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EDITORS PAGE

PARTICIPATION OF SOCIETY MEMBERS IN EDUCATION ACTIVITIES

The back cover of our brochure on "A Career in Physiology" carries a note to the effect that the central office of the society will supply the names of physiologists in any particular area who will be willing to give additional information on physiology and career planning. The response to this note has been far beyond expectation, about 50 inquiries a week.

We have been supplying the names of Society members in various areas with the hope that if they are contacted they will give advice to these young people. The Education Committee feels that this type of personal contact is one of the best means of recruitment. The brochure has whetted the appetite of many young students and we feel that one of the best means of following up this original stimulus is for the prospective student to talk with a professional physiologist. We hope all members of the Society will cooperate if called upon.

If we are to meet the demands for more trained physiologists we must recruit graduate students early in their training. Senior high school and early college is not too soon. The central office will continue to give out names of physiologists in particular areas. If any Society member does not desire to be contacted he should inform the central office of the Society.

LETTER TO EDITOR

Dear Sir:

I want to call attention to "The Jefferson-Dunglison Letters" recently published by the University of Virginia Press as edited by John M. Dorsey. I think that American physiologists will be delightfully surprised to find that they have a heritage in a new book. This Americana portrays the personality of Robley Dunglison in association with the last years of the life of Thomas Jefferson and the first years of the University of Virginia.

Among other features, there is a compact informative biographical sketch of the pioneer physiologist who wrote such highly regarded works as, "Human Physiology," "Elements of Hygiene," "General Therapeutics," "Syllabus of Lectures on Medical Jurisprudence," and "Medical Dictionary." In addition

to his many administrative duties connected with medical education, he took a lively interest in the experiments on digestion by William Beaumont, cared for a large family, and was physician to four presidents of the United States -- Jefferson, Madison, Monroe and Jackson. Dunglison was with Jefferson the final week of his life at Monticello and records his last words: "Is it the fourth?" To this our physician-physiologist replied: "It soon will be," and Jefferson "ceased to exist" at about one o'clock of the 4th of July exactly 50 years after his signing of the Declaration of Independence.

The letters themselves are "one of the most absorbing sets of documents in American medical history." It takes the reader behind the scenes of history. First, there is the arrival of Dunglison from England as imported talent for the faculty of the University of Virginia selected by a special agent sent to the Universities of Oxford, Cambridge and Edinburgh. The problem securing anatomical preparations is worked out. Jefferson feels that "time and experience as well as science are necessary to make a skillful physician, and nature is preferable to an unskillful one." Against this standard Dunglison qualifies as personal physician. No fees are charged, but Jefferson insists on paying. Student petitions for vacation are channeled through a proper table of organization, and so also the policing of student conduct. Rector Jefferson needs to know the exact price of books, their exact titles and publishers in order to make a business-like recommendation to the Board of Visitors and fulfill their wishes. What kind of diploma to award was carefully discussed.

The 120-page book is neatly done. It costs five dollars but gives the impression of belonging in a glass case. There is a valuable bibliographical note, and the index is unusually well done. It contains much variety and under the heading "Jefferson His Own Physician," John M. Dorsey, the editor, is at his best. Being a great student of human nature, it is natural for him to feature the health benefits of Jefferson's wisdom. For instance, the following sentence is, by itself, a whole package in health education: "His habit of using his mind as his own was his greatest health asset." The qualities of a well mind according to Jefferson are listed: 1) good humor, 2) integrity, 3) industry, and 4) science. Even the worth of a placebo for the patient was seen clearly by Jefferson without benefit of statistics.

I hope you will be pleased to hear how physiologist Robley Dunglison has been featured. I find it most satisfying to have our profession identified so closely with our early history.

Sincerely,
Walter H. Seegers

WILLIAM HENRY HOWELL

The following material was taken from various biographies of William H. Howell and particularly from material supplied by his daughter, Dr. Janet Howell Clark, a member of the American Physiological Society.

William H. Howell was the fourth person to serve as president of the American Physiological Society. He was one of the original members of the Society and active in its affairs during the first forty years of its existence, serving on council for twenty-three years and as president for six terms, 1905-1910. He had the honor of giving the first paper presented to the Society at its initial meeting in Washington in 1888. His professor and graduate sponsor was Henry Newell Martin one of the three original founders of the Society. To show the relationship of the activities of these two men and the early influence Martin had on Howell's career, the following bits are quoted from a lecture given by Dr. Howell on "The Early Days of the Biological Laboratory" at Hopkins.

"I entered the university in the fall of 1879, matriculating as a candidate for the A.B. degree in the Chemical-Biological course. Newell Martin was my advisor. My first meeting with him was when I called upon him in his room in the biological laboratory. I remember being surprised by his youthful appearance. He was cordial but the interview was brief. Martin was not an easy conversationalist. In the laboratory, at least, talking with him was usually quite brief and did not spread far away from the business in hand. In his home he was quite different, very cordial and ready to converse on all kinds of topics, although there was a certain abruptness or shyness in his manner which gave the impression that general conversation did not come easily to him.

"Martin's office was in the corner of the general laboratory which took up the top floor of the so-called Hopkins Hall. It was immediately above the general library of the University. To reach it one had to climb up a narrow stairway. The general laboratory was a large plain room with rows of working tables of a very simple character with stools to correspond. The laboratory had a preparation room opening out at one end. At the other, a doorway opened into a series of small rooms for research and offices. One special room housed the large Fick Pendulum Myograph which was the piece de resistance of the laboratory equipment and was always shown to visitors as a

demonstration of what was meant by experimental physiology. Distinguished visitors were usually shown through the laboratory. I remember particularly one visitor, Oscar Wilde, in whom we were all interested. When Martin escorted him through the laboratory Donaldson and I were in the research room preparing for an experiment which required gallons of calf's blood. We had managed to spill some of the blood on ourselves as well as on the apparatus. Donaldson, who was by way of being a poet himself, having published a volume of verse while at Harvard, was telling me about Wilde's lecture the night before and, standing on the operating table, was giving a fervid rendering of one of his poems when the door opened and Martin and Wilde entered the room. Martin hurried his visitor on. What Wilde thought of the peculiar, rather gory tableau can only be surmised. He was probably an antivivisectionalist anyway and may have carried away what he thought was first hand evidence of its cruel methods.

"The Department remained in this first laboratory for eight years (1876-1884). The students in the laboratory during this period fell naturally into two groups. One, consisting of medical graduates or those who were planning to enter the medical profession after completing the course in general biology, took work in animal physiology under Martin. The other, consisting of those who were looking forward to careers in zoology, took their advanced courses under Brooks. While there was a close association of the two groups at first, owing to the newness of the laboratory and its restricted quarters, there was a tendency to separate, which was augmented after the new laboratory was occupied in 1884 and physiology had one floor and morphology another. I belonged to the physiological side so that most of my work was under Martin.

"Martin's great contribution at the time was the discovery of a method for isolating the mammalian heart so that it could be kept alive on an artificial supply of blood. In physiological laboratories much work had been done on the cold-blooded heart isolated from the body, but no one before Martin had devised a method for such independent study of the mammalian heart. I remember well the first experiment done upon a cat's heart, which demonstrated that the method could be made to work successfully. Thereafter, for some years, Martin's energy and that of his advanced students were devoted to improving this technique and in carrying out a series of experiments upon the fundamental problems in cardiac physiology.

"The new Biological Laboratory, constructed in 1884, was relatively speaking an imposing structure. The building was probably, at that time, the best equipped institution for biological

instruction and research in the country. The construction of the new laboratory was a demonstration of the success of the Department of Biology. During the eight years in the old laboratory Martin had been extremely active in organizing the work, in planning and giving the lecture courses and in doing and inspiring research. But it is a curious and mysterious fact that after this great activity had brought him the recognition implied by the construction of a new laboratory, with amplified opportunities for instruction and investigation, his zeal began to lag. From the time he entered the new laboratory a kind of apathy became apparent in his work. For a time his work on the isolated heart was carried forward, chiefly by advanced students, but he had no new problems, no new methods were developed. He came to the University as the head of the Department of Biology in 1876 at the age of 28 years. During the first eight years, in his simple laboratory, he was everything that could be desired of a university professor, devoted to his work, zealous in teaching and research, and a source of inspiration to those who came into contact with him. During his second eight years, in his fine new laboratory, there was a perceptible and increasing decline in his activity and influence. He had, as it were, shot his bow. Some indication of this decline is found, I think, in the remark quoted by Sewall, his first associate in physiological work and probably his most intimate friend. In an appreciative tribute to Martin, Sewall states that on the occasion of his thirtieth birthday Martin said to him that he had had enough and was ready to quit. This cryptic remark is not explained, but made at the time that his prospects were the brightest and his work most absorbing, it seems to imply some kind of inward dissatisfaction which later may have grown to such proportions as to inhibit his activity.

"Martin had a most attractive personality -- somewhat under average size physically, he was very good looking, had charming somewhat boyish manners and impressed everyone with his quick intelligence and background of general culture. Michael Foster pays a high tribute to him as a student. He counted him as the most brilliant of the unusual group of young men who under the guidance of Huxley and Foster were to become the leaders in the foundation of that noble English school of biology that had its birth in the last quarter of the 19th century. Martin stimulated his students by example, rather than by precept, but in addition he treated them like comrades in research and won their affection and admiration by his personal kindness and by the example he set of ability, sincerity and modesty in his own investigations."

William Henry Howell was born at Baltimore, February 20, 1860. The family on both sides had lived in Maryland since early

colonial times. Dr. Howell went through the Baltimore public schools. In his senior year at the high school (City College) he became assistant to Professor Powhatan Clark, the teacher of physics and chemistry. This stimulated him to prepare for the study of medicine. In the fall of 1879 he entered the Johns Hopkins University as an undergraduate student. He took his degree of bachelor of arts in June 1881 and at graduation was awarded a graduate scholarship. Because of this scholarship he matriculated in the graduate school as a candidate for the degree of Doctor of Philosophy, instead of following his original intention of entering a medical course. Graduate work was followed for three years, during the last two of which he was awarded a fellowship in the University. His principal work in animal physiology was carried on under Professor Newell Martin. He received the Ph.D. in June 1884 and his dissertation was entitled "The Origin of Fibrin Formed in the Coagulation of Blood." It is interesting to note that his first paper was on coagulation and his last, which his daughter, Dr. Janet Howell Clark completed and published after his death, was "The Isolation of Thromboplastin."

Professor Martin was Dr. Howell's ideal of a teacher and researcher and had a great influence on him as a young student. He was brought up on Michael Foster's Textbook of Physiology which he always thought was the best textbook on the subject ever written in the English language.

In 1885 Dr. Howell was made chief assistant in biology and given charge of the laboratory course in animal physiology. He was promoted to associate and finally associate professor of biology and gave the lectures in animal physiology in the undergraduate course. He considered these years the golden period of his life. The spirit of the laboratory approached the ideal of scientific work, that is, a genuine interest and joy in adding something to knowledge whether or not it brought any external reward.

The spirit of research was in the atmosphere in Howell's laboratory. There was no pressure to produce results and there was no expectation that anyone was going to make a great discovery or even an important discovery. He deplored the keen competition by some investigators to secure results that would attract attention. He felt that such competitive pressure tended to distort values and set up standards that gave to scientific research something of the low motives of commercial warfare.

In 1889 Dr. Howell was offered the position of professor of physiology and histology at the University of Michigan. His first year there was far from happy. The student body was very tough

and roughhoused through every lecture. At the time Dr. Howell arrived only two professors were able to keep order in the classroom. One did it by withering sarcasm -- the other would quell a disturbance by taking off his coat and fighting the man responsible. As neither method was suitable to Dr. Howell's temperament and physique he developed his own method. When any man started a row he dropped him from the class which meant he could not get a degree. The measure was effective but the men repeatedly threated Dr. Howell's life. It was a nerve-wracking experience and may well have started the gastric ulcers that made him so uncomfortable later in his life.

In 1892 Dr. Howell went to Boston as associate professor of physiology under Dr. Bowditch (first president of APS) at Harvard. One year later he was made professor of physiology in the newly organized medical school at Hopkins. This was a particularly interesting and challenging position and brought him home to his native Maryland. He served in this position until 1918, acting also as dean of the medical faculty from 1899-1911. He always enjoyed administrative work and it never interfered with his research or teaching. He always said, "Administrative work is the easiest work in the world -- it is largely a matter of talking with other people and letting them talk to you."

In 1896 Dr. Howell edited the American Textbook of Physiology. In 1905 in the midst of an active life of research, teaching and administration he found time to prepare his own textbook of physiology which ran through 14 editions. After his death the text was continued under joint authorship as Howell's Textbook of Physiology. His textbook was, for a period of 30 or 40 years, the main source of written physiology for American medical students.

During his years as professor of physiology at Hopkins his research was concentrated mainly on three subjects -- the functional significance of the inorganic salts of the blood in the heart beat; the mode of action of the vagus; and the coagulation of the blood. In 1910 Dr. Howell isolated thrombin. In a Harvey Lecture he first described his early work on a new substance he later named heparin. His series of papers (1918-1924) dealing with his work on heparin was carried out at a time when he might well have given up research altogether. During these years he was suffering from gastric ulcers, was on a strict diet, and was far from well. In 1919 he was operated on twice for ulcers and was critically ill for a year, but research was his abiding interest and nothing could divert him from it.

Dr. Howell had great enjoyment in sports. He played excellent tennis and good golf. He always took a great deal of exercise.

During his vacations in Maine he sailed the Maine coast, with his children serving as the crew of his 30-foot sloop. After he gave up tennis he took up lawn bowling and became expert.

In 1917-18 he helped Dr. Welch organize the School of Hygiene. He was assistant director and professor of physiology at the School until 1926 when he became director of the School until his retirement in 1931. Dr. Welch had secured the funds for the School but as Dr. Howell often complained he had no concrete ideas about how it should be organized. The ideas for the scheme of the School and the scope of the work were almost entirely Dr. Howell's. Dr. Welch and Dr. Howell planned the School primarily as a research institute and it was a disappointment to Dr. Howell that after his retirement the School developed along more practical lines with less emphasis on research.

Dr. Howell greatly enjoyed the International Physiological Congresses and attended them regularly. He was president of the Boston International Congress in 1929. When Dr. Howell retired at 70 he acted as chairman of the National Research Council and commuted to Washington every day for the next three years. After that, with research funds from the Carnegie Corporation, he settled down to do research again in a laboratory in the Pathology Building at Hopkins. He kept this up until his death in February 1945.

In a letter, written at the age of 84, he said, "Old as I am I have no tendency at all to relive former days, indeed they never come to my mind unless an old student turns up. I seem to be occupied only with the present and the future." Howell, in contrast to his professor, Martin, continued to grow in stature, produce and look forward.

Joseph Erlanger, in his biographical memoir of Howell, wrote the following: "Howell was one of the best loved of American physiologists. A kindly disposition and unpretentiousness of manner endeared him to all who knew him well. He held firm but carefully weighed convictions which, however, were never obtruded on casual acquaintances. His strength of intellect, his wisdom, his moral fiber gave him the peace of mind and the sympathetic understanding of his fellow men that were so apparent to all who knew him. He will be remembered not only for his important contributions to physiology, as an inspiring teacher and as an able and considerate administrator, but equally for his fine personal attributes -- a calm, simple philosophy of life combined with the strength of character that enabled him to live in the light of that philosophy."

To exemplify Dr. Howell's strong convictions on medical education the following is cited from parts of a letter written by him to Sir William Osler, then professor of medicine at Oxford but formerly at Hopkins. The letter dealt with the argument of full-time versus part-time clinical professors in medical schools.

October 5, 1911

My dear Sir William:

Your note about the great discussion which has been disturbing us so much was received and appreciated. I am afraid that I do not wholly agree with your point of view and I am exceedingly sorry that you can not advocate the view that the majority of us believe in, namely that it would be a great advantage to the science of medicine if the clinical teachers were relieved of the distractions of an outside practice....

Your statement that the clinical men have done better scientific work than the laboratory men implies that in your opinion we are a sorry lot. If the clinical men have been able to carry out a successful private practice and earn handsome incomes and in the little time left have contributed to medical science work of more value than those who have given all their time to such labors -- why, it is evident that the laboratory men are a mediocre lot or the clinical men are a set of geniuses. I don't accept your statement myself and in making it you have been, I believe, unjust. If you had contented yourself with saying that their work on the whole had been of more value I could let it pass without comment, but to say that their scientific work has been of more value is a horse of another color. Did you really look into the investigations from the laboratory side in a critical way? I hope not, for I should be sorry to have you entertain such a poor opinion of our productiveness. I will not attempt to present the arguments on our side as I know that you are familiar with them. In Man's Redemption of Man, you have paid the highest tribute to investigative work in medicine and declared your belief that "the leaves of the tree of science have availed for the healing of the nations." For my part I am convinced that the development taking place in consequence of the penetration of methods of experimental investigation into the clinical branches must inevitably lead to the formation of a new body of clinical teachers. We have the opportunity to lead the movement and my pride in the school has made me desire earnestly that we shall have this honor (at Hopkins).

With best wishes and congratulations on your new honors.

Sincerely yours,
W. H. Howell

THE AMERICAN PHYSIOLOGICAL SOCIETY AND THE FEDERATION

In April 1960, the members of the Society requested, by a motion at the business meeting, that Council re-examine the relationship between the APS and FASEB, and place before the Society data which might aid the members to decide whether to continue membership in the Federation (as now organized or in modified form). The Federation Board, by simultaneous action, decided to re-examine the usefulness of the present type of combined meeting to all of the members of the Federation. This bilateral evaluation is certain to be rewarding to APS and FASEB members.

Some of the questions often asked about the Federation are:

1. Does the Federation meeting function optimally to create interaction among different groups of experimental biologists? Do physiologists attend sessions in biochemistry, pharmacology, etc., and do biochemists, pharmacologists, etc. attend sessions in physiology with sufficient frequency to justify the joint meetings?

There are no data available at present on the amount of interaction among members of different societies. However, the Federation plans to conduct a survey at the 1961 meeting to obtain objective information on "cross-over" of members at scientific sessions to determine whether a large number of members of one Society do attend sessions of another Society or whether the Societies in fact are meeting quite separately even though in the same city at the same time. The APS plans in addition to obtain opinions of members who attend the Federation meeting (and possibly also of those who stay away) regarding advantages and disadvantages of the present Society, Intersociety and Federation programing.

The attendance at four Federation meetings held in the same location (Atlantic City) in 1950, 1954, 1956, and 1959 is shown in Table 1. If increasing attendance represents a sign of satisfaction with the meetings, there is little cause for concern. The Federation meetings attract about four times as many registrants who label themselves physiologists as do the Fall meetings (Table 2).

2. Is the annual meeting of the Federation becoming too large?

The number of simultaneous sessions is shown in Table 3. It will probably increase if no further restrictions are placed on the presentation of ten-minute papers. Will the convention facilities of any city be able to provide 35 or more rooms of appropriate size for simultaneous sessions in the next five years? A separate APS April meeting would permit a wide choice of meeting sites in all areas of the country.

3. Are the scientific exhibits alone (especially the commercial exhibits of new equipment) of sufficient value to members to justify the Federation meeting?

Some APS members believe that they are. Experience has shown that few exhibitors believe it worthwhile to set up exhibits at smaller meetings, such as the Fall meetings of the APS, and it is likely that a smaller separate APS Spring meeting would attract few if any exhibitors. The 1959 meeting of the Federation yielded a profit of $43,741 (see Table 4); much of this came from fees paid by the exhibitors of scientific equipment.

4. What does the Federation office now do in arranging for the April meeting -- that would have to be done by the APS office if the APS held its own April meeting?

The Federation maintains adequate staff and facilities for staging the Spring meeting. The costs of this activity are supported entirely by the income from registration fees and sales of exhibit space.

The facilities and services of the annual meeting include:

a. Physical arrangements and negotiations for meeting rooms
b. Projection and public address equipment and services
c. Registration services
d. Tickets, programs and abstract sales and distribution
e. Guard and security services and insurance protection
f. Arrangements and negotiations for special events and social affairs
g. Audit and control of monies received
h. Receipt, processing, and printing of abstracts

i. Preparation, editing, and printing of program
j. Sale and management of industrial and scientific exhibits
k. Setup, management and operation of exhibit of publications of the constituent societies
l. Physical arrangements and management of press room facilities

5. Is FEDERATION PROCEEDINGS itself of sufficient value as a publication to warrant continued membership in the Federation?

A subscription to FEDERATION PROCEEDINGS goes to each regular member of the APS in return for his annual assessment of $4. The subscription includes:

a. Program of Spring meeting
b. Abstracts of papers given at Spring meeting
c. Membership directory
d. Proceedings of symposia and special sessions at Spring meeting
e. Proceedings of other symposia as supplements to FEDERATION PROCEEDINGS. The December 1960 issue, as an unusual example, had two supplements: a 165-page symposium on "Cold Acclimation" and a 196-page annotated bibliography on "Laboratory Animals." FEDERATION PROCEEDINGS published 1475 pages in 1960 including 413 pages of supplements.

The regular non-member subscription rate for FEDERATION PROCEEDINGS is $8 per year; therefore, the constituent societies provide their members with the journal at 50% of the regular price.

6. How does the Federation Placement Service benefit APS members?

The Federation provides a mechanism for exchange of information concerning employment opportunities and scientific manpower availability through the operation of Placement Information Service. The costs of providing this service are absorbed by the revenue derived from a share of the registration fees, subscriptions and other income of the Placement activity with no direct assessment on the constituent societies. The activity provides the following services:

a. Printing and distribution of quarterly bulletins
b. Physical arrangements, negotiations for space and equipment, management and operation of interview facilities at the Spring meeting
c. Compilation and distribution of fellowship and assistantship lists
d. In 1960 there were 163 persons registered with a primary interest in physiology

7. What business services does the Federation office provide to the APS office?

By action of the Federation Board each constituent society is provided, without charge, one room at Beaumont House for a central headquarters. (The APS Executive Secretary-Treasurer occupies this room.) Additional office space is made available at rental rates established by the Federation Advisory Committee. (The APS publications staff pays rent for its space.) For all office space at Beaumont the Federation provides:

a. Heating and air-conditioning
b. Lights, electricity and water
c. Janitorial services
d. Local telephone service
e. Receptionist services
f. Parking and lunch room facilities
g. Conference rooms

In addition, because of the concentration of centralized facilities at Beaumont House, the Federation is able to provide, at cost, certain business services for its constituent societies. These services comprise the activities designated as:

a. Accounting Office
b. Purchasing Office
c. Personnel Office
d. Circulation Office
e. Printing and Duplicating Department
f. Mail and Stock Room

The cost of these activities is shared proportionately by all organizations at Beaumont (APS Executive Secretary Office; APS publications staff; Pharmacology publications staff; and various Federation activities). The formula for determining the proportionate share of the costs which each organization absorbs is approved by the Federation Board. Rather than initiate elaborate, time-consuming and expensive accounting procedures, a

generally accepted principle is used of charging as "overhead" a percentage (12.3% in 1959) of the direct expenses of each organization using Beaumont House.

In return for this, the Federation office provides for:

a. Bookkeeping and accounting
b. Financial reporting
c. Budgeting and budgetary controls
d. Processing of cash receipts and disbursements
e. Banking, auditing and internal controls
f. Billing and collection of dues, subscriptions, etc.
g. Processing and preparation of payrolls, related tax reports, group insurance and pension procedures
h. Fiscal responsibility of grants and contracts
i. Preparation of federal and state tax and other fiscal reports
j. Processing orders and sales for books, reprints, single copies of journals, abstracts, etc.
k. Advisory services on fiscal, investment and management policies and procedures
l. Personnel management, recruitment and preparation and maintenance of personnel records, and reports for hospitalization, group insurance and workmen's compensation insurance
m. Procurement of supplies and equipment
n. Shipping and receiving of supplies and equipment, and messenger and mail room service
o. Providing equipment and facilities for printing, duplicating and addressing services
p. Processing and maintenance of subscription records
q. Preparation and maintenance of equipment records and control thereof
r. Professional services for independent audits, general legal services, etc.
s. Preparation and maintenance of investment records

8. What does the Federation do for biological science in general?

By virtue of its representation of a broad area of science, the Federation is in a unique position to perform services and carry on special activities of benefit to biology as a whole. Such services and activities are financed by funds obtained from various sources for these specific purposes and involve no taxation or assessment on the general funds of the constituent societies. Examples of activities carried on by the Federation that benefit

and are of service to research and education in broad areas of biology, and consequently of benefit to the constituent societies are:

a. Compilation of the National Register of Experimental Biologists
b. Management and operation of the Office of Biological Handbooks
c. Conduct of a study of the use of electronic computers for indexing, storage and retrieval of published scientific information
d. Administration of a survey of manpower needs in the basic health sciences
e. Publication of proceedings of special symposia of interest to biologists held at times other than in connection with the Spring meeting
f. Provision of public information services for member societies

In addition, since the Federation employs permanent administrative staff and possesses permanent facilities, it administers, at cost and upon request of the societies, certain special projects for which funds are specifically raised. Such projects include:

a. Fifth International Congress on Nutrition
b. International Symposium on Cold Acclimatization
c. Ad hoc committees for advisory services, screening for travel awards, etc.
d. Trustee for the International Physiological Trust Fund
e. Storage and distribution of "The Pharmacologist" and the career brochures for the Pharmacology Society

However, the Federation has not been active in recruitment of biologists. The APS and ASPET have written and distributed separate brochures, "A Career in Physiology" and "A Career in Pharmacology."

9. What does the APS (General Fund and Board of Publication Trustees) pay to the Federation annually?

The actual payments in 1959 were:

Federation Assessment ($4 per regular member)	$6,514
Office rent at Beaumont (BPT)	6,028
Business service charge (BPT)	36,082
Business service charge (General Fund)	3,144
	$51,768
Less 1959 reimbursement	2,510
Actual payments	$49,258

10. What is the Federation reimbursement to the APS?

By annual action of the Federation Advisory Committee, a portion of the income from the annual meeting is paid to the constituent societies as reimbursement of their expenses in connection with programing the meeting. Reimbursement is made on the basis of the total number of members of each society attending the meeting. One dollar of each registration fee is set aside in a special fund which is divided among the societies. The reimbursement for a particular society is calculated as follows:

$$\frac{\text{No. APS members registered}}{\text{Total No. members registered from all societies}} \times \text{amt. in Spec. Fund}$$

= the amount of the reimbursement to APS.

11. What would the cost be to the APS if it withdrew from the Federation and operated a central office and Spring meeting itself?

This is difficult to predict. Rental of office space and conference facilities might cost $20,000 (4000 sq. ft. at $5.00/sq.ft.). The APS would require its own accountant-bookkeeper, switchboard operator-receptionist, clerk-typists, subscription clerks and convention manager (total salaries approximately $31,200). The direct costs of an April meeting (unless held in University buildings) would be about $18,000. Printing of annual directory and symposia papers would be about $7,000, auditing and legal fees $1,500 and supplies and office equipment (partially non-recurring) would be $10,000. The estimated total cost is $87,700 for the first year and about $83,000 a year thereafter.

However, there would be additional income. Registration fees at the April meeting (2000 at $10) would provide $20,000. Each APS member now pays $4 of his annual dues to the Federation; if APS dues remained the same, this would provide $7,200/year. The $49,258 now paid to the Federation would be available to support the APS office. There may or may not be some small additional income from outside sources, but this could not be relied upon on an annual basis. The total income would be about $76,458. This is $11,242 short of the cost to operate the first year and $6,542 short of the cost for operating subsequent years.

TABLE 1. FEDERATION OF AMERICAN SOCIETIES FOR EXPERIMENTAL BIOLOGY ANNUAL MEETING GROWTH[1]

	1950	1954	1956	1959
Attendance				
Scientists	3975	5675	6476	8838
Exhibitors	254	385	434	946
Guests	399	375	435	298
Press	---	18	35	245
	4628	6453	7380	10,327
Program				
Total no. of sessions	118	146	186	234
No. of simultaneous sessions[2]	14	21	22	30
Total no. of papers	1200	1539	1915	2475
Exhibits				
Industrial	82	92	102	156
Institutional	---	3	10	10
Member	---	17	21	12
	82	112	133	178
Special Meetings	17	32	43	49

[1]Only annual meetings held in same location (Atlantic City) are included, in order to have a better basis for comparison.

[2]Wednesday morning sessions.

TABLE 2

	Attendance of Physiologists at Spring Meetings				Attendance at Fall Meetings
	Members	Non-Members Physiol. Interest	Grad. Students Physiol. Interest	Total	Members and Non-Members
1956	639	1046	115	1800	526
1957	610	1141	233	1984	513
1958	791	1417	229	2437	448
1959	786	1476	248	2510	613
1960	840	1315	397	2552	788

TABLE 3. SIMULTANEOUS SESSIONS[1] AT FASEB MEETINGS IN ATLANTIC CITY

Society	1950	1954	1956	1959
Physiology	5	6	5	7
Biochemistry	4	6	5	7
Pharmacology	3	3	3	4
Pathology	1	2	2	2
Nutrition	1	2	2	2
Immunology	0	2	2	2
Intersociety	0	0	3	6
	14	21	22	30

[1](Wednesday A.M. Sessions)

TABLE 4. SUMMARY OF FASEB FINANCES, 1959

1. Net Worth on December 31, 1959

Land and buildings	$144,758	
Other assets	301,277	
Total assets		$446,035
Deduct - Mortgage payable	37,500	
Other liabilities	29,461	
Unearned income	227,177	
Total liabilities		$294,138
Capital or net worth		$151,897

2. Total Operations for 1959

	Total	General Funds	Restricted Funds
Income	$382,847	$275,834	$107,013
Expenses	349,100	236,440	112,660
Net earnings	$ 33,747	$ 39,394	$ (5,647)

3. General Funds Operations for 1959

	Total	Federation Proceedings	Annual Meeting	Placement Service	Other
Income	$275,834	$109,395	$149,398	$ 9,418	$7,623
Expenses	236,440	104,318	105,657	18,842	7,623
Net earnings	$ 39,394	$ 5,077	$ 43,741	$(9,424)	-0-
Allocations of Registration Fees as directed by Fed. Board	-0-	8,840	(22,100)	13,260	-0-
Earnings after allocations	$ 39,394	$ 13,917	$ 21,641	$ 3,836	-0-

4. Net Cost of Operating Beaumont House for 1959

Total cost	$ 50,020
Less - Rental income received	7,516
Net cost absorbed by Fed. activities	$ 42,504

ANALYSIS OF SESSION ATTENDANCE AT SPRING MEETING

One of the questions that arose during the Council's study of the relationship of the Society to the Federation was, "How many members attend sessions other than those of the APS and how many members of other Societies attend APS sessions." There have been speculations and a great deal of guessing but no factual data with which to answer this question.

The Federation is also anxious to obtain factual information on the total attendance at various types of sessions as well as cross attendance between Societies and has agreed to conduct a survey at the 1961 Spring meeting. It will be done somewhat as follows.

Each Society will have a different colored badge that can be spotted easily in an audience. Those registering will be issued a colored badge corresponding to the Society of their choice. Each session chairman will have a co-chairman or an assistant who will take several spot checks of attendance during the session by noting the numbers of different colored badges in the audience.

Each registrant will be issued a post card upon which he is to record the sessions he attended each day. At the end of the week the card is to be mailed to the Federation office in Washington, D.C.

If the Spring meetings continue to grow as they have in the past few years some plan of staggered meetings, prolonged meetings, etc. must be devised. If staggered meetings are to be planned, with which Society should the APS meet simultaneously -- with which Society or Societies does the APS have the greatest crossover? The data collected in this survey may help form the basis for some plan for future meetings. If the data are to be meaningful it is imperative that everyone cooperate. Questionnaires and report forms always are a nuisance but if the APS is to provide its members with better meetings your cooperation is earnestly requested.

AIBS TRANSLATION PROGRAM

The American Institute of Biological Sciences is currently translating and publishing seven Russian research journals in biology. These journals are translated with support from the National Science Foundation. It is hoped that this material will aid biologists in research, give some idea of the work done by Soviet scientists in the field of biology, and also bring about a better international understanding among scientists.

Because of the support of the National Science Foundation, the AIBS can offer these translations at a fraction of their publication cost, with even further price reduction to AIBS members and to academic and non-profit libraries.

The journals currently being translated are: Doklady: Biological Sciences Section; Doklady: Botanical Sciences Section; Doklady: Biochemistry Section; Plant Physiology; Microbiology; Soviet Soil Science; and Entomological Review.

In addition to its program of Russian Biological Journal translations, the AIBS has instituted a separate program of translation and publication of selected Russian monographs in biology.

The AIBS has translated and published six Russian monographs and one monograph is in the process of being published. In addition, several prominent monographs in various biological areas are being considered by the AIBS and the National Science Foundation for translation and publication. The monographs that have been published are: Origins of Angiospermous plants by A. L. Takhtajan; Problems in the Classification of Antagonists of Actinomycetes by G. F. Gauze; Marine Biology, Trudi Institute of Oceanology, Vol. XX, edited by B. N. Nikitin; Arachnoidea by A. A. Zakhvatkin; and Arachnida by B. I. Pomerantzev. The manuscript for Plants and X-rays by L. P. Breslavets is in the final stages of preparation and should be published early in 1960.

Additional information pertaining to this program may be obtained by writing to the American Institute of Biological Sciences, 2000 P Street, N.W., Washington 6, D.C., U.S.A.

NEW STYLE MANUAL FOR SOCIETY JOURNALS

The AMERICAN JOURNAL OF PHYSIOLOGY, the JOURNAL OF APPLIED PHYSIOLOGY, PHYSIOLOGICAL REVIEWS, and FEDERATION PROCEEDINGS are among 76 journals which have already officially adopted the new "Style Manual for Biological Journals."

The Manual was prepared by the Committee on Form and Style of the Conference of Biological Editors and published (in December 1960) for the Conference by the American Institute of Biological Sciences. The Committee, composed of knowledgeable editors from several fields of biology, worked diligently to produce a manual that could serve for all biological journals. Numerous compromises obviously had to be made, in some matters alternative procedures were accepted, and some items were omitted on which common agreement could not be had. In anticipation of a revision and enlargement of the Manual within a few years, suggestions for changes and additions will be welcomed by the Committee.

Authors submitting papers to the APS journals are urged to follow carefully the Style Manual in the preparation and presentation of their papers. In cases of manuscripts returned to authors for revision of their presentation, reference will be made to pages and sections of the Style Manual for instructions.

An important editorial change in our Journals will be the use of the abbreviations of periodicals listed by "The Chemical Abstracts Service," rather than those listed by the "Quarterly Cumulative Index Medicus." While both we and the Committee on the Style Manual would prefer a different list of journal abbreviations, it is necessary that the adopted list be available to any author in his institution's library. The "Chemical Abstracts" list is more easily available than any other at the present time.

We shall continue our practice of listing references by numbers, serially in the text and in the list of References, and also of omitting titles of journal articles in the AMERICAN JOURNAL OF PHYSIOLOGY and the JOURNAL OF APPLIED PHYSIOLOGY. For PHYSIOLOGICAL REVIEWS, the "Handbook of Physiology," and symposia papers in FEDERATION PROCEEDINGS, the citations listed at the end of the paper will be arranged in alphabetical

order (first author) with references numbered in the text, and titles of journal articles cited may be included.

Copies of the "Style Manual for Biological Journals" may be obtained from your University bookstore, or from:

The American Institute of Biological Sciences
2000 P Street, NW, Washington 6, D.C.

The price is $3.00 per copy, postpaid.

1961 TEMPERATURE SYMPOSIUM

A symposium on "Temperature - its Measurement and Control in Science and Industry" sponsored jointly by the American Institute of Physics, the Instrument Society of America and the National Bureau of Standards will be held in Columbus, Ohio, March 27-31, 1961.

Temperature ranks as one of the most important of the physical quantities, and its measurement and understanding have provided some of the most difficult and challenging problems in experimental and theoretical physics. The 200 papers scheduled for presentation come from universities, government and military research laboratories, and industrial research laboratories in this country, as well as from research centers in Australia, Germany, Netherlands, Canada, Soviet Russia, and Great Britain.

The symposium is organized into 16 sessions, devoted to such topics as: Basic Concepts of Temperature, Temperature Scales, Thermocouples, Resistance Thermometers, Gas Thermometers, Spectrascopic Methods, Pyrometry, Miscellaneous Methods, Automatic Methods for Measurement and Control, Measurement in Dynamic Systems, Special Sources of Temperature, Cryogenics, Plasmas, Temperature Measurement in Geophysics, Temperature Measurement in Astrophysics, and Temperature Measurement in Biophysics and Medicine.

Persons interested in the symposium may obtain further information by writing to V. W. Sikora, Instrument Society of America, 313 Sixth Ave., Pittsburgh 22, Pennsylvania.

PAGE CHARGES IN APS JOURNALS

The favorable balance between income and expense of our archival Journals, the AMERICAN JOURNAL OF PHYSIOLOGY and the JOURNAL OF APPLIED PHYSIOLOGY, which has existed up to 1959, has now ended. A deficit of around $9,000 from their operations was experienced in 1960. A considerably larger deficit, of $35,000 to $50,000, is projected for 1961 unless prompt measures are taken to obviate it. Rising costs of manufacture and services, combined with a larger number of papers published each year, are the expense factors responsible.

Increased net income from more efficient management practices instituted over the last 12 years has helped to keep a favorable balance, but there is little more that can be accomplished along these lines. The increase in subscription prices in 1958 gave needed relief but the Board of Publication Trustees considers that a further increase is undesirable at this time. Indeed, the present price is some handicap in promoting new subscriptions, particularly from abroad, even though the price of our Journals per million words published is lower than that of most other biological journals. Many scientific journals, including a majority of those in biology, are currently plagued with increasing costs and unbalanced budgets. Their solutions to the problem include chiefly: a) support through grants from Federal agencies; b) publication of less material, even though this leads to pressure for the birth of new journals which tends to disperse the already inadequate support for publication in a field; and c) institution of page charges to be borne by the funds that support the researches.

A number of leading journals are now adopting or seriously considering the third solution, that of page charges. Most of the journals in the field of physics have used this system for ten years or more; the "Proceedings of the Society for Experimental Biology and Medicine" has used it for several years. The experience of all that have adopted it has been highly satisfactory.

All government agencies and many private organizations that make research grants are now agreeable to allowing payment of page charges from such grants. Some agencies, in their instructions accompanying grant-application forms, plan to suggest that applications include a budget item for publication costs.

The Board of Publication Trustees plans to institute a system of page charges this year after June 30, probably simul-

taneously with several other journals. This will apply to the AMERICAN JOURNAL OF PHYSIOLOGY and the JOURNAL OF APPLIED PHYSIOLOGY. The amount of the page charge has not been finally determined, but is tentatively set at $15 per printed page. (The cost of manufacture of these two Journals now averages about $38 per page.) Page charges will be assessed only if the author's supporting funds can accept them. Editorial decision on the acceptability of any paper for publication will not be influenced or concerned with the ability of authors' supporting funds to page charge assessments. The experience of journals that have had page charges for some years is that 95% of these assessments are honored, and no question is raised about the others.

FIRST INTERNATIONAL PHARMACOLOGICAL MEETING

At the International Physiological Congress in Buenos Aires, August 1959, an International Section on Pharmacology was formed as a subdivision of the International Union of Physiological Sciences. It has now been decided to hold the First International Pharmacological Meeting in Stockholm, August 22-25, 1961. The date has been so chosen to allow visitors to the International Congress of Biochemistry in Moscow, August 10-16, 1961, to attend the convention in Stockholm on their way back from Russia. The scientific program will be restricted to topics under the general heading of "Mode of Action of Drugs." For further information write Secretary General Dr. Arvid Wretlind, Karolinska Institutet, Stockholm 60, Sweden.

The Section on Pharmacology, International Union of Physiological Sciences (IUPS), will receive a grant from the National Institutes of Health, Dept. of Health, Education and Welfare, for the purpose of paying travel expenses for American Scientists to the First International Pharmacological Meeting in Stockholm.

Applications should be made in triplicate to Dr. Carl F. Schmidt, President of the Section on Pharmacology of the IUPS, Dept. of Pharmacology, University of Pennsylvania, School of Medicine, Philadelphia 4. Please give full name, age, address, nationality, earned degree(s), academic affiliation, membership in any biological society, field of research. Please refrain from applying if you are a holder of any government or private grant which allows travel funds. The deadline is May 1, 1961.

STATUS AND VIEWS OF SENIOR PHYSIOLOGISTS

Report of Committee on Senior Physiologists

Last summer the Committee on Placement of Senior Physiologists (Dill, Adolph, Fenn and Landis) wrote each member of the Society born before 1895. The letter of inquiry is appended. To the 225 letters there were about 125 replies. The Committee has studied these replies and prepared the following analysis together with 14 selected constructive comments. Unfortunately, we cannot assume that the 125 replies reflect the views and status of the 100 who did not reply. Certainly some of the latter group are too ill to write; perhaps some are too discouraged to write.

As an experiment, news items about 26 of those who replied are appended with the thought that some such device for communicating among the 225 "old-timers" might be welcomed.

While our inquiry was well-received by this group the replies merit the attention of physiologists of all ages. They contain many words of courage, encouragement and wisdom.

Financial problems. There were few dire complaints. Almost all said "no problems"; some did not mention finances. A few are badly pinched by inflation plus a fixed dollar income. One expressed resentment at missing out by a year or so on social security as well as CREF and felt these should be made retroactive. One expressed the view that since TIAA received valuable dollars and now pays in less valuable dollars, TIAA should increase dollar payment. This however, seems obviously impossible for any insurance company on a large scale basis.

Impression: Our impression is that retirement annuities plus life-long economical habits of physiologists seems to make financial problems of retirement not serious for the large majority. How serious the situation may be for others and especially for those who did not respond, the Committee has as yet no way of knowing.

Research facilities. In responding on research facilities, 34% said they were provided in their original department and 18% reported them available elsewhere in their institutions. In 7% only a desk and library privileges were available. The remainder

did not desire them or had already moved to a new job in another institution.

Impression: If modest laboratory space is wanted, it is usually provided. Some feel hesitant about using space. Others say their institution is too crowded to offer space.

Willingness to move. To the question about willingness to move, 27% said they had already moved, 7% were willing, 52% unwilling and 12% were noncommittal.

Impression: The majority prefer to work in their present location but personal preferences vary greatly. Friends, home ties, family ties or illness of relatives often are deterrents to moving.

Changes in retirement rules. No fundamental changes were mentioned; one reported a change from age 65 to age 68. One school added compulsory contribution to retirement funds by all faculty members. One institution had no retirement age.

Research support from Government. Many have obtained Government grants often with part-time salary as well. This requires an institutional tie.

Impression: 100 retirees present a rather encouraging picture. Most are relieved at handing over administrative duties and having a more elastic schedule of research, writing or recreation.

Extra jobs are interesting: Practice (for physicians); writing a newspaper column; editing journals; deanships; research in non-university laboratories; teaching in another medical school or a college; supervising student research in college; writing; consultantships.

Complaints. These are amazingly few. One advocates total restudy of retirement in view of greater life expectancy and shortage of experienced physiologists. He feels that universities are "dodging their responsibilities." One feels talents are being wasted and should be used.

Selected constructive comments

1. "Best place for a retired scientist is in a small laboratory without administrative duties for as long as he can make use of it and with freedom to get away from it whenever he feels like it. The problem to set before the wise men of today is simply

this: how can each individual be given the chance to labor as long as he has the will and health to work. Sometimes, 'the race is not to the swift nor the battle to the strong.' It may be that the last work of the old man's hands will serve society best -- and him as well."

2. "Now, I am going to outline a plan for your consideration, not all parts of which are original. Include a considerable number retirees on your committees. Everyone but the people actually directly affected has a decisive part in our destiny except the ones most concerned. Consider that over half of all persons over 65 are actually retired while still actively engaged in customary activities as efficiently as anyone over 50. Yet those who have been forcibly retired are regarded as rubbish. Why not give them some chance to work for the Society in fields they know best, committee work, consultation on recurring issues, central office work maybe, etc."?

3. "I think what you are undertaking is extremely important. It seems to me that 66 is a very early age to remove people from their work, at least as a routine policy. Of course there are many who want to stop working at this age, and they certainly should be allowed to do so. But there are others who yearn for the relative simplicity of life which comes with relinquishing one's administrative activities. I think some valuable work could be obtained by reassessment of men's abilities during their retirement years."

4. "Your letter of June 30 reminded me how casually I have thought of retirement. This probably has been a wish not to look into the face of the fact, and may be usual."

5. "The one thing that, more than anything else, during this disturbing and transitional period has provided a centralizing thread of continuity and sanity amid the convulsions going on within and around me has been the generous five-year, renewable USPHS grant...."

6. "At 81 I do not look forward to further jobs, but even so, I am not idle."

7. "The attitude of the University toward support of research after retirement is good but largely on an individual basis depending upon department chairmen."

8. "To have time to read, to work in the lab, and to think about my research problems, is a luxury I haven't had for years. I feel younger in heart and spirit -- though older in my joints."

9. "Retirement regulations at our institution have changed this year insofar as continued employment of Emeriti is permissible from year to year, whereas formerly no such possibilities existed."

10. "I feel quite strongly that it is a mistake for a retired department head to remain active in the same department. His constant presence cannot but interfere with the freedom of his successor. It may be flattering to hear complaints from former pupils and associates about the sorry state of affairs under the new man, but a serious attempt at reversing roles will convince the oldster that he is doing his successor and his institution a disservice by listening."

11. "If physiologists as well as other people would take a little thought of the probabilities of the future as they pass through life there would not be so much demand for the problems of the Senior Citizens to receive special attention nor would these citizens have so many problems."

12. "Dr. Daggs might like to consider the suggestion of writing (or have written) for THE PHYSIOLOGIST a series of biographies of older physiologists still living, pointing out the role they played in their good days."

13. "I should be willing to move to another institution for teaching or research, since what makes life most worth living is the opportunity to work in a chosen field."

14. "Another sort of thing I think I should enjoy, if there were an opportunity, is part-time editorial work on a physiological journal. My health is excellent."

Our Committee has little to add to the above summary and excerpts; the facts and quotations speak for themselves. We suggest that there should be more year-to-year appointments for senior people and more elasticity in the interpretation of retirement rules.

We also suggest that a study be made at one of the older "steady state" institutions to see what the actual requirements of space and dollars would be if all those over 65 were given office and, if needed, laboratory space as long as they wanted it. Could there be a sort of office and laboratory insurance policy which a man could take out and contribute to while he was young so that he could be assured of this after 65? If so, how much would it cost? Perhaps some studies of this sort have been made already by some institutions.

We recommend that a study be made of the APS membership by taking all those who were members of the Society at any time in their lives, born between 1885 and 1895. Presumably this would include most of our present group plus a number of others. Let us tabulate what happened to the others. What percentage in other words, of the total membership of the Society is likely to reach retirement and what percentage is likely to want to continue work? Then a chart could show the ages at which they got into the APS and the ages at which they got out by death or otherwise and how they finished the course.

The members of your Committee are examining further the need for studies such as those recommended above. Comments from readers of THE PHYSIOLOGIST will be appreciated. We would like particularly to hear from the 100 who did not answer our inquiry.

Dear Dr. _____

Dr. Daggs has suggested that our Committee on Placement of Senior Physiologists prepare an article for THE PHYSIOLOGIST on the status of physiologists who have retired or who will do so within the next few years. Our Committee lacks up-to-date information from this group. Hence, I proposed to Dr. Daggs that we address a letter of inquiry to each member of the Society born prior to 1896. I hope you will reply prior to August 15, 1960 so that a report can be prepared for presentation at the Fall Meeting and subsequent publication in THE PHYSIOLOGIST.

In general, we hope you will prepare a brief account of your solution, accomplished or planned, of the problems of post-retirement years.

Specifically, here are suggested topics that you may wish to cover briefly:

Financial problems.
Research facilities available.
Willingness to move to another institution for teaching or for research.
Have retirement regulations of your institution changed?
Success in obtaining Government grants to support post-retirement research.

Sincerely yours,

D. B. Dill, Chairman
Committee on Placement of
Senior Physiologists

W. O. Fenn, E. M. Landis
E. F. Adolph

NEWS ABOUT SENIOR PHYSIOLOGISTS

William R. Amberson since his retirement at Maryland has been conducting research on the formation of protein-protein complexes between muscle enzymes and the fibrous muscle proteins at MBL, Woods Hole, Mass. His project is supported by NIH.

Percy M. Dawson, 87, continues his writing and is within easy reach of Stanford libraries.

D. B. Dill after retirement from civil service in April 1961 expects to join Sid Robinson as "Research Scholar."

Richard C. de Bodo after his retirement in 1961 hopes to continue his research at NYU with support from NIH.

Lester R. Dragstedt after retirement at the University of Chicago was appointed research professor of surgery at the Univ. of Florida. His research is supported by an NIH grant.

Hiram E. Essex since his retirement spends two days a week at St. Mary's College, Winona, Minn. as director of undergraduate research. The College has an NSF grant to support this project.

Mabel P. Fitzgerald, who was a member of the Haldane Pike's Peak party, is living in retirement at 12 Crick Road, Oxford, England.

Alexander Forbes on his retirement 12 years ago transferred his research activities to Harvard's Biological Laboratories.

Esther M. Greisheimer since her retirement in 1956 has been professor emeritus of physiology and research professor of anesthesiology at Temple with adequate research support.

At 81, Carl G. Hartman is research director of the Margaret Sanger Research Bureau, New York.

A. Baird Hastings is in full-time research at the Scripps Clinic and Research Foundation, La Jolla, Calif.

After her retirement at the Mayo Clinic, J. F. Herrick moved to Madison, where she is conducting research in the Cardiovascular Laboratory of Charles W. Crumpton.

Roy G. Hoskins, consultant to the Office of Naval Research, has received the Navy Superior Civilian Service Award for his

contributions to the Navy's biological research program. He also has been cited by the Endocrine Society for his service as scientist, author, editor, historian, teacher, friend, and wise counselor.

Frank P. Knowlton, 85, is confined to a nursing home with arthritis. His address is RD#2, Jamesville, New York, c/o G. L. Gravott.

Jerzy Kaulbersz writes that in Poland, retirement at age 70 may be delayed three years by vote of the faculty.

Franklin C. McLean, professor emeritus, Department of Physiology, University of Chicago, recently received an NIH grant for continuing his research on bone.

Stuart Mudd on his retirement in 1959 became director of microbiological research at the VA Hospital, Philadelphia. He is also professor of microbiology in the Department of Public Health and Preventive Medicine, Univ. of Pennsylvania.

W. J. V. Osterhout, 89, continues research in the Rockefeller Institute.

Wilder Penfield since his retirement in June has realized his plan for a "second career." He has published one historical novel, is writing another and has begun a biography of Alan Gregg.

After 36 years Navy duty, John R. Poppen became a medical consultant to the aircraft industry in California.

Carlos I. Reed has been painting his North Carolina home, gardening and writing book reviews -- over 100 in the past three years.

Dr. Charles Sheard, because of recent illness, has been forced to give up his teaching assignment at Tulane Univ. in the Department of Ophthalmology and also his secretarial position with the American Board of Opticianary and other allied interests. He is at home in Stewartville, Minn., and getting along just fine.

Charles D. Snyder, 89, welcomes visitors. His plan to write a book on "Physiology of the Liver" has not been realized.

W. W. Swingle on retirement in 1959 was given a three-year appointment as senior research associate in Princeton's Department of Biology. Research grants will permit him to continue in the field of adrenal physiology.

J. E. Thomas since his retirement from Jefferson in 1956 has been head of physiology at the College of Medical Evangelists.

For five years after his retirement, Carl J. Wiggers edited "Circulation Research." Since then as honorary professor in the Frank E. Bunts Educational Institute he has a busy life lecturing, writing, attending scientific meetings, and puttering around his home.

Wallace O. Fenn has been named "Distinguished Senior Professor" at the University of Rochester. This is a newly created title at the University.

S V S

LONDON

The Society for Visiting Scientists, which came into existence during the war, offers at its house, 5 Old Burlington St., London W.1., England, a center at which foreign and overseas scientists visiting the United Kingdom may meet informally with other visitors and with British scientists.

The President of the Society is Prof. A. V. Hill and members of the Council are Prof. Niels Bohr, Denmark; Dr. D. W. Bronk, U.S.A.; Sir Macfarlane Burnet, Australia; Sir Henry Dale, Great Britain; Prof. Jacques Hadamard, France; Sir Kariamanikkam Krishnan, India; Prof. Wilder Penfield, Canada; and Dr. S. Siddiqui, Pakistan.

The Society provides club and restaurant facilities and there is accommodation for overnight stay for a limited number of visitors. There is a small library. Contact is maintained with a large number of scientists abroad and through its information service and in other ways the Society is able to assist the activities of scientists on short visits to Great Britain. Students from overseas, studying in England, are brought together in the activities of the Overseas Science Student Association for which the Society provides a home.

Further information may be obtained from the Assistant Secretary, Miss E. Simpson, 5 Old Burlington St., London W.1.

FIFTH BOWDITCH LECTURE

Micropuncture Studies of Tubular Function in the Mammalian Kidney

CARL W. GOTTSCHALK

It is a great privilege and pleasure to give the annual Bowditch Lecture to the American Physiological Society. This is especially true since I have the greatest personal and professional admiration for our retiring President (R. F. Pitts) who has contributed so importantly to the field of renal physiology. Like you, I deeply regret his absence from these meetings and join with you in all good wishes for his speedy recovery. It is not inappropriate that the name of Dr. Bowditch be associated with the material I wish to present today, since the thoughts and experiments leading up to the current ones began when I was a Research Fellow in the physiology department which he founded and my interest in the micropuncture approach stems from Dr. Bowditch's current successor.

I wish to describe for you some experiments carried out in my laboratory the past several years in which we have utilized the technique of micropuncture to study renal function (3,4,5,7,8). In essence, we have attempted to extend to the mammalian kidney some of the fundamental observations of Dr. A. N. Richards and his collaborators. The experiments deal with localization and mechanism of tubular function with special emphasis on the mechanism for concentration and dilution of the urine. Several parameters will be considered including the net movement of water, osmotically active solutes, sodium, chloride, and urea, with mention of pH. At the beginning I would like to make it clear that I am not using "we" in an editorial sense but to include my valued colleagues. Miss Margaret Mylle with her marvelous technical skills has contributed importantly to the work and Dr. William Lassiter has had the major responsibility for the radioisotope measurements. The sodium determinations are the results of our group working in collaboration with Dr. Karl Ullrich in Dr. Bodil Schmidt-Neilsen's laboratory at Duke University.

The work was supported by grants from the American Heart Association and by PHS Grant H-2334. The author was an Established Investigator of the American Heart Association.

We have worked primarily with white rats but have used a number of other small rodents to take advantage of special anatomical features of their kidneys. Under pentobarbital anesthesia, a laparotomy is performed, the left kidney exposed and a portion of its surface illuminated with a Knisely quartz rod illuminator from which mineral oil issues onto the surface of the kidney. The surface of the mammalian kidney presents as a maze of short segments of convolutions primarily of the proximal convoluted tubule. Distal convolutions can be distinguished, however, with a high degree of accuracy by their special optical properties. Only rarely can we sample fluid from Bowman's space, since glomeruli are seldom located directly beneath the capsule. Following micropuncture and collection of a sufficient quantity of fluid, the tubule is injected with dye, the kidney macerated in hydrochloric acid and the punctured tubule isolated by microdissection. The site of puncture is localized and appropriate measurements made of tubular length.

A word about the major anatomical portions of the mammalian tubule is in order, since our studies represent anatomical-physiological correlations. The proximal convoluted tubule is considered to extend from the glomerulus to the thin descending limb of the loop of Henle. The proximal tubule is divided into two parts, the pars convoluta, which is the portion accessible to micropuncture, and the pars recta, which forms the first portion of the loop of Henle. The descending limb of the loop of Henle is composed of a thick part, the pars recta of the proximal tubule, followed by a thin segment of variable length. The ascending limb of a long loop has both a thin and thick segment, but a short loop has only the thick ascending limb. At least in the rat, the thick ascending segments of both long and short loops begin at the same level, the boundary of the inner and outer zones of the medulla, and extend up into the cortex to touch their own glomeruli at the macula densa. In the rat, approximately 70% of the nephrons have short loops. The distal convolution begins at the macula densa and extends to its junction with one or more other distal convolutions to form a collecting duct.

As to the microanalytical methods: osmolality was determined by the ultramicrocryoscopic method of Ramsay and Brown; this is a beautifully direct and precise method and requires only 10^{-6} ml of fluid. Ramsay's electrometric chloride titration method has similar volume requirements and accuracy. Inulin, used as a measure of net water movement into and out of the tubule, and urea were determined in separate experiments with the C^{14} label in a windowless flow proportional counter. In appropriately loaded and infused rats, 0.1 μl was a sufficiently large collection for these measurements since its radioactivity

was at least twice background. Control experiments showed that the specific activity was the same for plasma and urine and that the clearances of inulin-C^{14} carboxylic acid and urea-C^{14} were the same as that of the chemically stable compounds. Sodium was determined on a similarly small sample by flame photometry with a S.D. of $\pm 2\%$. pH was measured with the quinhydrone microelectrode of Pierce and Montgomery on a sample 0.05 μl in size with a S.D. of ± 0.06 pH units.

You will recall that in their classical mammalian micropuncture study, Walker, Bott, Oliver, and Mac Dowell (11) found proximal tubular fluid to be isomotic with plasma, a fact which we have abundantly confirmed as shown in figure 1. You will note that proximal fluid was always isomotic with vena cava plasma -- our reference value throughout these experiments -- even though the final urine was highly concentrated, only slightly hyperosmotic during solute diuresis or hypo-osmotic in rats with diabetes insipidus.

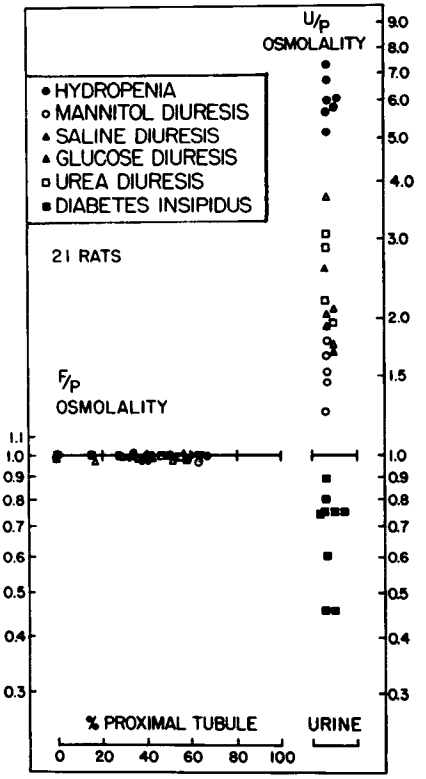

Fig. 1. Osmolality ratios of proximal tubular fluid and urine in rats.

From tubular fluid/plasma (F/P) ratios of creatinine and glucose in phlorizinized rats, Walker and collaborators estimated that approximately 60% of the water of the glomerular filtrate was reabsorbed by the mid-point of the proximal tubule, a value that agrees closely with our results. Although there was quite considerable variation among values for individual tubules, our average F/P inulin ratio was 3 at the end of the proximal convolution indicating that two-thirds of the water had been reabsorbed by that point. In figure 2 the same values are plotted reciprocally and indicate the per cent of filtered water remaining at any point. The dotted line, indicating average values, has been arbitrarily drawn as a curvilinear function. Extrapolation of function to the inaccessible last one-third of the proximal tubule, the pars recta, is hazardous, since there are anatomical differences between the two parts of the tubule and there may be functional differences as well, but a reasonable guess would be that 25% of the filtered water reaches the end of the proximal tubule. Since proximal fluid remains isosmotic, it immediately follows that two-thirds of the filtered solute is also reabsorbed in the proximal convolution. Sodium and associated anions are, of course, the major solutes present and in the nondiuretic rat we found the F/P sodium ratio to be as predicted by the Gibbs-Donnan equation, correcting for plasma water. Even though there is no detectable difference between tubular fluid and plasma, this is still consistent with the active transport of sodium since the proximal epithelium appears to be sufficiently permeable to water so that it follows rapidly upon the reabsorption of any solute. Therefore, the sodium ratio normally remains essentially 1.0. When a nonreabsorbable solute, such as mannitol, is added, one would expect a drop in the F/P sodium ratio if the reabsorption of sodium occurs by active transport. Our results

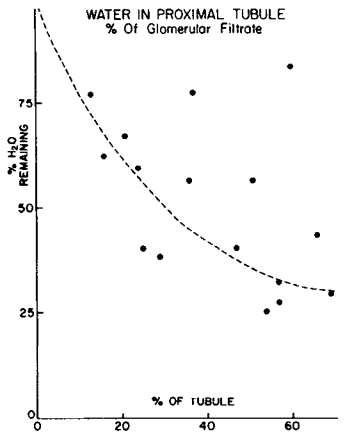

Fig. 2. Per cent of filtered water remaining at various points along the proximal tubule of nondiuretic rats.

demonstrate this, for ratios as low as 0.77 were found during mannitol diuresis, confirming the data of Windhager and Giebisch (12). Ratios in an intermediate range were found in rats loaded with urea, which is also reabsorbed proximally. The difference in chemical concentration plus the finding by S. Solomon (9) of a negative transtubular potential difference fulfill the criteria for the active transport of sodium by the proximal epithelium.

In apparent contrast to the amphibian kidney, we found a fall in pH relative to arterial blood in the proximal tubule of the rat (fig. 3). Although the maximum difference in pH is not great, if, as seems likely, the pCO_2 of proximal fluid remains approximately 40 mm Hg, the HCO_3^- concentration must fall to about

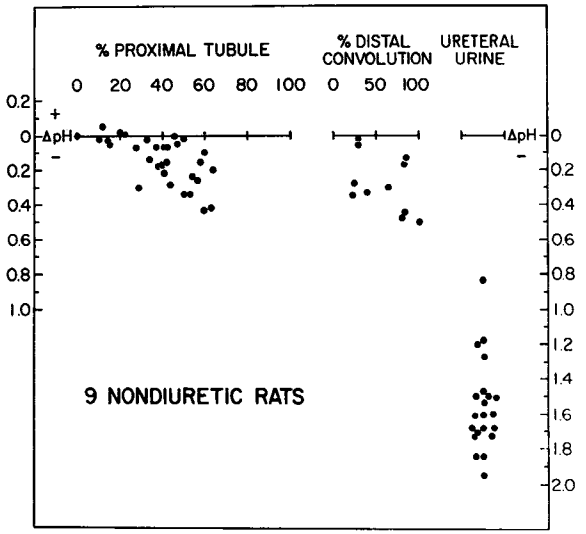

Fig. 3. Difference in pH of tubular fluid and ureteral urine from that of arterial blood in 9 nondiuretic rats. Minus pH values represent acidification relative to arterial pH.

10 mM/l. As expected under these circumstances, Walker and collaborators (11) found the proximal F/P chloride ratio to rise to approximately 1.4, a finding that we have confirmed. If the transtubular potential is about -20 mV (9), it is evident that chloride is not in electrochemical equilibrium across the proximal epithelium, but in contrast, H^+ and HCO_3^- may be. It seems most likely that this represents a Na^+:H^+ exchange mechanism with the sodium pump creating a potential that causes diffusion

of H^+ into the tubular lumen resulting in carbonic acid formation with subsequent dehydration and back diffusion of carbon dioxide and water. Since most of the filtrate is reabsorbed here, the proximal tubule accounts for the major part of the HCO_3^- reabsorption in the kidney and, by inference, H^+ secretion. Further acidification occurs in the distal convolution and collecting ducts.

It is worth emphasizing that only one mechanism for the proximal reabsorption of sodium is required since the preferential reabsorption of HCO_3^- out of the water permeable tubule leads to a chemical gradient of chloride favoring its passive movement out of the tubule although decreasing the electrical gradient.

Now to skip to the distal convolution. Wirz (13) found that the fluid in the early distal convolution was hypo-osmotic and remained so throughout the distal convolution in the absence of antidiuretic hormone (ADH), but became isomotic by the end of the convolution when ADH was present. We have also amply confirmed these findings. When ADH is present and the kidney is concentrating maximally (fig. 4), early distal fluid is quite hypo-osmotic but becomes isosmotic by the mid-distal presumably due largely to the outward diffusion of water. The fluid never becomes more than isosmotic in the distal convolution. Hence, the final and hyperosmotic phase of urine concentration occurs in the collecting ducts.

The hypotonicity of the early distal fluid also indicates that the tubular segment from which this fluid issues, that is, the thick ascending limb of the loop of Henle, is water impermeable in the presence or absence of ADH. The hypotonicity of this fluid could be due to either the reabsorption of solute in excess of water in the loop or to the secretion of water into the loop. If it is due to solute reabsorption, it must represent the reabsorption of sodium chloride since this is the only solute present in sufficient concentration, the reabsorption of which could lead to this degree of hypotonicity.

To differentiate between these two possibilities, diuresis was induced by the infusion of either the non-reabsorbable solute, mannitol, or sodium chloride. When mannitol was the loading solute, the limit of the early distal hypotonicity was an F/P osmolality ratio of 0.6. Late distal fluid was again isosmotic and the final U/P osmolality ratio quite low reflecting the extent of the diuresis. Similar results were obtained with glucose loading. When sodium chloride was the loading solute, the early distal hypotonicity was much more marked. Many samples had an osmolality ratio less than 0.6 with a minimum

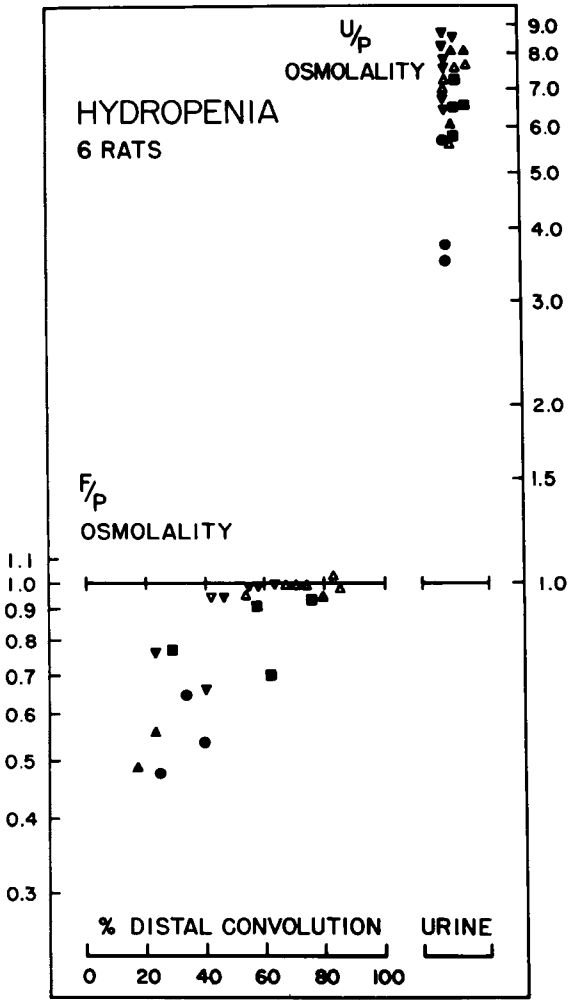

Fig. 4. Osmolality ratios of fluid from the distal convolution and of urine during hydropenia. Different symbols refer to different rats.

of 0.3. The results are shown superimposed in figure 5 and constitute, we believe, strong evidence that the early distal hypotonicity is due to the reabsorption of sodium chloride in excess of water in the loop of Henle. It is this mechanism, which we will return to in more detail a little later, that is primarily responsible for the hypertonicity of the medulla.

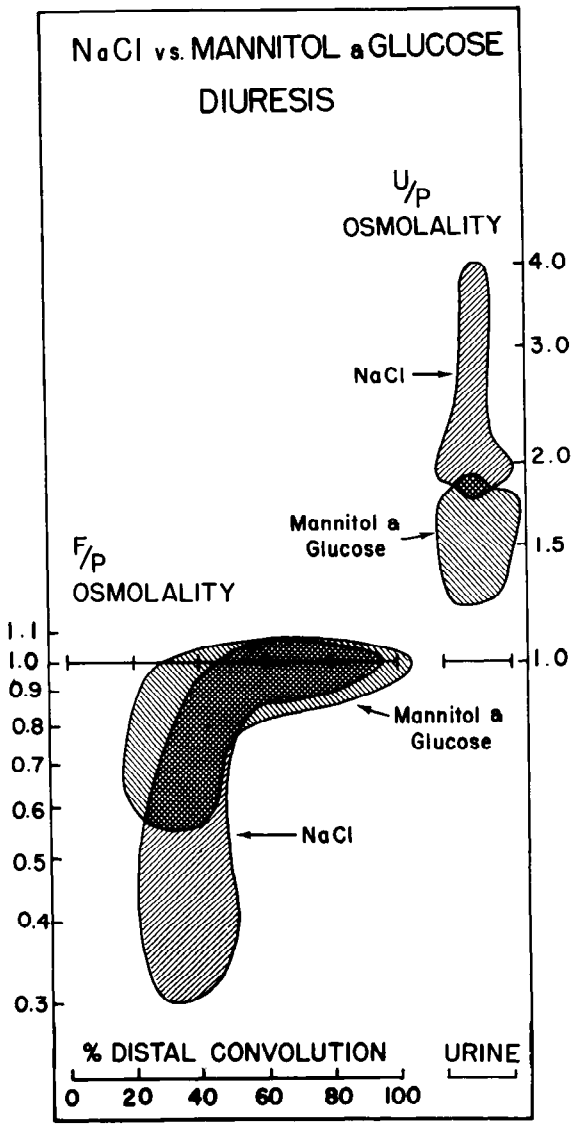

Fig. 5. Comparison of the osmolality ratios of fluid from the distal convolution and of urine during hypertonic sodium chloride diuresis with the ratios during hypertonic mannitol and glucose diuresis.

Based on the assumption that the F/P inulin concentration ratio provides a true measure of net transtubular water movement, we can now offer more definitive evidence that the early distal hypotonicity is due to reabsorption of solute in excess of water in the loop. The F/P inulin ratio averaged 6.7 in seven samples of fluid from the early distal convolution and increased progressively along the convolution. By extrapolation, the ratio of the fluid entering the distal convolution was about 5, corresponding to 20% of the volume of the glomerular filtrate. The proximal and distal inulin ratios are shown together in figure 6.

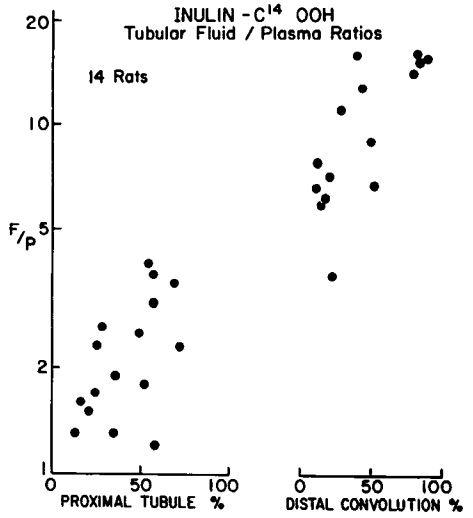

Fig. 6. Inulin ratios of fluid from the proximal tubule and distal convolution of nondiuretic rats.

The ratio in the early distal was approximately twice that of the fluid entering the loop of Henle, indicating the loss of approximately one-half of the water entering the loop. Yet since the fluid leaving the loop was distinctly hypo-osmotic, the net operation of the loop must involve the loss of solute in excess of water. In the distal convolution itself, both water and solute reabsorption continue, but water loss exceeds that of solute since the fluid becomes isosmotic. A similar situation holds in the collecting ducts for the marked increase in inulin concentration up to an average U/P ratio of 690, exceeded the increase in osmolality ratio which averaged 6.4. Even though the concentration ratios change markedly, the "actual quantity" of water and solute lost from the collecting ducts is small in comparison to that which is lost from the proximal convolution.

The sodium determinations on distal fluid are of interest. The F/P sodium ratio was approximately 0.6 in the early distal fluid of nondiuretic rats, a reflection of the activity of the sodium pump in the ascending limb of the loop of Henle. Since the sodium concentration remained approximately the same along the distal convolution, yet the inulin ratio rose, one may conclude that the epithelium of the distal convolution also actively transports sodium. During urea and mannitol diuresis the distal sodium concentration was one-half or less that in the nondiuretic animal. These data are a further indication of the importance of the water permeability of the tubule and the presence of unreabsorbed solute in determining the sodium concentration of tubular fluid. Although there may well be differences in the sodium pump mechanism in various parts of the tubule, one is not justified in concluding this merely on the basis of differences in sodium concentration since such differences may merely reflect differences in water permeability or the presence of water secondary to unreabsorbed solute.

I would now like to direct your attention to the net movement of urea in the tubules of the concentrating kidney. The handling of urea appears to be quite complicated, and I wish to emphasize that the relations may be different in other conditions or species. In the proximal convolution of the nondiuretic rat the urea F/P ratio quickly rose to about 1.5 but little further. At any point along the nephron, the F/P ratio of any solute divided by that for inulin gives a measure of the amount of that solute present relative to the amount filtered. Thus in the late proximal convolution, the ratio of 1.5 divided by 3 indicates that 50% of the filtered urea was lost out of the proximal convolution. This is presumably due to diffusion along its concentration gradient but the urea concentration of cortical interstitial fluid is unknown and active transport cannot be excluded.

Table 1 shows the amount of urea present at various points along the tubule. Although 50% of the filtered urea was lost proximally, the fluid that has traversed the loop of Henle contained an amount of urea equal to that filtered, since the inulin and urea ratios were the same. Obviously, there was addition of urea to the tubular fluid in the loop of Henle. There was some and variable loss of urea from the distal convolution and a large amount was lost from the collecting ducts since the urea clearance was only 13% of the glomerular filtration rate in these nondiuretic rats. All of the movement of urea may be passive and the addition of urea to loop fluid by no means necessarily indicates the active transport of urea. This is so since the large amount of urea lost from the collecting ducts and the action of the countercurrent system presumably result in a high concen-

tration of urea in the medullary interstitium and the diffusion of urea into the water-permeable descending limb of the loop of Henle. These data, however, do not permit one to include or exclude the possibility of active transport of urea by the mammalian kidney.

TABLE 1. AVERAGE FLUID TO PLASMA INULIN AND UREA RATIOS IN THE RAT KIDNEY

	Proximal Late	Distal		Ureteral Urine
		First 1/3	Last 1/3	
Inulin F/P	3.0	6.9	14.9	690
Urea F/P	1.5	7.7	10.5	90
Urea F/P / Inulin F/P	0.5	1.1	0.7	0.13

So far, I have discussed the findings in the proximal and distal convolutions from which data we can describe only the net operations of the loop of Henle. The operations of the loop have proven quite complicated involving a counter current mechanism as originally proposed by Dr. Werner Kuhn and his associates Hargitay and Wirz (6,15). They proposed that the loop of Henle functioned as a countercurrent multiplier system in which the urine was concentrated in the descending limb of the loop and then diluted to its isosmotic value in the ascending limb. It is theoretically possible to establish an osmotic gradient in a hairpin loop by either water transport from descending to ascending limb or solute transport in the opposite direction. In either system the initial effect, that is, the gradient at any level, can be quite small and is multiplied in the longitudinal axis of the loop. The final concentration in the collecting ducts was proposed as an osmotic equilibration with the progressively hyperosmotic loop.

The original experimental evidence was a study of the osmolality of kidney slices by Wirz, Hargitay and Kuhn (15). They found that the osmolality of the fluid was identical in all adjacent structures at any level in the kidney and that there was an increasing osmotic gradient from cortex to tip of the papilla. The cortex itself was isosmotic with plasma. Since we now know that early distal fluid in the cortex is consistently hypo-osmotic and their technique did not demonstrate this, we must suspect that post-mortem diffusion occurred in their slices. Therefore, before we can confidently conclude that the osmolality increases in all medullary structures, the fluid in each type must be sampled directly by micropuncture. Fortunately the anatomical features of the kidney of certain desert rodents makes this possible. In the Golden Hamster, Kangaroo Rat, Psammomys and others,

the papilla of the medulla is quite elongated and extends extrarenally into the upper portion of the ureter. By cutting away the upper portion of the ureter, one can visualize the tip of the papilla and with proper illumination distinguish and perform micropuncture on all the major types of structures, i.e., loops of Henle, collecting ducts and vasa recta. As predicted by the countercurrent hypothesis we found (fig. 7) in the concentrating kidney that the osmolality of fluid from the tip of the loop of Henle was essentially the same as that from adjacent collecting ducts. This was true in the nondiuretic animal as well as during glucose diuresis. We also confirmed the earlier finding of Wirz (14) that blood from the vasa recta has the same osmolality as collecting duct urine at the same level in the papilla.

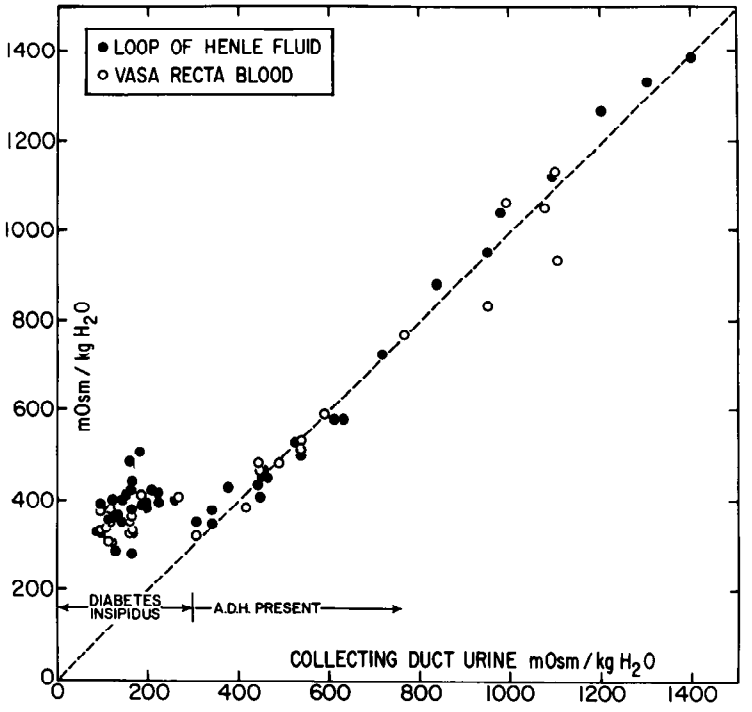

Fig. 7. Relation between the osmolality of collecting duct urine and fluid from loops of Henle and vasa recta blood in various normal desert rodents and in hamsters with experimental diabetes insipidus. Some of the values obtained in the presence of ADH are from DI hamsters following the administration of exogenous vasopressin.

We have found (fig. 8) that sodium and associated anions are the major solutes present in the fluid at the tips of long loops of Henle and together with urea account for almost all of its osmotically active solute. You will note that the concentration of both sodium and urea increased with increasing osmolality. In contrast, urea was the major solute in the collecting duct urine and the concentration of sodium was quite low. In table 2 are representative values for several parameters of loop fluid and collecting duct urine. Although the osmolalities were the same, the collecting duct inulin concentration was 10 times that in the loop; urea was present in much higher concentration in collecting duct urine than in loop fluid, with the opposite being true for sodium and chloride. You will note that the average inulin ratio of 11 in the loop fluid in these hamsters is higher than that of the fluid in the beginning of the distal convolution in rats. This is as expected, since the hamster loops were long, originating from juxtamedullary glomeruli, and extended to the tip of the papilla, while the collections in the rat were from nephrons with short

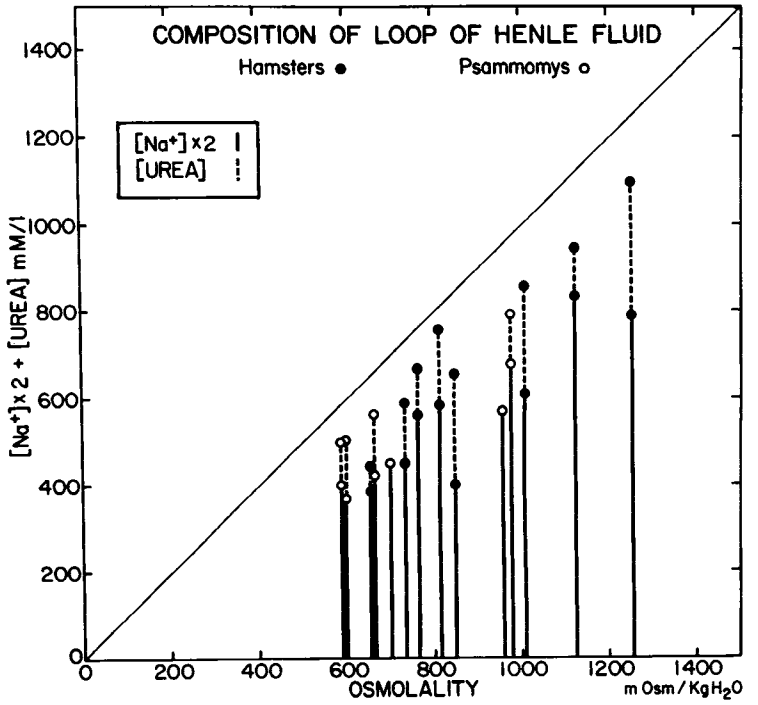

Fig. 8. Relation between osmolality and sodium and urea concentration in loop of Henle fluid from hamsters and Psammoys.

loops extending to the boundary of the inner and outer zones of the medulla. Since the long loops dip deeper into the increasingly hyperosmotic medulla, the water removed from them should be greater than from the short loops of superficial nephrons. This also points up the fact that there are certain to be variations in some parameters of the composition of distal fluid depending on whether the nephron has a long or short loop. This does not include osmolality, apparently, since the osmolality of proximal and distal fluids were the same in Psammomys obesus as in the usual laboratory rat. Psammomys is a North African desert rat in which all nephrons have long loops which dip deeply into the papilla. Nevertheless at a time when the urine was very hyperosmotic early distal fluid was hypo-osmotic as in the rat and hamster.

TABLE 2. REPRESENTATIVE ANALYSES OF LOOP OF HENLE FLUID AND COLLECTING DUCT URINE IN THE HAMSTER PAPILLA

	Loop of Henle Fluid	Collecting Duct Urine
Osmolality F/P	2.8 (22 samples)	3.0 (25 samples)
Inulin F/P	11 (11 samples)	122 (14 samples)
Urea F/P	17 (9 samples)	54 (9 samples)
Sodium F/P	1.9 (12 samples)	0.3 (16 samples)
Chloride F/P	2.8 (15 samples)	0.8 (10 samples)

The details of operation of the countercurrent mechanism are unknown and one can propose numerous variations of the countercurrent hypothesis which will explain the facts presently available. We agree that the active transport of sodium on which the system depends is accomplished by the nephron and that the loop of Henle functions as a countercurrent multiplier. The exchanges in the vasa recta, as in other blood vessels, are probably passive and they are believed to function as countercurrent diffusion exchangers, making the system more efficient by minimizing loss of solute from the medulla in the blood leaving the medulla. According to this view, the loop of Henle functions as a source of sodium (and chloride) ions for the medullary interstitium and as a result of its hairpin-like shape and permeability characteristics, an osmotic gradient is established in it as well as in the other medullary structures. Another general feature is that all exchanges are believed to take place between the lumina of the various structures and the adjacent interstitium and not directly between tubular lumina. The great theoretical advantages of the countercurrent mechanism are that one can explain all water movement as being secondary to previous solute movement eliminating the necessity of postulating active

water transport and that at no given level in the medulla are there large osmotic differences established and maintained by tubular structures only one cell layer thick. The large osmotic gradients are in the longitudinal axes of the several medullary structures and are thus maintained over distances that even in a rat kidney measure in terms of a centimeter and not in microns. Our present working hypothesis (5) which is based on the assumption that there is no active transport of water, follows (fig. 9).

"Sodium, by an unknown active mechanism, and chloride, as a result of the electrochemical gradient established, are believed to be transported out of the relatively water impermeable ascending limb of the loop of Henle into the interstitium of the medulla until a gradient of perhaps 200 mOsm/Kg of water has been established between the fluid of the ascending limb and interstitium. This single effect is multiplied as the fluid in the thin descending limb comes into osmotic equilibrium with the interstitial fluid by the diffusion of water out of, and probably the diffusion of some sodium chloride into, the descending limb, thus raising the osmolality of the fluid presented to the ascending limb. In this fashion, an increasing osmotic gradient is established in the direction of the tip of the papilla, and yet at no level is there a large osmotic difference between luminal and interstitial fluid. In contrast, the epithelium of the collecting ducts in the presence of antidiuretic hormone is believed to be water permeable and functionally sodium impermeable (net transport is probably small although there may be diffusion into, and active transport out of, the collecting ducts). This results in diffusion of water out of the collecting ducts into the hyperosmotic medullary interstitium until the fluid remaining in the collecting ducts becomes correspondingly concentrated. It is apparent that in order for the urine to be significantly concentrated the flow through the loops of Henle must considerably exceed the flow through the collecting ducts. This is accomplished under the influence of ADH by diffusion of water out of the distal convolution into the interstitium of the cortex, reducing the volume and increasing the osmolality to the isosmotic level of the fluid presented to the collecting ducts."

Ullrich and associates (10) have demonstrated by microcatheterization of the collecting ducts of hamsters that not only water but also osmotically active solutes, including sodium and urea, are lost from the collecting ducts and that hydrogen and ammonium ions are added. Our studies in the rat kidney also demonstrate this (except for ammonia which we have not studied) and we can add chloride to the list of those substances lost from the collecting ducts. It is likely that the fluid reabsorbed from

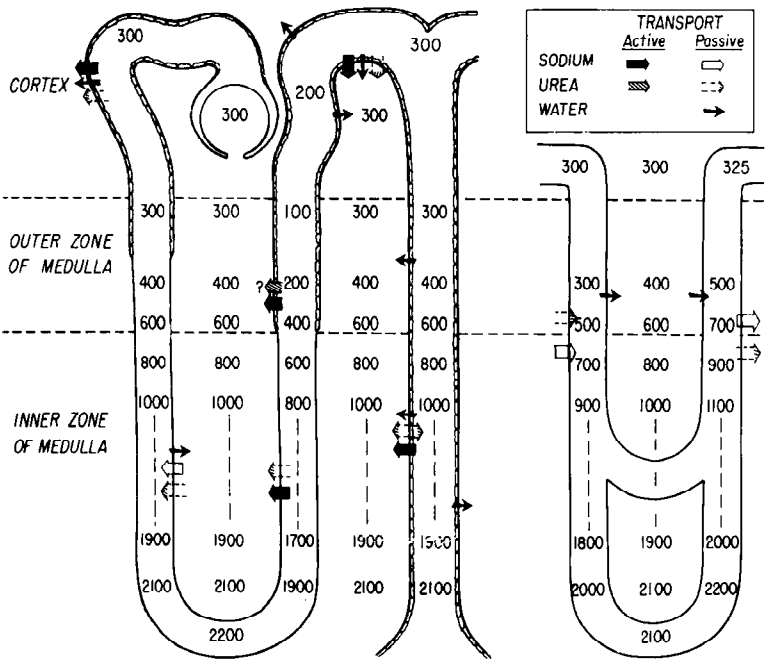

Fig. 9. Diagram depicting the countercurrent mechanism as it is believed to operate in a nephron with a long loop and in the vasa recta. The numbers represent hypothetical osmolality values. No quantitative significance is to be attached to the number of arrows and only net movements are indicated. As is the case with the vascular loops, all loops of Henle do not reach the tip of the papilla, and hence the fluid in them does not become as concentrated as that of the final urine, but only as concentrated as the medullary interstitial fluid at the same level.

Numerous variations of the countercurrent hypothesis are compatible with presently established facts: in absence of definitive evidence, we prefer the hypothesis illustrated above. One of the most attractive variants is that part of the Berliner hypothesis (2) which attributes active sodium transport to the thin ascending limb of the loop of Henle, since this has the unifying feature of placing this fundamental mechanism in all parts of the nephron. Even if this is the case, the back leak may be so large when the interstitial sodium concentration is very high that the net flux is inward as diagrammed above.

the collecting ducts in the concentrating process is not of constant composition at all levels in the medulla. Although hypoosmotic to the tubule urine remaining, it probably has an increasing osmolality and decreasing volume as the tip of the papilla is approached.

The role of urea in the concentrating mechanism is poorly understood. Diffusion of urea from the collecting ducts appears to result in a high concentration of urea in the medullary interstitium and, in turn, diffusion into the lumen of the water-permeable descending limb of the loop of Henle. Whether there is loss of urea, by either diffusion or active transport, from the ascending limb of the loop is unknown but it seems likely at least under some circumstances. If there is loss by diffusion, then apparently the epithelium of that portion of the ascending limb in which the loss occurs is more permeable to urea than to water. Perhaps the difference between thick and thin segments of the ascending limb is important here. In the non-steady state characterized by an increase in urine flow, the concentration of urea in the medullary interstitium may temporarily be higher than in the collecting duct urine. Then, diffusion would occur into the collecting ducts and the excretion of urea would be increased, the so-called "exaltation" of excretion of urea.

The vasa recta also participate in this mechanism and apparently function as countercurrent diffusion exchangers. As noted earlier they make the mechanism far more efficient resulting in a higher osmotic gradient by minimizing the loss of solute from the medulla in the blood leaving the medulla. The osmotic equilibration of the blood in the vasa recta with medullary interstitial fluid probably is due not only to the diffusion of solute into their descending, and out of their ascending limbs, but also results in large part from the diffusion of water in the opposite direction. This short-circuiting of water across the tops of the vascular loops may be, at least in part, responsible for the seemingly rich content of red cells in the vasa recta at the tip of the papilla. The efficiency of the countercurrent exchange in the vasa recta is critical, for they probably remove not only the blood entering the medulla, but also the water that diffuses from the thin descending limbs of the loops of Henle and the collecting ducts. This water, with solutes isosmotic for the particular level of the medulla, presumably moves into the vasa recta because of the gradient of its chemical potential established by the colloid osmotic pressure of the plasma proteins, since the hydrostatic pressures in the capillaries and interstitium are the same. The more nearly the osmotic pressure of the blood leaving the medulla approaches that of the blood entering it, the less solute will be lost from the medulla, and hence the higher the osmotic gradient established.

What is the effect of ADH on the countercurrent mechanism and how is dilution of the urine accomplished? Fortunately, we have had an opportunity to approach this problem by studying a series of rats and hamsters with experimental diabetes insipidus

(D.I.) in which there was presumably little or no ADH secretion. Dr. J. D. Crawford of the Massachusetts General Hospital established diabetes insipidus by producing focal hypothalamic anodal electrolytic lesions following which the voluntary daily water intake of the animals approximated their body weight. Osmolality determinations in these rats confirm Wirz's earlier finding that in the absence of ADH, the epithelium of the distal convolution is relatively water impermeable since the fluid remained hypo-osmotic throughout the convolution.

In 3 D.I. rats loaded with 0.7% sodium chloride solution and pretreated with 9α - fluoro-hydrocortisone to stimulate their sodium reabsorptive mechanism, the F/P osmolality ratio was 0.2 - 0.3 throughout the distal convolution. In a group of similar rats loaded with mannitol, the F/P osmolality ratio was 0.5 - 0.7 throughout with the exception of several late distal samples which were isosmotic. We have no reason to suspect any difference in the amount of ADH in the two groups and we believe the fluid here was not so dilute as in the rats loaded with sodium chloride probably simply because of the high concentration in the tubular fluid of the non-reabsorbable solute mannitol. In both groups, the final urine was not so dilute as the distal fluid, suggesting that water continued to be removed in the collecting ducts as Berliner (1) has suggested would be the case.

The effect of ADH on distal permeability to water is illustrated when one compares the result of solute loading in normal hydropenic rats and in rats with diabetes insipidus. With mannitol loading (fig. 10) the early distal fluid was equally dilute in both cases. It remained dilute in the rats with diabetes insipidus, but was isosmotic in the last half of the distal when ADH was present. During sodium chloride diuresis (fig. 11) the early distal fluid was slightly more dilute in the D.I. rats reflecting either increased sodium chloride reabsorption secondary to the 9α fluorohydrocortisone or slight water loss before the earliest collections during hydropenia. The difference in permeability to water of the epithelium of the distal convolution in the presence and absence of ADH is striking.

The findings in the medullary structures in the hamsters with diabetes insipidus are of greater interest. Here, in contrast to the normal hamsters, there was always a considerable osmotic gradient between loop of Henle fluid and vasa recta blood on the one hand and collecting duct urine on the other. Moreover, the osmolality in the loops was variable with a constantly dilute urine. The greatest difference in osmolality between the loops and collecting duct urine was 330 mOsm/l. Urine osmolality varied from 95 to 245 mOsm/l and was always hypo-osmotic to

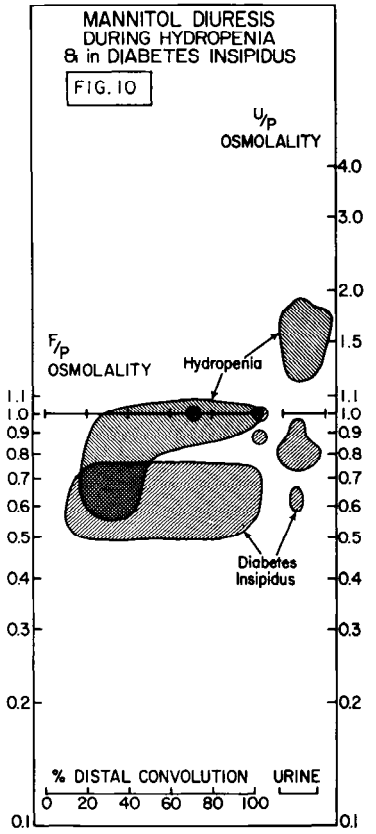

Fig. 10. Comparison of osmolality ratios of fluid from the distal convolution and of urine during mannitol diuresis in normal hydropenic rats and in rats with experimental diabetes insipidus.

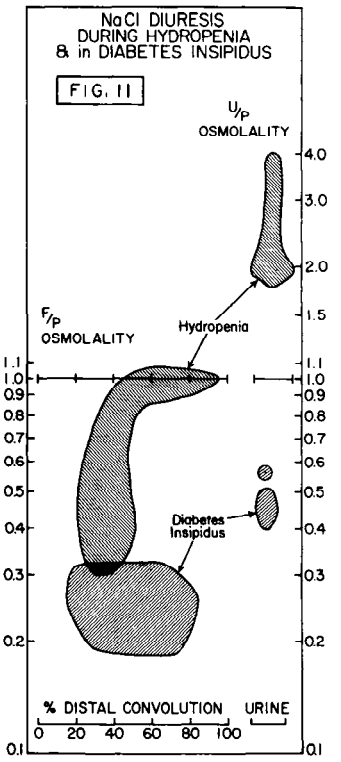

Fig. 11. Comparison of osmolality ratios of fluid from the distal convolution and of urine during sodium chloride diuresis in normal hydropenic rats and in rats with experimental diabetes insipidus.

vena cava plasma. Osmolality in the loop structures ranged from 285 to 515 mOsm/l and was always hyperosmotic to vena cava plasma. The osmolality of loop of Henle fluid and vasa recta blood were equal as during hydropenia indicating that ADH has no effect on the permeability to water of the descending limb of the loop of Henle. Following the administration of exogenous vasopressin, the osmolality of the collecting duct urine increased until it was the same as that of the medullary loops. These observations constitute direct evidence of an effect of ADH on the

permeability to water of the collecting duct epithelium. Thus in the absence of ADH, the permeability of the collecting duct membrane is one of the major factors limiting the amount of water that diffuses into the hyperosmotic medullary interstitium. When ADH is present, however, their permeability appears so great that the parameters of volume flow into the collecting ducts and interstitial osmolality are the limiting ones. The volume of water removed from the collecting ducts is, in turn, one of the determinants of the interstitial osmolality.

It is not surprising that the loop fluids are hyperosmotic when the urine is hypo-osmotic, since dilution of the urine is accomplished largely by sodium reabsorption in the medullary portion of the water impermeable ascending limb of the loop of Henle. In other words, the countercurrent mechanism in the loop of Henle and vasa recta continues even in the absence of ADH although the osmotic gradient established is not so steep as when ADH is present. It remains to be determined why the maximum osmolality at the tip of the loop in the D.I. hamsters without vasopressin was not as high as in the hydropenic normal animals. It is due in part to the absence of urea in high concentration (1) but an effect of ADH on the sodium pump and medullary blood flow are also possible. In addition, the D.I. hamsters were infused with a hypo-osmotic solution of sodium chloride which may have led to an increase in medullary blood flow and also to an increase in loop of Henle flow secondary to an increase in glomerular filtration rate, both of which would lead to a decrease in the osmolality of the medulla. This is so, since in a countercurrent system, the gradient established will be an inverse function of some power of the flow rate through the hairpin loops.

To summarize the course of events in concentration and dilution of the urine in three sentences. In both cases the countercurrent mechanism in the medullary loops is operative. When the final urine is hypo-osmotic, in the loop of Henle the tubular urine is slightly concentrated and then diluted, and remains dilute as it flows through the relatively water impermeable distal convolution and collecting ducts. In the presence of ADH, the tubular urine in the loop is concentrated even more, then diluted, becomes isosmotic in the distal convolution, with the final concentration occurring in the collecting ducts presumably due to the diffusion of water into the hyperosmotic medullary interstitium.

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WORKSHOP ON THE TEACHING OF UNDERGRADUATE PHYSIOLOGY

The Education Committee of APS will sponsor a Workshop on the Teaching of Undergraduate Physiology at the University of Massachusetts from August 7 thru 18, 1961. Dr. Paul R. Gross of New York University will be the director of the Workshop. Discussion leaders of national prominence in teaching and research will be in attendance. Participants will be chosen from applications received from college teachers in the New England and upper Middle Atlantic States. Further information and application forms can be secured from Dr. Ray G. Daggs, Executive Secretary, 9650 Wisconsin Ave., Washington 14, D.C.

HYPOTHALAMIC CONTROL OF ACTH RELEASE: SIMILARITIES IN CONTROL SYSTEMS FOR ENDOCRINE AND VISCERAL FUNCTIONS[1]

GEORGE SAYERS

A study of the neural control of the pituitary is in effect a study of the neural control of the entire endocrine system. Of the endocrines in the higher vertebrates only the pituitary has an important regulatory link with nervous system. No significant modification of secretory function of the thyroid, the adrenal cortex, the gonads, the islets of Langerhans or the parathyroid is exerted by neural connections to these glands.[2] The pituitary has a direct neural connection of functional significance. However, the pituitary also has a vascular connection, the portal system of vessels, which course between the median eminence of the hypothalamus and the adenohypophysis. Here is indeed an interesting functional link, a short vascular path to carry chemical mediators from the nervous system to the adenohypophysis. In this brief review we cannot consider the control of each of the pituitary hormones; ACTH will be used to exemplify the the general features of hypothalamic control of the pituitary.

Release of ACTH occurs in response to stimuli which have been known for some time to induce alterations in blood pressure and in respiration. There is obviously no good reason for setting the pituitary-adrenal cortex system off in a special category as far as regulation is concerned. The effective stimuli, the receptors, the neural pathways and the central integration for ACTH release have so much in common with stimuli, receptors, pathways, and integration long associated with control of visceral functions that we are compelled in my opinion to bring the terminology for ACTH release into line with established physiological usage. The term stress has had long and popular usage among endocrinologists to denote stimuli which induce activation of the pituitary-adrenocortical system. Stress carries the connotation that stimulation of the adrenal cortex requires actual damage to the organism. We are now

[1] Taken from the introductory talk given at the session on Hypothalamus at the Federation Meetings in Chicago, April, 1960.

[2] The adrenal medulla is considered a component of the autonomic nervous system in formulating such a generalization.

in a position to state unequivocally that release of ACTH is accelerated by a number of stimuli which induce no damage to the organism. Common everyday occurrences such as exercise, change in environmental temperature or emotional reactions induce ACTH release. The terms stress, stressor serve no useful purpose in the area of adrenocortical physiology and should be dropped in favor of the appropriate designation - stimulus.

Figure 1 is a schematic representation of the main features of the adenohypophyseal-adrenal cortex relationship. ACTH acts on the fasciculata and perhaps the reticularis to increase the rate of secretion of cortisol and of corticosterone. The glomerulosa or outer zone of the cortex which secretes aldosterone is under control of adrenoglomerulotropic hormone (AGTH), a hormone elaborated by tissue in or near the pineal gland.

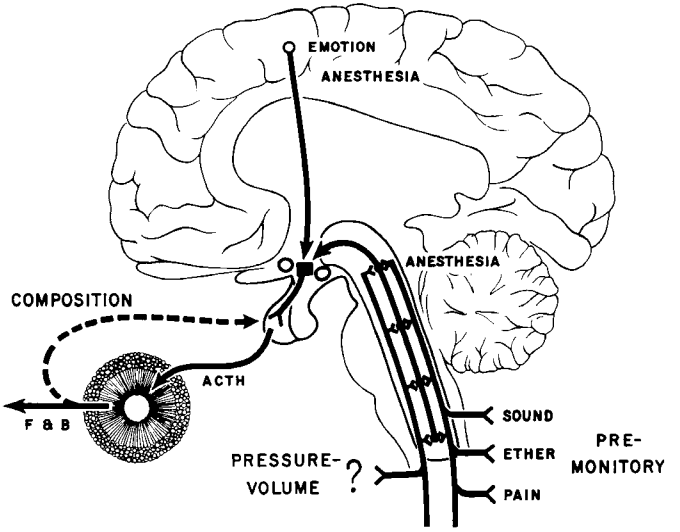


Fig. 1. Schematized representation of the control of ACTH release.

The general features of ACTH release are worthy of note. First, a great number and variety of stimuli are effective in inducing such release. Second, the response is quite rapid in onset. For example, within a minute after application of a painful stimulus the blood level of ACTH is increased. The nervous system mediates the action of the variety of effective stimuli. Impulses arising from stimuli acting at the periphery are carried by afferent paths into spinal cord and into brain stem. Spinal paths and cranial nerves may carry these impulses into the reticular formation for integration from whence they are transmitted to the hypothalamus. Midbrain, diencephalon, neocortex, the limbic

system undoubtedly have connections with hypothalamus which play a part in regulation of ACTH release. Investigations now in progress suggest that both excitatory and inhibitory influences may be exerted by these higher centers.

The hypothalamus is the neural center in regulation of ACTH release. This center is the focal point of convergence of the variety of impulses, traveling from above and from below, to induce ACTH release. Of considerable interest is the fact that hypothalamic influence over the adenohypophysis is mediated not by a neural path, but by a unique type of link, the portal venous system, which arises in the median eminence and travels along the infundibular stem into the adenohypophysis. The median eminence and its vascular connection to the adenohypophysis may be considered the "final common path" of the variety of impulses converging on the adenohypophysis to induce ACTH release.

Present thinking considers the median eminence - adenohypophysis relationship to be governed by a chemical mediator - corticotropin releasing factor (CRF). By an as yet unknown process CRF is released in the area of the capillary network in the median eminence and transferred to the portal vessels which distribute themselves in the adenohypophysis. The chemical mediator may be released at nerve endings in the median eminence.

As pointed out above, the neural phase of the regulatory system probably involves inhibitory as well as excitatory components. However, it has been known for some time that the secretion of the adrenal cortex itself exerts an important inhibitory influence over ACTH release. As the titer of corticosteroid in the blood increases the rate of ACTH releases decreases. One site of action of the corticosteroids appears to be the adenohypophysis. However, the steroids may also exert an indirect effect by acting on neural structures such as the hypothalamus. The rate of release of ACTH at any given instant appears to be determined by the algebraic sum of inhibitory and excitatory components (neural and steroid feedback), acting on the adenohypophysis.

Now let me draw attention to similarities between the system regulating ACTH release and the systems regulating blood pressure, respiration, antidiuretic hormone (ADH) release, and adrenoglomerulotropin release. At the outset it is well to point out that the dominant site of integration for respiration and for blood pressure is not the hypothalamus but centers lower in the brain stem. However, if one considers the hypothalamus as a part of the reticular formation then all these activities endocrine

and visceral are integrated to a major degree in a single albeit highly complex area of the higher nervous system.

Respiration, blood pressure and secretory activity of the adrenal medulla, the adrenal cortex and the neurohypophysis are modulated by complex systems of regulation which have been evolved for the maintenance of both the chemical composition and the volume of the body fluids. As experimental data accumulate on the regulation of ACTH release, adrenoglomerulotropin and antidiuretic hormone (ADH), one is struck by the

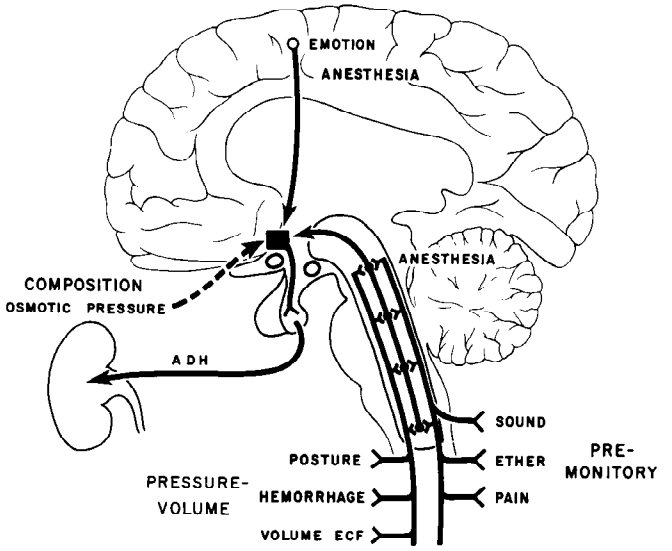


Fig. 2. Schematized representation of the control of ADH release.

similarities between neuroendocrine and neurovisceral regulatory systems. Both systems respond to a great variety of stimuli and they utilize receptors, peripheral pathways, spinal cord pathways, and brain stem integration. The central nervous system receives and integrates information from chemoreceptors and from pressure and/or volume receptors. This information is translated into modification of both visceral and endocrine activities. Of considerable interest is the fact that the anticipation of a traumatic insult sets off a sequence of changes in the viscera and in the endocrine glands which are in many instances difficult to distinguish from those which occur in response to actual physical injury. Furthermore, one is struck by the fact that the stimulus may set in motion an indiscriminate number of endocrine and visceral activities. The teleologic approach, to the effect that this serves a useful purpose, must not be accepted

without question. Whether the indiscriminate response is "good" or "bad" for the organism remains to be clearly defined. It would be of interest to determine at what point in time, after the initial indiscriminate response, more selective and appropriate activities are directed toward the mitigation of the aberrations peculiar to a given insult.

We do not have enough information to classify the neural processes controlling ACTH release in terms of neural pathways and integration centers. The best we can do is to classify the stimuli which are effective in inducing such release. Receptors responsive to changes in the chemical composition of the body fluids and receptors responsive to changes in pressure and/or volume of body fluid compartments serve important roles as components of the regulatory systems in question. In addition

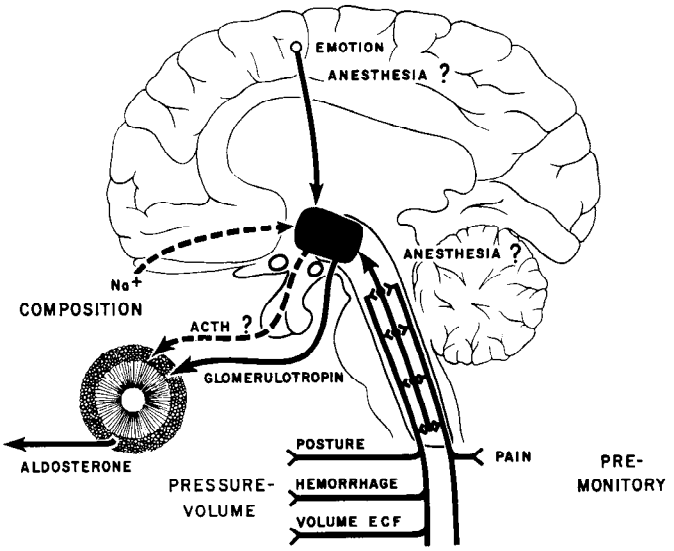


Fig. 3. Schematized representation of the control of adrenoglomerulotropin release.

to these stimuli one must consider painful stimuli (arising outside or inside the organism), emotional reactions, conditioned reflexes and other complex activities of the higher centers acting to induce changes in secretory activity of the endocrines or in the status of the viscera. It is difficult to find a term with which to embrace these various stimuli and reactions. "Anticipatory" is suggested since the neural processes involved are in most instances concerned with the mobilization of the organism for an anticipated event.

The following classification of the stimuli which act on visceral and endocrine functions emphasizes the similarities among the regulatory systems in question. The stimuli may be divided into three categories:

1. Composition. Stimuli which represent changes in the chemical composition of the body fluids and which act on chemoreceptors. Respiration and blood pressure are influenced by the pH or the pCO_2 of the blood, ACTH release by the titer of corticosteroids or of a metabolite the concentration of which is a consequence of an excess or of a deficiency of these hormones and ADH release by the osmolarity of the plasma.

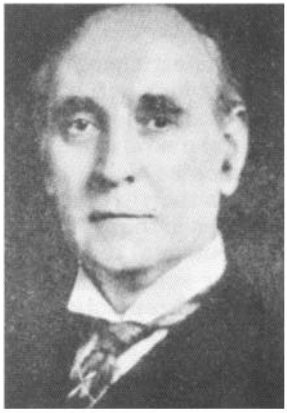
2. Pressure-volume. Stimuli which represent changes in the pressure or the volume of body fluids and which activate pressoreceptors or volume receptors. Respiration and blood pressure are modified by these stimuli. We are now aware that ADH is released in response to volume changes as well as by osmotic changes in the body fluids. Stretch on the right atrium or pulse pressures in the carotid artery influence the rate of secretion of aldosterone. No definitive experimental data have as yet been presented to implicate pressure or volume in ACTH release. However, circumstantial evidence has been collected in our own laboratory to suggest that ACTH release is also influenced by this category of stimulus.

3. Anticipatory. Stimuli which induce fright, pain, noise or emotional reactions, pleasant or unpleasant, are known to increase rate of elaboration of ADH, ACTH and adrenoglomerulotropin, to stimulate respiration and to alter blood pressure. The animal anticipates danger and the activation of visceral and endocrine activities is mobilized whether an actual physical insult occurs or not. Much work remains to be done in this important area. We are yet in a most elementary stage of knowledge in regard to the neural processes involved when unconditioned reflexes, conditioned reflexes, emotional reactions and affective experiences, bring about alterations in rate of ACTH release.

Similarities in the general organization of the regulatory systems modulating visceral and endocrine activities are schematized in figures 1, 2 and 3.

SOME PAST, PRESENT AND FUTURE ASPECTS OF INDICATOR-DILUTION TECHNICS[1,2]

EARL H. WOOD



George Neil Stewart
1860-1930

Most of you probably do not know that this session on indicator-dilution technics was conceived and arranged to honor Dr. George Neil Stewart's pioneering and very important contributions to this field. This is especially appropriate because this particular time is, to the week, the 100th anniversary of his birth. Prof. Chester Hyman called the attention of the officers of our Society to the coincidence of our meeting time and Dr. Stewart's birth; hence, Dr. Hyman is the "father" of this session. I hope and trust that our efforts this afternoon will in some measure do justice both to Dr. Stewart and to Dr. Hyman's excellent suggestion.

According to instructions received from the Program Committee, only the first ten minutes of this opening presentation are to be devoted specifically to some historical background and a tribute to Dr. Stewart, with the remaining twenty minutes to be given to considerations of indicator-dilution technics of my choosing. These instructions gave rise to my rather sweeping title, namely "Some Past, Present and Future Aspects of Indicator-Dilution Technics."

Past Aspects

The past aspects will be devoted in large part to Dr. Stewart. To give some idea of the framework of his academic and scien-

[1]Read at the meeting of the Federation of American Societies for Experimental Biology, Chicago, April 13, 1960. Portions of the studies reported herein were supported by Research Grant H3532 from the United States Public Health Service.

[2]Photograph reproduced with permission from C. J. Wiggers (41).

tific life, I can do no better than recite excerpts from his curriculum vitae (18,19,20,28,41).

George Neil Stewart, physiologist, was born in London, Ontario, on April 18, 1860. His parents returned to Scotland shortly thereafter, and he was brought up in the small fishing village of Lybster, on the northeast coast of Scotland. He attended the University of Edinburgh and attained an M.A. degree in physics, with honors in mathematics in 1883.

The demand for physicists and mathematicians apparently was not so great at that time as it is today because, to be more certain of a livelihood, Stewart changed to medicine. In the study of medicine, he quickly became interested in biologic processes, particularly the application of physical methods to the elucidation of these processes.

He must have been an excellent student because he was awarded a number of academic honors and scholarships for which, owing to the scarcity of such appointments in those days, the competition must have been extremely keen. He became a MacKay Smith Scholar and was awarded a B.S. degree from Edinburgh in 1886, a D.Sc. degree in 1887, and an M.D. degree in 1890.

He studied electrophysiology in Berlin with the authority of that day, Prof. du-Bois-Reymond. He served as a demonstrator in physiology, Victoria College, Manchester, from 1887 to 1889, and as an examiner in physiology in Aberdeen, Scotland. He was a George Henry Lewis scholar at Cambridge from 1889 to 1893 and he studied in Strassburg in 1892. His early work on circulation times using indicator-dilution technics was done at Cambridge and Strassburg.

He accepted a post as an instructor in physiology with Bowditch at Harvard Medical School from 1893 to 1894. In 1894, he became professor of physiology and histology at Western Reserve University School of Medicine, serving there until 1903. At that time, he became professor of physiology at the University of Chicago. He returned to Cleveland as professor of experimental medicine and director of the H. K. Cushing laboratory in 1907, in which post he served until his death on May 28, 1930, just short of 30 years ago.

This skeleton of his career provides only a partial picture of the man. To provide a more extensive portrayal, I can do no better than to quote excerpts from an article written by Prof. Sollmann after Stewart's death. Sollmann was an early pupil of

Stewart from the time of the latter's arrival in Cleveland and later became his intimate friend and colleague over the many years that Sollmann served as head of the Department of Pharmacology at Western Reserve University. This article was published in the Bulletin of the Academy of Medicine of Cleveland under the title, "George Neil Stewart, An Appreciation"(27). Excerpts from it follow:

"By the death of George Neil Stewart on May 28, 1930, the School of Medicine has lost a great man and a loyal friend. His greatness was founded in a rude past which the rapid current of events has rendered almost legendary. I was among the students who awaited his first lecture in 1894. On the morning of his arrival in Cleveland, the boat on which he sailed from England having been delayed, he came almost directly from the train to the lecture room, with a sheaf of tracings in his hand. He began to speak; and as in the turning of a hand, physiology was transformed to our young minds from the dead traditions of textbooks into a living language, into a living thing, a tissue of function interwoven with structure. The quickening of life is always notable; this was the more notable in that it marked the introduction of new methods into the teaching of physiology; methods which have since become the universal practice in America, but which were originated largely by Stewart....

"The chief innovation, however, was the laboratory course, which furnished the background, the foundation of observations and experiments, upon which the structure of logic was reared. At that time, experimental courses in physiology were given in but few schools, and consisted almost entirely of some muscle-nerve work, and a few test-tube experiments on digestion, saliva, and urine. Stewart was probably the first physiologist in the world to make mammalian experiments a part of the regular course....

"The teaching covered not only physiology, but also histology and considerable biochemistry, and was given separately to medical and to dental classes. Nor were the courses slighted; the work was thorough, so far as it went, and offered a natural correlation between these subjects which had considerable value. While all this was going on, Stewart was also writing his 'Manual of Physiology with Practical Exercises,' a monumental work, which embodied his ideas of the teaching of physiology, and which was so sound, so thorough and so attractively written that its successive eight editions remained for many years the standard textbook for medical students. The literary finish and the scientific excellence of this work must astonish doubly when one considers the conditions of stress under which

it was produced. There were no secretaries or typewriters. Every word was written by Stewart in longhand, chiefly in the small hours of the night, after the fatiguing toil of the day. The printing was finished during the summer vacation in England, under great pressure of time, which, however, was not permitted to mar the perfection for which Stewart always strove....

"At that time, there was a wide gap between clinical and experimental medicine. The value of scientific medicine to civilization was not yet appreciated, and funds for medical research and teaching were very limited. Every available penny was put into the laboratory departments, and there were no clinical chairs in America that received more than a nominal salary. Clinical teachers, therefore, could not afford the time for laboratory training or experimentation. They observed at the bedside, but could not subject their observations to experimental analysis. The laboratory workers were more or less isolated from the clinic. The gap was bridged only by the hazard of personal friendship, the need of some less fortuitous method of bridging was strongly felt. In those days it would have appeared folly to entertain the expectation of the funds needed for the solution of the problem which time has evolved; namely, the establishment in the medical clinics of fully paid staffs with thorough scientific as well as clinical training, and of such size as to leave leisure for experimental as well as clinical work. It seemed much more feasible to establish a department of Experimental Medicine, which should have the task to build the badly needed bridges wherever and whenever occasion offered. This plan was tendered to Stewart, if he would return to Western Reserve. The venture captured his imagination and he yielded.

"The University recovered a great man, and the experiment could be undertaken. There were noteworthy gains, but there was also a loss to Stewart and to medical education for his new duties restricted his contact with students, and Stewart was greatest in the classroom. He lost the stimulus of frequent and systematic contact with students and generations of students lost the stimulus of Stewart's teaching.

"To the end, Stewart was the loyal master and the warmhearted friend, to whom I could take any problem, personal or scientific, for wise counsel and sympathetic understanding.

"Such was Stewart, as he was known to me. Such he was to his students, and to his later assistants and associates. He was a great scientist, a brilliant writer, but above all, a great teacher, who left his mark on all who came under his spell; and the mark was good."

In concluding these considerations of Stewart, the man, I should like to suggest that in addition to his great inherent capabilities, his early training in physics and mathematics was in large part responsible for his remarkable contributions to physiology. These capabilities and training also led to his wide diversity of interests, which seem astounding in this day and age, when all investigators are forced to become more or less specialists by the hard fact that it is impossible for a single person to encompass more than a small segment of the immense body of knowledge that now exists in every field of science.

In the course of his career, Stewart did investigative work on the following subjects: color vision, electrophysiology, cardiac nerves, circulation time, otoliths, muscle proteins, electric conductivity, permeability of erythrocytes, resuscitability of the central nervous system, calorimetric measurements of blood flow, epinephrine output, and adrenal insufficiency. These comprise, indeed, an imposing list of interests.

Few would doubt that Stewart's most important contributions were his conception and application of indicator-dilution technics to the measurement of blood flow and his estimates of blood volume on the basis of the determination of circulation time and blood flow (29,30,31,32,33). These contributions are so well known as not to require repetition. They are placed in proper perspective by Dow's (7) excellent review of this subject. Dr. I. J. Fox, of our laboratory, recently completed a painstaking review (9) of this field and brought up two points of disagreement with Dow's excellent assessment of Stewart's contributions.

Dow stated that Stewart's rejoinders in his articles published in 1921 (31,32,33) were unfairly belittling to the criticisms of his early work contained in the more recent and excellent papers of Henriques, 1913 (15) and Bock and Buchholtz, 1920 (3). Without question, both these papers significantly improved on Stewart's technics; however, one can scarcely blame Stewart for his ire at finding in each of these papers a statement to the effect that a technic based on a "new" principle, but one resembling Stewart's was being employed. I am sure that Dow would agree that the contributions of these later authors did not constitute a new principle but rather an improvement in the application of the principles clearly enunciated previously by Stewart.

Dow also made the statement that Stewart "firmly believed that the pattern of a 'square wave' injection of salt solution, even of one made into the jugular vein, was reproduced in the arteries without quantitatively significant distortion." Dow's interpretation is highly questionable in view of the fact that Stewart, by

means of his telephonic detection device, noted the presence of a definite "rise time" to the peak concentration of indicator and even gave a good explanation for this longitudinal dispersion of the indicator particles, namely that of laminar flow. He (30) stated as follows: "But there is always a certain thinning out of the column (of injected saline) at its front and rear, as can be well shown by the somewhat gradual increase and decline of the sound in the telephone." Stewart appreciated that this "smearing" increased as the distance between the injection and sampling sites was increased, as in the case of comparing injections into the left ventricle and the jugular vein.

Stewart was aware of the effect of laminar flow on the dispersion of an indicator along a tube, and he performed experiments with blood and water flowing in tubes of various sizes, demonstrating that the fastest traversal time of indicator was somewhat more than half the traversal time calculated by the "flow x volume" formula that would pertain if the mixture of dye and blood maintained a square-wave front during traversal of the tube (30).

Finally, he was even aware of the possibility of errors being introduced into his technic by use of a hypertonic and diffusible indicator substance. To circumvent these difficulties, he suggested the possibility of using serum as an indicator substance, since he found that the electric resistance of serum was two to five times less than that of whole blood (30).

Present Aspects

In the transition from the past to the present, the contributions of Hamilton and his group are paramount and need no recounting. Suffice it to say that the designation of the technic as the "Stewart-Hamilton method" is more than justified.

Application of methods for continuous recording is certainly one of the more important of the recent developments in this field. However, just as Hamilton's discontinuous sampling technic was antedated by the work of Vierordt (39) reported in 1858, a forerunner of continuous recording, namely continuous auditory monitoring, likewise was used by Stewart in the 1890's, and excellent continuous recordings were attained by Gross and Mittermaier (13) in 1926 (fig. 1). These curves, which were obtained by injection of the indicator at a constant rate, are closely similar to those published in recent years in studies that have led to reapplication of constant-rate infusion technics (12,21,24).

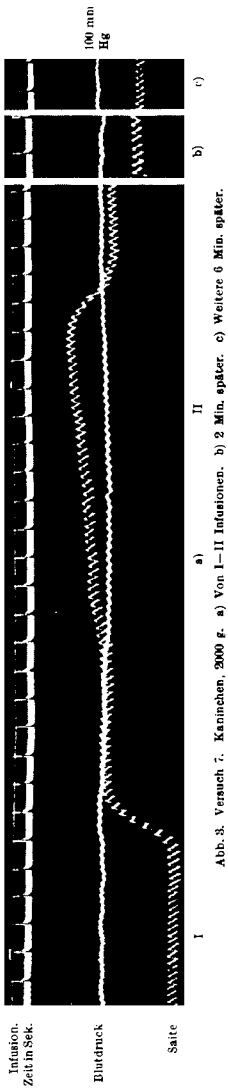


Abb. 3. Versuch 7. Kaninchen, 2000 g. a) Von I—II Infusionen. b) 2 Min. später. c) Weitere 6 Min. später.

Fig. 1. Continuous recording of variations in conductivity of carotid arterial blood of rabbit before, during and after constant-rate infusion of 2% solution of sodium chloride into jugular vein between points I and II. Note that after the initial rapid increase in conductivity (NaCl concentration) of the blood, there is a plateau in concentration lasting about 4 seconds, which is terminated by a secondary increase in concentration caused by systemic recirculation of the indicator as the injection continues. From Gross and Mittermaier (13).

Clinical diagnostic applications of indicator-dilution technics have been assuming increasing importance (12,36,37, 38,42). However, the potential clinical value of the method was visualized by Hamilton and his associates in the early 1930's (14).

The diagnostic use of indicator-dilution technics has attained a most important application in conjunction with cardiac catheterization (12,36,37, 38,42). These applications have been broadened by the development of new indicators, the most important of which is indocyanine green, known in our laboratory as Fox green, after Dr. Irwin J. Fox, who played such an important role in its development (9, 36). The structural formula of this dye, which was synthesized particularly for this purpose in the Eastman Kodak Laboratories, is shown in figure 2.

This dye has greatly simplified the continuous quantitative recording of dilution curves in arterial blood in the presence of arterial hypoxemia (fig. 3). It also has made possible the continuous quantitative recording of dilution curves by photometric methods from the venous circulation, which has led to the development of highly sensitive methods for the detection and quantitation of left-to-right shunts in patients who have congenital heart disease, and the simultaneous quantitation of systemic and pulmonary blood flow in such patients as illustrated in figures 4 and 5. Study of regurgitation via the valves in the right side of the heart also has been simplified (fig. 6).

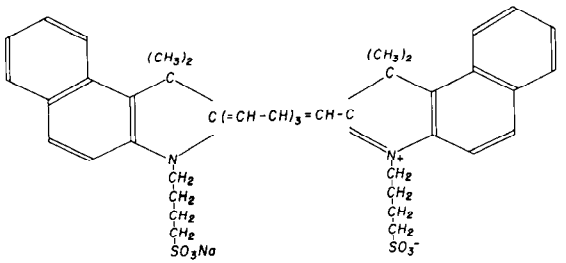


Fig. 2. Structural formula of indocyanine green. This valuable indicator dye and its several less valuable forerunners were synthesized in the Eastman Kodak laboratories in 1956 and 1957 by Drs. G. S. Brooker and D. W. Heseltine, at the instigation of Dr. I. J. Fox, of the Mayo Foundation. Indocyanine green is commercially available from Hynson, Westcott and Dunning, Inc., Baltimore, under the trade name cardio-green.

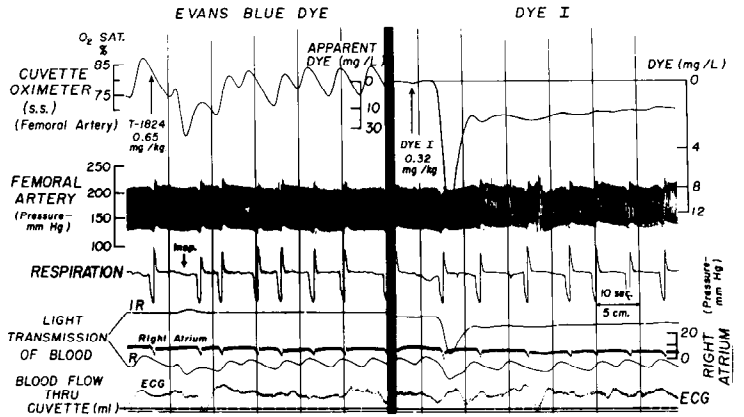


Fig. 3. Arterial dilution curves recorded after successive injections of Evans blue and indocyanine dye I into pulmonary artery of anesthetized 15.5-kg dog breathing room air. Fluctuations in arterial oxygen saturation, commonly found under these circumstances, produced large variations in the transmission of red light (R) during the recording of both curves. The single-scale (s.s.) oximeter recording of the Evans blue curve is uninterpretable because of these fluctuations, while the dye I curve is undistorted despite the fact that the variations in transmission of red light by the blood were undiminished. (Reproduced with permission of the authors and publisher from a chapter by I. J. Fox and associates in H. A. Zimmerman, Intravascular Catheterization. Springfield, Ill.: Thomas, 1959, p. 782.)

Recent developments in methods involving the continuous injection of dye deserve mention. These technics, unlike conventional sudden single-injection procedures, allow the continuous measurement of blood flow. Such continuous measurements have valuable application in the important but difficult-to-study unsteady-state conditions associated with the cardiovascular compensatory reactions induced by cardiovascular stress.

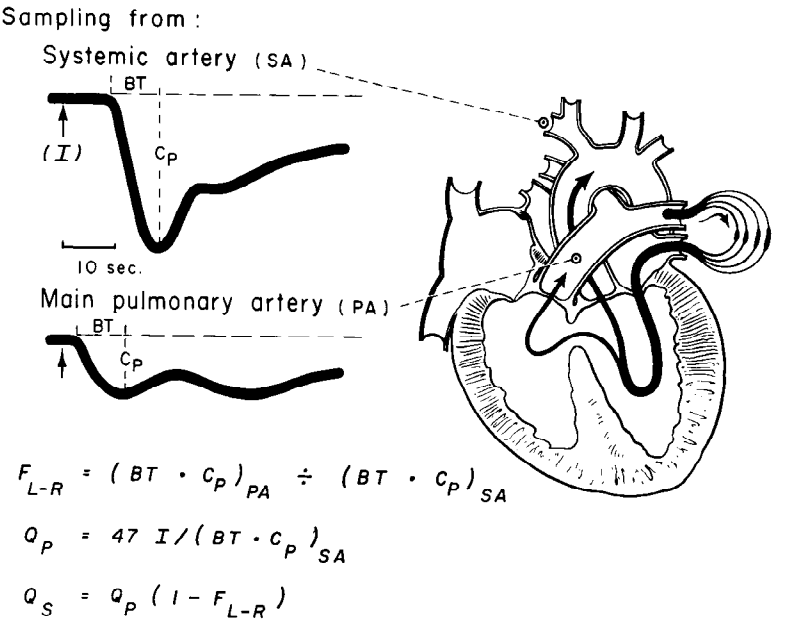


Fig. 4. Measurements and equations required for calculation of pulmonary blood flow, magnitude of left-to-right shunt and systemic blood flow from dilution curves recorded simultaneously from a systemic artery and main pulmonary artery after injection of indicator into distal pulmonary artery in patient with left-to-right shunt via ventricular septal defect. A diagram of the central circulation is shown on the right, and dilution curves recorded from a systemic artery and the pulmonary artery are on the left. Vertical arrows indicate the instant of dye injection. Pulmonary flow (Q_p) is calculated from the initial forward-triangle portion of the systemic arterial curve, as described by Ramirez de Arellano and co-workers (23). The fraction of the pulmonary flow composed of shunted blood (F_{L-R}) is the ratio of the area of the forward triangle of the pulmonary arterial curve $(BT \cdot C_p)PA$ to that of the forward triangle of the curve recorded simultaneously at the systemic artery $(BT \cdot C_p)SA$. Systemic flow (Q_s) is calculated by multiplying the pulmonary flow (Q_p) by the fraction of unshunted blood $(1-F_{L-R})$.

These recent applications of continuous-injection technics are based on double-sampling methods, which make possible correction for recirculated indicator (fig. 7).

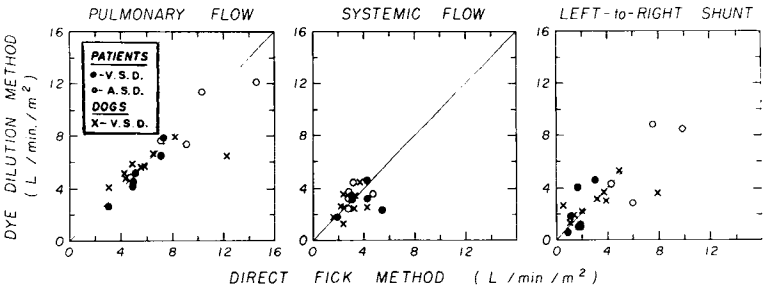


Fig. 5. Comparison of flow values obtained by dye-dilution method illustrated in figure 4 and by direct Fick method in 12 patients and 9 dogs with intracardiac shunts. Note the absence of systematic differences in the values obtained by these methods and that the magnitude of the differences between the two methods is within the margin of error for the Fick method when applied to measurement of pulmonary and systemic blood flow in the presence of a left-to-right shunt. (Reproduced with permission of the publisher from Wood (42).

These technics recently have been extended and improved by the simultaneous use of two indicator dyes (fig. 8).

Future Aspects

To lead briefly into some of the many possible future developments, let us consider briefly the problem of recording dilution curves from sites in the central circulation, namely the cardiac chambers, pulmonary artery and aorta. It has been recognized that the changes in concentration at these sites during passage of an indicator must occur in a stepwise fashion with each heartbeat. Recordings of such changes in the aorta have been used by Holt (16) to calculate the end diastolic and systolic volumes of the left ventricle; however, evidence exists that the mixing requirements in the ventricle on which such calculations are based may not be fulfilled (35). Accurate recording of stepwise changes in concentration requires close attention to the dynamic-response characteristics of the recording instrument. Studies in recent years have shown that there is indeed considerable distortion or smearing when a dye-blood mixture traverses a system consisting of either blood vessels inside the body or tubes outside the body (10). The degree of this distortion in the case of a catheter-densitometer system is determined in great part by two factors (41) the volume of the systems, that is, the volume of the "dead space" between the tip of the catheter and the detecting element of the densitometer, and (18) the rate of blood flow through this system (1).

The dynamic response of a given catheter-densitometer system is determined by the rate of blood flow through it. The

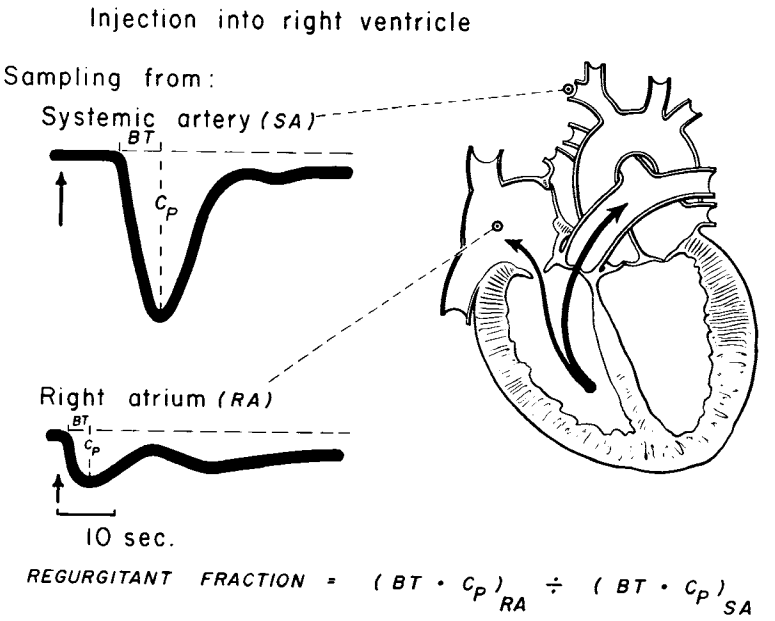


Fig. 6. Method of localizing and estimating regurgitant flow through tricuspid valve. A diagram of the central circulation in tricuspid regurgitation is shown on the right, and dilution curves recorded from a systemic artery and the right atrium are on the left. Vertical arrows indicate the instant of dye injection into the right ventricle. When dye is injected just downstream to the incompetent tricuspid valve, a portion of the dye is regurgitated through the valve and is detected almost instantaneously at the right atrium, producing the abnormal initial concentration peak illustrated in the lower curve. If the initial portion of each curve is considered as a triangle, the area of these triangles can be calculated by the formula $A = 1/2\ (BT \cdot C_P)$. The fraction of the dye regurgitated into the right atrium (regurgitant fraction) is related to the ratio of these areas by the equation given in the lower part of the figure. Recent well-controlled studies in dogs with induced mitral (6) and aortic (1) regurgitation indicate that this indicator-dilution technic is superior to previously described methods for the detection and quantitation of valvular regurgitation.

effect of variation in the rate of blood flow through such a system is illustrated in figure 9, and the effect of the resulting variations in the dynamic response on the contours of dilution curves recorded from the pulmonary artery by this system is shown in figure 10. Such studies have demonstrated that reasonably accurate recording of such dilution curves requires a blood flow of more than 150 ml per minute through this particular densitometer system, which includes a sampling catheter of a minimal length of 40 cm to reach the pulmonary artery of a dog from the external jugular vein (8).

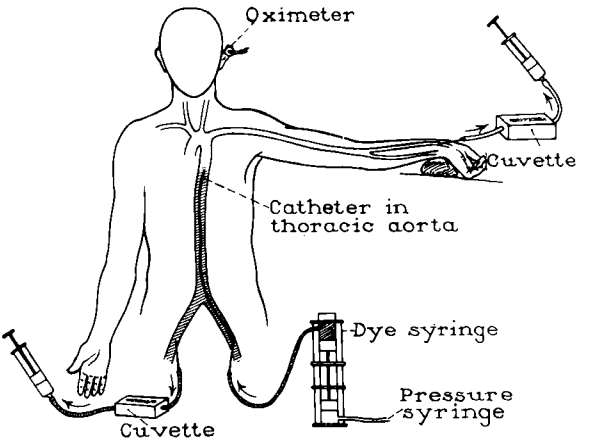
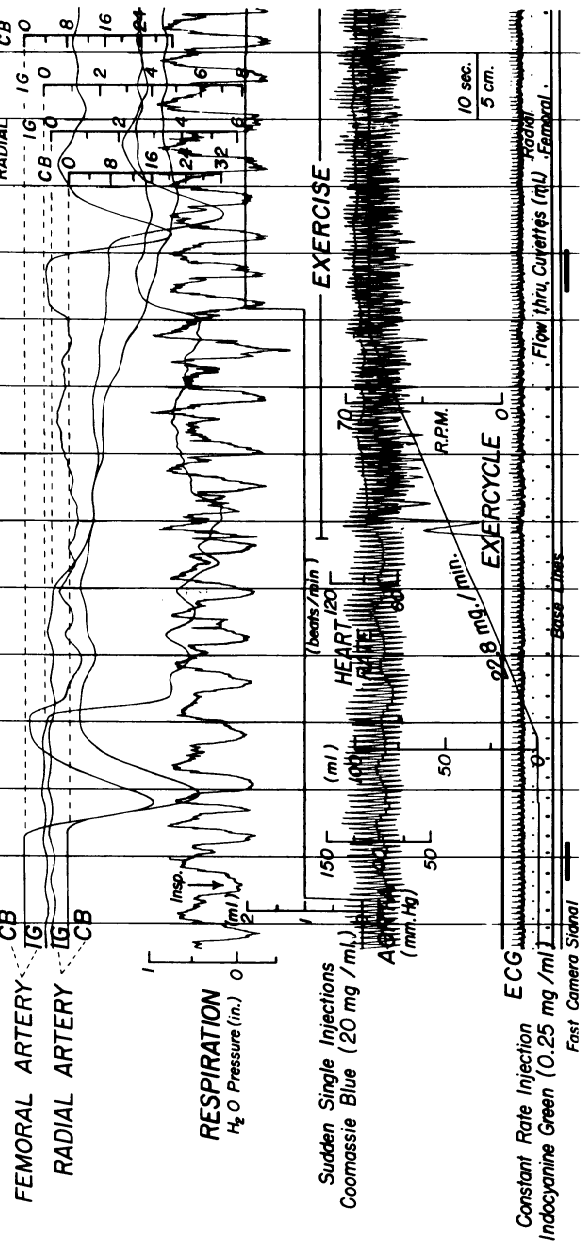


Fig. 7. Diagram of assembly for continuous recording of thoracic-aorta flow by constant-rate dye injection. Measurement of the concentration of dye at the femoral artery and the rate of dye injection into the thoracic aorta allows calculation of blood flow in the thoracic aorta. Only recirculated indicator reaches the arteries arising from the aortic arch; therefore, the continuous recording of indicator concentration at the left radial artery makes possible a correction for recirculated indicator, so that flow in the thoracic aorta theoretically can be measured for any duration of injection desired. The earpiece oximeter likewise indicates recirculation of indicator. Reproduced with permission of the authors and publisher from Grace and associates (12).

It is difficult or even impossible to attain blood flows of this magnitude through such a sampling system. Therefore, attempts have been made to recover the actual curve present at the tip of the catheter, using a numerical recursive method of calculation based on the curve recorded by the system and the measured response of this system to a stepwise change in the concentration of indicator (5,11). An example of the "true" dilution curve recovered in this manner from a curve recorded by a system with a relatively poor dynamic response is shown in figure 11, along with a curve recorded simultaneously by a system having a fast response for comparative purposes.

This technic for recovery of "true" dilution curves is not practical for wide-scale application, since it requires an extremely large number of accurate measurements of the recorded curves followed by extended arithmetic calculations. However, attainment of practicality is possible by use of modern electronic technics for the handling of data. These extended calculations have been done in a very short period of time by means of a general-purpose digital computer (11). Likewise, use of an analogue digital conversion system could reduce the measurement time to a matter of seconds.


(mg/L)
FEMORAL
RADIAL
CB
IG
FEMORAL ARTERY
RADIAL ARTERY
RESPIRATION
H2O Pressure (in.)
Insp.
Sudden Single Injections
Coomassie Blue (20 mg/ml.)
ARTERIAL PRESSURE (mm. Hg)
HEART RATE (beats/min.)
EXERCISE
R.P.M.
EXERCYCLE
22.8 mg./min.
10 sec.
5 cm.
Flow thru Cuvettes (ml.) Radial Femoral
Base Lines
Constant Rate Injection
Indocyanine Green (0.25 mg/ml.)
ECG
Fast Camera Signal

Use of magnetic-tape recordings and electric analogue computer technics to solve this problem and other problems of analysis involving dilution curves is also a promising approach the feasibility of which has been demonstrated in preliminary studies (40).

Perhaps the most promising approach to attaining high-fidelity recordings of dilution curves from sites in the central circulation in closed-chest dogs or man is the development of a catheter-tip densitometer for indocyanine green. Dr. Michael Polanyi, of the American Optical Company, has made important progress in this regard by the development of a catheter-tip oximeter. This instrument is based on the reflection principle (22) and the necessity of extreme miniaturization is largely avoided by use of fiber optics to transmit the incident and reflected light beams from the external end of the catheter to and from the blood flowing past the tip of the catheter. Successful operation of such an instrument as a densitometer requires use of a two-color (dichromatic) assembly, so that the nonspecific effects on the reflectance of blood caused by variations in blood flow past the tip of the catheter can be compensated for as has been accomplished previously for variations in blood flow through the oximeter (43,44).

Fig. 8. Original photokymographic recording of physiologic variables as well as arterial dilution curves recorded simultaneously at abdominal aorta and radial artery with onset of exercise during constant-rate injection of indocyanine green (I.G.) into thoracic aorta and nearly simultaneous sudden injections of Coomassie blue dye (C.B.) into right atrium of 35-year-old, 80 kg man. At the onset of the recording, while the subject was at rest, a sudden single injection of Coomassie blue was made into the right atrium, and the resulting dilution curve was recorded via the red photocell circuit (C.B.) of the oximeters at both the radial artery and the abdominal aorta (femoral artery). Note that this injection had no effect on the recordings of the concentration of indocyanine green (I.G.). Injection of indocyanine green at a constant rate was begun immediately afterward, and its concentration at the abdominal aorta (femoral artery) was recorded by the infrared circuit of the "femoral" cuvette (I.G.). Recirculated indocyanine green was recorded by the infrared circuit of the left radial arterial cuvette (I.G.). Thirty seconds after the start of the constant-rate injection, the subject started exercising, as shown by the recording of the rate of rotation (R.P.M.) of the bicycle ergometer (exercycle). A second sudden single injection of Coomassie blue was made immediately after termination of the constant-rate injection. Note that injection of indocyanine green produced a small deflection on the red photocell circuit (C.B.) of the femoral cuvette, which would be expected, since indocyanine green absorbs a small amount of light in the red region of the spectrum. Note the decrease in difference of concentration of indocyanine green between femoral and radial arterial blood shortly after the onset of exercise and the decrease in area of the Coomassie blue curves, indicating increases in blood flow in the lower part of the body and in cardiac output, respectively (17).

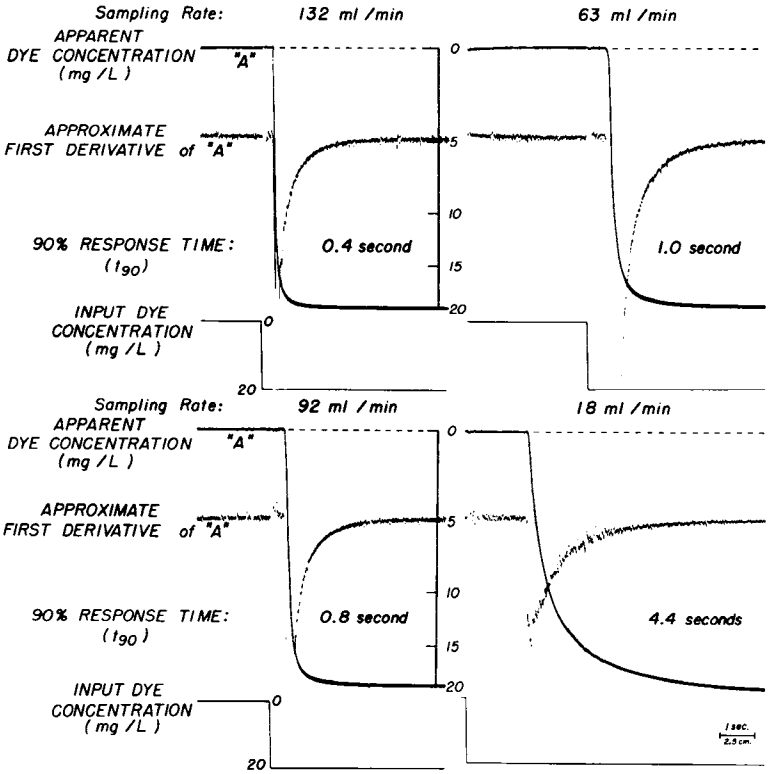


Fig. 9. Effect of rate of blood flow through catheter-densitometer system on dynamic response of this system to stepwise changes in concentration of indocyanine green. The catheter was a No. 7 F. cardiac catheter 40 cm long, with an internal diameter of 1.5 mm. The volume (dead space) of the system from the catheter tip through the detecting chamber of the Waters XC100A densitometer was 0.9 ml.

The four panels are recordings of the response of the system and the approximate first derivative of this response at the four different rates of blood flow indicated above each panel. The square-wave changes in dye concentration were produced by means of a solenoid-activated valve assembly (10). Note the 10-fold increase in the time required for 90% response of the system when the flow rate was decreased from 132 to 18 ml/min. The effects of these changes in dynamic response on the contours of dilution curves recorded by this identical system from the pulmonary artery of a dog are shown in figure 10. These recordings of the square-wave response and its first derivative were used for the calculation of the "true" (recovered) curve at the catheter tip illustrated in figure 11.

The problems of developing a dichromatic densitometer for indocyanine green, which is insensitive to changes in blood oxygen saturation, have been solved recently (34). Such a dichromatic

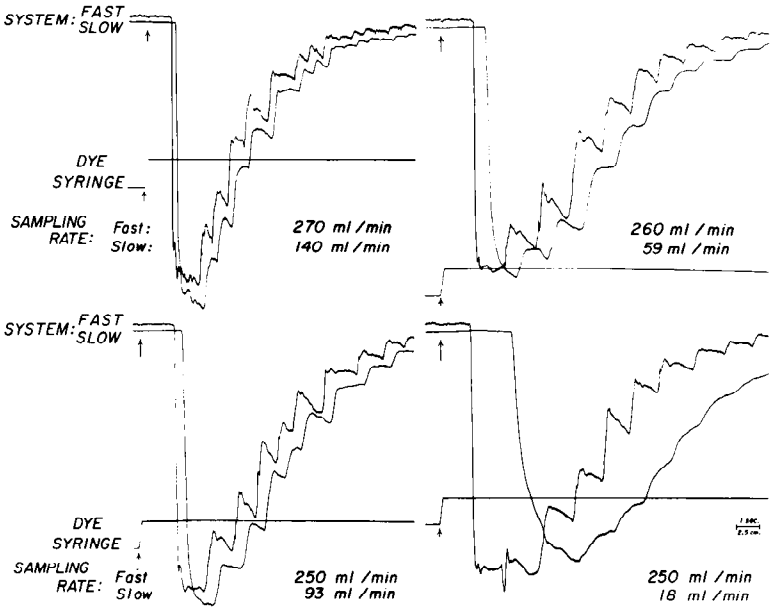


Fig. 10. Effect of variation in dynamic response of catheter-densitometer system on contour of dilution curves recorded by this system from pulmonary artery after injections of 2.5 mg of indocyanine green into superior vena cava of 25-kg dog.

The two dilution curves shown in each of the four panels were recorded simultaneously from the same site just downstream to the pulmonary valve by two densitometer systems. For details of the physical make-up of the "slow" system, see the legend of figure 9. The "fast" system consisted of an identical densitometer and a catheter only 8 cm long, so that the dead space of this system was reduced to 0.3 ml; consequently, its 90% response time to a square-wave change in dye concentration was decreased to 0.1 second when the blood flow through the system was maintained at 250 ml/min. The dynamic responses of the slow system at approximately the different flow rates indicated on the four panels are shown in figure 9. The galvanometer tracing labeled "dye syringe" is a recording of the instant and volume (1 ml) of dye injection. The sensitivities of the two densitometers were closely similar. The peak deflections of the curves in each panel were equivalent to a dye concentration of approximately 25 mg/liter. Note that in comparison to the fast-system curve there is some damping of the slow-system curve even at the fastest flow rate (140 ml/min.) that it was possible to achieve through this 40-cm catheter system.

instrument also has the important advantage of being insensitive to the nonspecific changes in the optical density of blood caused by the addition of nonisotonic solutions or variations in the carbon dioxide tension of the blood (25). See figure 12. These variations have been an important possible source of error in mono-

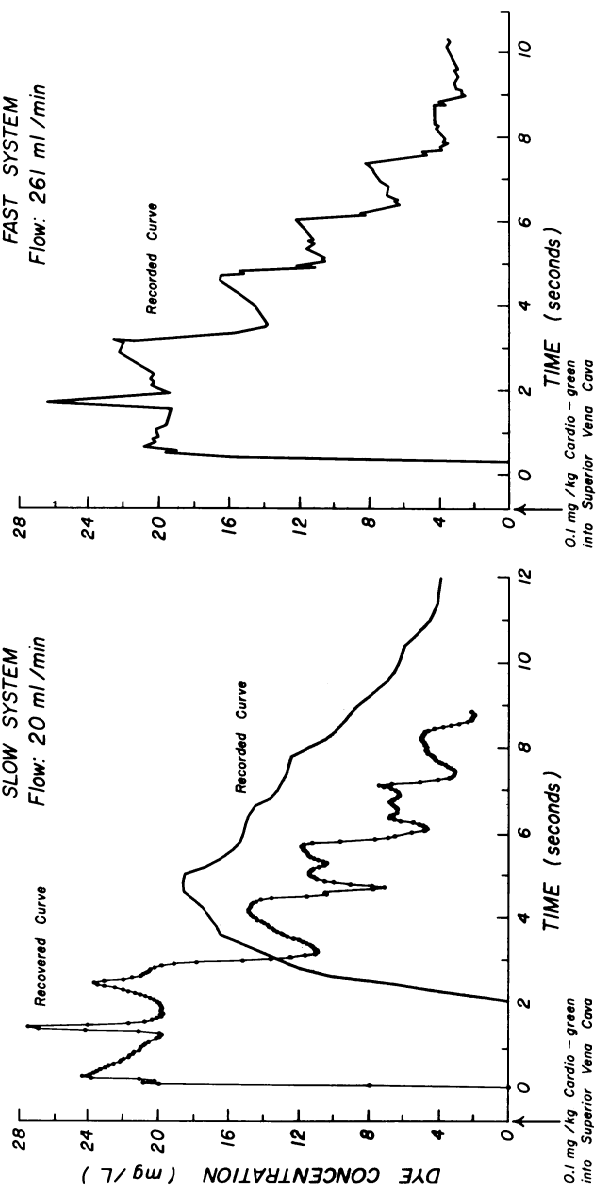


Fig. 11. Comparison of dilution curves recorded simultaneously from same site in pulmonary artery of a dog by two catheter-densitometer systems (one with slow and one with fast dynamic response) with "true curve" at catheter tip (recovered curve). The "true curve" was calculated (11) from the curve recorded by the slow system and the response of this system to a stepwise change in dye concentration shown in figure 9. For the physical make-up of the slow and fast systems, see the legends of figures 9 and 10. Note the similarity in contour of the "true curve" recovered from the slow-system recording and the curve recorded by the fast system.

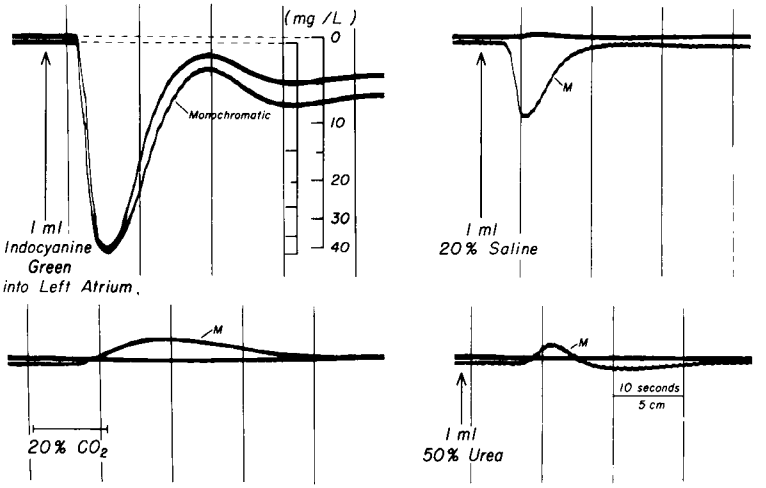


Fig. 12. Variations in optical density of blood recorded from same site in femoral artery of a dog after three maneuvers producing "nonspecific" alterations in optical density of blood compared with dilution curve obtained after injection of 2.5 mg of indocyanine green into left atrium of anesthetized, 14-kg dog. These "dilution curves" were recorded simultaneously by two densitometers; one was a conventional monochromatic densitometer for indocyanine green (Waters XC100), and the other was a compensated dichromatic densitometer recently described (34). Although the two instruments have approximately the same sensitivity to the dye, the dichromatic device is almost completely insensitive to the nonspecific alterations in optical density caused by the changes in carbon dioxide tension produced by four breaths of 20% carbon dioxide in oxygen or by injections of 1 ml of nonisotonic solutions into the left atrium. This insensitivity of the dichromatic device also pertains to the nonspecific alterations caused by changes in blood flow through the instrument. These effects are common and important possible sources of error in monochromatic densitometric measurements on whole blood.

chromatic measurements of indocyanine green in whole blood as carried out by densitometers described heretofore.

The use of a dichromatic densitometer of either the catheter-tip or more conventional design also will make possible the quantitative recording of dilution curves from selected sites in the central circulation during recording of cineangiograms with injections of indocyanine in solution with the radiopaque medium (26). It appears probable that combination of this technic with the recording of cinedensigrams (4) from the same site in the circulation may increase the quantitative aspects of cineangiography, which, after all, is an indicator-dilution technic (26).

A Final Word

In this attempt to honor George Neil Stewart on the 100th anniversary of his birth, I perhaps have dwelt too much on the past. I should like to close by emphasizing that the basic mixing and dilution processes involved in these technics play a fundamental role in many biologic processes (2). Hence, in the foreseeable future, the importance of dilution studies and their applications will continue to expand as the knowledge of biologic processes increases.

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CROSS WORD PUZZLE

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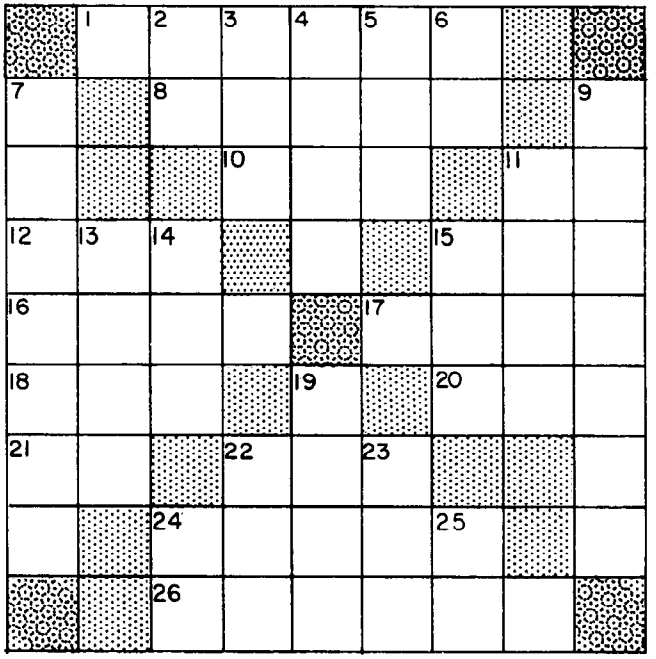

ACROSS

1- Past President of APS
8- Name known in renal physiology
10- Insulation unit
11- Expression of glee
12- Lady of the house
15- Source of heat
16- Past President of APS
17- Past President of APS
18- Expressions of surprise
20- A theater in WW II
21- Nurse
22- Female name
24- Past President of APS
26- Past President of APS

DOWN

2- Since
3- Medical installation in Wash. D.C.
4- Past President of APS
5- Jewish Territorial Organization
6- Silence!
7- Bearded Past President of APS
9- Past President of APS (possessive)
11- Secretary APS 1908; to seek
13- Member of B.P.T.
14- Elders
15- Observe
19- Past President of APS
22- Narrow inlet
23- French summer
24- Lead
25- Thoroughfare