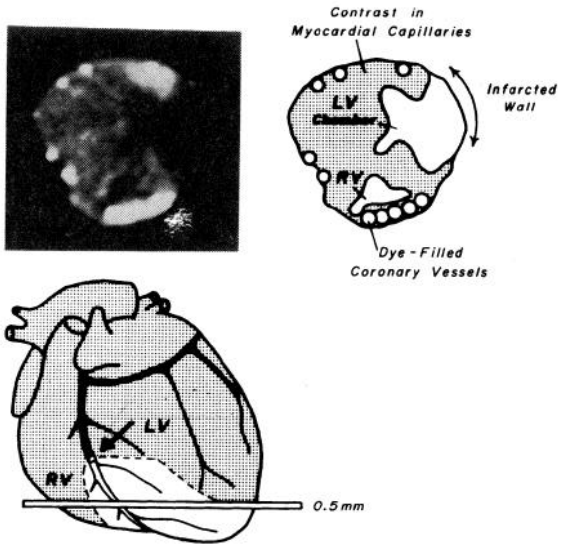


Fig. 9. Use of transverse section image of heart (at location indicated by lower panel) to indicate epicardial coronary (bright spots) and transmural distribution of roentgen contrast agent (i.e., blood "content" of myocardium). A branch of the left anterior descending coronary artery was ligated in an anesthetized dog. Contrast agent was injected into the right coronary and left main coronary arteries and the heart arrested so as to permit a 14 second duration scan in the prototype SSDSR scanner. The gap at "3 o'clock" consists of both blood filled chambers and unopacified free left ventricular wall. The roentgen opacity of blood and unperfused myocardium are virtually identical and hence indistinguishable in this photograph.

Acknowledgements

The authors acknowledge Mr. Ralph Sturm who did much of the early work in the design of the DSR and the assistance and suggestions from many colleagues in the Biodynamics Research Unit. Expert technical assistance was provided by Messrs. R. W. Roessler, C. R. Hansen, and M. A. Wondrow. Thanks to Ms. M. C. Fynbo and Ms. M. A. Engesser and their colleagues for preparing the manuscript and illustrations.

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Design and Analysis of Experiments in the Animal and Medical Sciences(Vols. 1,2,3). John L. Gill. Iowa State Univ. Press, Ames, 1978. (430, 310, and 182 pages, illus., $14.00, $11.00 & $7.00).

For the physiologist beyond a one-semester statistics course, but without the time or inclination to be a professional statistician, John Gill's three-volume work will provide an excellent reference. Too often we accept a simple t-test between means, or use a Computer Center package without understanding its inherent assumptions. "A sharp axe is dangerous in the hands of a blind woodsman," according to Gill. In describing the various tests, Gill gives the model, some theory, the computational procedure, and then the appropriate tests. His style is almost conversational. His goal was to chart a course "in the middle channel between the depth of mathematical theory and the shallows of a few pat formulas." He has succeeded. References to the original literature and pithy quotations abound. From his present position as professor of biometry in Dairy Science, his examples and exercises are almost exclusively physiological—a welcome difference from books by statisticians working with social scientists. Not only are the usual topics covered, but also the more sophisticated topics of multivariate analysis and analysis of covariance. In Volume 2, extensive discussion is given to the problem of lack of complete randomness that occurs when each animal of a group is followed in time with repeated samples taken or treatments given.

Although very high quality paper is used, the publisher has used a common typescript. This distraction is soon overcome as one begins to appreciate the careful use of italics, Greek letters, capitals and boldface (for vectors and matrices) to provide some order out of the chaos of statistical notation. The notational conventions used were selected to conform as closely as possible with the recommendations of the Committee of Presidents of the Statistical Societies.

The Appendix (Volume 3, paperback) is a delight of easy reading, extensive tables and a series of 21 figures to estimate the power of various statistical tests (probabilities of error of Type II — failure to obtain a significant difference though a real difference exists in the "population"). A glossary of symbols and answers to odd-numbered exercies are included.

A major thrust of this book is the design of experiments, including the discriminatory power of various alternative tests and the sample size required for significance, given an estimate of variability. Because non-parametric tests are "not exonerated from a requirement of equal variance," even though the distribution may be highly non-normal, Gill gives little discussion to these approaches, but instead provides extensive discussion on the design of experiments and the effect of departures from normality.

Although these books are probably too sophisticated for beginners, the students using them as a text would have a firm foundation, a good source for further growth, and an excellent reference. For the scientist seriously concerned about using powerful and adequate statistics, they are an excellent source of help and understanding.

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Basic Biology Course: Unit 4, Communication Between Cells; Book 11 - Hormones. M.A. Tribe and M.R. Eraut. Cambridge Univ. Press, New York, 1979. 223 pp. 32 figs. Hardcover $23.50; Limp $7.95.

This course is constituted of a series of learning manuals. The present volume aims to instruct the student in those aspects of intercellular communication mediated by the circulation or diffusion of specific chemical entities identified as hormones. The attempt is made to do this by succinct representation of the pertinent "facts" in bold statements and diagrams directed at the accomplishment of specific teaching "objectives." As a result the substantive content becomes too sparse and too dogmatically presented to engage the student's geuine intellectual interest. Moreover, such presentation fails to impart an appreciation for the proximate nature of scientific knowledge and for the continuing struggle necessary to find a clear distinction between what is really known and what is inferred. These limitations are balanced by the very definite advantages of clarity, explicitness, and brevity. However, in this reader's view, this volume may serve to make the learning of a limited amount very easy for the student, but it will totally fail to induce him to learn a lot. Teaching thus becomes simply the transfer of information rather than the induction of sustained interest and enthusiasm. The latter requires style which is totally lacking in the sterile format of this volume.

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Basic Biology Course: The Enzyme Game. Derek Peacock and Michael Tribe. Cambridge Univ. Press, New York, 1979. 70 pp. illus. (Price not set)

The Enzyme Game is a cleverly designed exercise for students to test and extend their knowledge of the experimental characterization of enzymes. Using a prior basic understanding of proteins in general and enzymes in particular, a group of students (the "research group") is challenged "to determine as far as possible the structure and mechanism of action of an enzyme." At the start, a minimal set of information about the enzyme (a real-life case known to the instructor) is provided to the group, along with a summary of possible experimental techniques that could be used for further characterization. The students then must decide which experimental studies to pursue and obtain pertinent data sets from a data bank held by the instructor. The time needed to plan experiments and assess data is provided by "research grants" obtainable from the "Research Council" (also the instructor). While an initial grant of time is provided at the beginning of the game, further time needed to complete the objective is earned by presentation of periodic written and oral reports to the "Council" as well as mock publications for the "Journal of Enzymology." The entire exercise requires approximately 6-9 hours, which can be subdivided into 1-1/2 hour periods. This makes the Game a convenient teaching tool adaptable to laboratory or workshop sessions that may be associated with regular biochemistry course work.

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Uterine Physiology: Proceedings of a Brook Lodge Workshop. E.A. Friedman, M.L. Noah, and B.A. Work, Jr., Eds. P.S.G. Publishing Co., Littleton, Mass., 1978.

The comprehensive title of this highly limited monograph stands in direct contrast with restricted scope of the book's content. The text of 130 pages consists of very brief and, at times, superficial coverage of such varied topics as uterine contractility and circulation, cervical dilatation, and mechanisms of labor. These presentations are too brief to be especially informative and their content is for the most part a repetition of material already easily available elsewhere. The discussions provide little additional insight into the subjects covered.

The book serves only to provide a public record that this group of authors convened under the stated auspices and cursorily renewed the cited topics. There would be little impetus for either the clinician or physiologist to acquire this added volume.

Roy Hertz

The Mechanics of the Circulation. C. G. Caro, T. J. Pedley, R. C. Schroter, and W. A. Seed. Oxford Univ. Press, 1978. 543pp. 268 illus. $46.00.

This book is a product of collaboration of a physiologist, a mathematician, an engineer, and a physician. The collaboration is remarkably smooth. Like a good sculpture which leaves no chisel marks on the marble, there are no marks of individual specialization in this book. All is well integrated toward the physiology of circulation. Mathematics is avoided whenever practicable, and mechanics is presented in readily comprehensible terms.

The first part presents the basic ideas of fluid and solid mechanics without tears. The style should be especially receptive to students of physiology and medicine. The second part deals with the mechanics of circulation. In six chapters, the authors discuss successively the blood, the heart, the systemic arteries, systemic microcirculation, systemic veins, and pulmonary circulation. The presentation is masterful and up-to-date. Current concepts are critically evaluated. Many of the original contributions are the authors'.

Stressing mechanics in the study of circulation physiology is not new, but a book dealing exclusively with this subject is. The authors have made the case that mechanics is useful to physiology very convincing. After reading the book, one would wonder how can circulation physiology be understood without such a study of mechanics. It cannot! I recommend this book to all physiology teachers and students.

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PROCEEDINGS OF THE FIRST ANNUAL MEETING OF THE INTERNATIONAL COMMISSION OF IUPS ON GRAVITATIONAL PHYSIOLOGY

- To the memory of Otto H. Gauer († 22 January 1979), Member of the Commission since its start in 1974

The First Annual Meeting of the International Commission of IUPS on Gravitational Physiology was held in conjunction with the 30th Annual Fall Meeting of the American Physiological Society, October 15-19, 1979, in New Orleans, Louisiana. The activities of the Commission were conducted in its capacity of Guest Organization of APS. They included an Open Meeting and a Symposium entitled "Procedural Approaches to Gravitational Physiology."

The following 88 pages contain the proceedings of the meeting, which are published by arrangement with APS and with the support of NASA. We hope to find ways and means to publish also the proceedings of future meetings - the Second Annual Meeting will be held during the XXVIII International Congress of IUPS in Budapest, July 13-19, 1980.

Areas encompassed by the Commission's activities include the effects on physiological systems of humans, animals and plants of changes in magnitude or direction of the force environment, such as in the weightlessness of space flight, in acute and chronic acceleration, in vibration, and in simulated weightlessness. Also included is the role of gravity in the manifestations of scale effects in animals and plants. The following papers deal with various aspects of many of these areas.

H. Bjurstedt, Sweden, Chairman
O. G. Gazenko, USSR
R. Margaria, Italy
N. Pace, USA
H. Saiki, Japan
A. H. Smith, USA