CONTENTS

FREDERIC SCHILLER LEE
1878 - 1939

Frederic Schiller Lee was the seventh president of the American Physiological Society serving during the first World War years of 1917 and 1918. He was born at Canton, N.Y. June 16, 1859. He took his A.B. degree at St. Lawrence University where his father, John Stebbins Lee, was President. After a few years spent in teaching he entered Johns Hopkins University in 1881 as a candidate for the Ph.D. degree, doing his work in physiology under Newell Martin, one of the founders of the American Physiological Society. He received his doctorate in 1885, his dissertation being on the subject of arterial tonicity. The following year he studied at Leipzig working with Ludwig and von Frey. The result of the year's work was a paper on the electrical phenomena accompanying muscular contraction which was published in the "Archiv. f. Anat. u. Physiol." 1887, page 204. When he returned to the United States he taught for a year at St. Lawrence University, and was then called to Bryn Mawr College as associate in physiology and histology. After four years at Bryn Mawr he went to Columbia University, College of Physicians and Surgeons, to be demonstrator in physiology with Dr. Curtis. The rest of his academic life was spent at Columbia. He was made adjunct professor of physiology in 1895 and succeeded Curtis as the Dalton Professor of Physiology in 1904. In 1920 he was made research professor.

At the time of his election to the Society in 1888 Dr. Lee was Associate in Physiology at Bryn Mawr. From the beginning he took an active part in the work of the Society. For nine years, 1895-1903, he held the office of Secretary-Treasurer and for seventeen years was a member of the Council. During this period he appeared frequently on the scientific program at meetings and was a member of a number of important committees that were concerned with determining policies of the Society. His influence in the Society was not limited to his official and scientific contributions. His personal qualities, particularly his unfailing courtesy and consideration as Secretary were recognized and appreciated by his fellow members and contributed greatly to the success and pleasure of the meetings.

Throughout his academic career Dr. Lee was an active contributor to experimental physiology. His early papers upon the function of the semicircular canals, vestibular sacs and the lateral lines in fishes in reference to body equilibrium are well known. Much of his later work was concentrated upon the experimental study of muscular fatigue and its practical bearings upon industrial occupations. In this field he was a recognized authority and his services were called upon by the Government in investigations of working conditions in the industries. He was a member of the New York State Commission on Ventilation and took an active part in its investigations and in the preparation of its valuable report which played such an important part in subsequent studies upon ventilation in schools and factories. In addition to his numerous scientific papers Dr. Lee was the author of several books: "Scientific Features of Modern Medicine", 1911; "The Human Machine and Industrial Efficiency", 1918; a translation of Verworn's "Allgemeine Physiologie", 1899; a

revision of Huxley's "Lessons in Elementary Physiology", 1900; and the editing of Curtis' manuscript on "Harvey's Views on the Use of the Circulation of the Blood", 1915. Dr. Lee died December 14, 1939.

ANNOUNCEMENT
of the
E. GELLHORN NEUROPHYSIOLOGY PRIZE

Dr. E. Gellhorn, Professor Emeritus of Neurophysiology of the University of Minnesota, has elected to make a bequest to the Department of Physiology of the University of Chicago to establish the E. Gellhorn Neurophysiology Prize and Lectureship Fund. The Department of Physiology has agreed to match the amount of the bequest by inviting gifts to the fund. The income of the endowment will be used to make an annual award of $200 to be known as the E. Gellhorn Neurophysiology prize. The prize will be awarded to a candidate for the M.D. or for a Ph.D. in any department of the University of Chicago who shows outstanding promise in neurophysiology. The awarding of the prize will be the responsibility of a committee selected by the Chairman of the Department of Physiology. When no suitable candidate is available, the earnings of the endowment for that year can be used for an E. Gellhorn Lecture in Neurophysiology.

Professor Gellhorn is a distinguished neurophysiologist who was formerly associated with the University of Illinois School of Medicine and then the Department of Physiology of the University of Minnesota. He has not been associated with the University of Chicago but selected this university as the one in which to encourage medical and graduate students to enter the field of neurophysiology.

Gifts to the E. Gellhorn Fund should be sent to Professor Dwight J. Ingle, Chairman of the Department of Physiology.

APS AND YOUTH*

E. M. LANDIS

At seventy-five years of age, the American Physiological Society occupies a position resembling that of a parent surrounded by a number of very active offspring. From age 19 in 1906 to age 46 in 1933, APS has seen the birth of societies for Biochemistry, Pharmacology, Pathology, Immunology and Nutrition, as well as the birth and growth of the Federation itself. During all of this period of fission, budding and adoption, the parent Society has itself grown to the point at which attention should be given periodically to values that tend sometimes to be overwhelmed. A seventy-fifth anniversary should include some mention of the ways in which the Society shapes the lives and aspirations of young people as they are just beginning their career in physiology.

Most of us, if we have time to recollect at all, will remember a particular meeting of the Society that provided the setting for reporting our first step in research and supplied the stimulus of testing the validity of our efforts before a national group. How vividly we remember this will differ, depending upon temperament and circumstance. For several reasons, I happen to remember mine very clearly indeed.

In 1927 the Society met at Rochester, New York, with Wallace Fenn as host. While several of us youngsters sat in the lecture hall waiting for out part of the program, some others who had made their debut a year or so earlier pointed out to us the men whose work we had studied and whose papers we were nowabout to hear. They took special pains to call our attention to Dr. A. J. Carlson. We were warned that if he rose to ask a question we were really in serious trouble.

Dr. Carlson, as I remember very clearly, sat on the very first row and far to one side. Immediately after I ended the summary of my paper, and even before I could get back to my seat, peripheral vision told me that he was already on his feet. Not one, but several, questions followed. To my great and easily recalled relief, Dr. Carlson seemed content with the results of a few control studies that could not be included in a brief ten-minute paper. But he had still more questions by the time he reached the demonstration that followed. From this meeting there developed an exchange of letters and then, over the years, a friendship in science which is the first and most important contribution that the American Physiological Society offers to youth.

The late Carl J. Wiggers, whom we miss deeply on this occasion, commented at some length on this role of the Society in his book "Reminiscences and Adventures in Circulation Research." He attended his first meeting in 1905 and had not yet decided to follow a career in physiology. He describes his paper, his vigorously stated disagreement

*Address given at the Convocation celebrating the 75th Anniversary of APS, August 27, 1963, Coral Gables, Florida.

with results already published by Leonard Hill and J. J. R. Macleod, his successful demonstration after the paper was given, and the compliments he received during this demonstration from Macleod himself. Carl Wiggers expressed his feeling as follows: "My first attendance at the meetings of the American Physiological Society elated me in many ways. There was the thrill of achievement, the congratulations upon it and the satisfaction of seeing demonstrations of well-known investigators such as Brodie, Erlanger, and Yandell Henderson. There was also the feeling that I had started an acquaintanceship with some of the leading American physiologists."

Returning to my own favorite meeting in 1927, it is worth noting that the list of those elected to membership included young men named Detlov Bronk, Ralph Gerard, A. Baird Hastings, Fred Hitchcock, Milton O. Lee, and Maurice Visscher. Another young man named Donald Gregg was awarded the Porter Fellowship.

To William T. Porter young physiologists owe a special debt of gratitude for a number of reasons. As others will no doubt describe, he was brave enough to establish and edit the American Journal of Physiology beginning in 1898 so that the growing number of young physiologists in this country might have close at hand a mechanism for publishing the results of their researches. Simultaneously his mechanics were making kymographs, stimulators, time-markers, and other instruments so efficiently and economically that young physiologists were no longer handicapped by the impossibly high cost of equipment imported from abroad. By this means he implemented very literally his conviction that "The student in physiology should perform the classical experiments on which the science rests. The laboratory teaching of physiology should be brought within the reach of every school." In 1914 William Porter presented the American Journal of Physiology to the Society. Then, beginning in 1921, he provided funds from the Harvard Apparatus Company and asked the Society to designate annually a young physiologist to receive a Research Fellowship. At that time research stipends were very few and William Porter was one of the first to recognize the importance of encouraging students in their desire to begin a career in physiology. From 1921 to the present, thirty-five young men and women have received research fellowships through the Porter Fellowship Committee and the Council of the Society with funds totalling seventy thousand dollars granted by the Directors of the Harvard Apparatus Company. Now, in a time of abundant financial support for research, we should remember on occasions like this that William Porter and our Society were among the very first to point the way and also to act.

The special offerings of the American Physiological Society to its members and others, young and old, continue without interruption after the first meeting and the first ten-minute paper, and in ways that are as diverse as are the talents of individuals. In addition to their primary research publications, some can contribute to Physiological Reviews, or, in recent years, to the Handbook of Physiology. Others, as chairmen of scientific sessions, can combine their research experience with their talent for eliciting instructive discussion. They can even extract benefit perhaps from the enthusiastic discussor who "happens to have a slide in

his pocket" and an hour of comments in his head. Still others, by arranging and participating in symposia, develop their arts in the tactful separation of the essential from the nonessential and in the pointing out of fruitful paths for future research. Some members are elected to Council, and even become President. These are honors and responsibilities that can be compared to lightning - sudden, perhaps a bit erratic at times and followed by much noise. It is a rare President who manages to complete his business meetings without getting tangled in a web of parliamentary procedure - a web woven by motions, amendments, tablings, and other ingenious devices produced by delighted members more expert and alert in these matters than is the President. It is a rare meeting that does not include a challenge of the ten-minute paper which most of us continue to support because of the place it holds in our own memories of our first steps in physiology.

All of this is simply to say that in this Society of ours youths of all ages are offered a whole span of graded challenges and opportunities to make an entire lifetime in physiology especially rewarding. It is a privilege to share in this anniversary of a youthful seventy-five-year-old Society.

PHYSIOLOGY FOR PHYSICIANS

The new APS publication, Physiology for Physicians, which started January 1, 1963 as a monthly 4 to 8 page publication primarily for practicing physicians proved quite successful in its first year of operation under the editorial leadership of Julius Comroe. There were approximately 5000 subscribers for 1963.

Dr. Eugene Stead of Duke University has replaced Dr. Comroe as Chairman of the Editorial Board. The Editorial Board now consists of Drs. E. A. Stead, Jr., J. H. Comroe, Jr., M. I. Grossman, I. M. London, I. H. Page, R. F. Pitts, S. Wolf, and J. B. Wyngaarden. The editors promise some interesting and useful articles for 1964.

The articles are not only of interest to practicing physicians but many interns, medical students and teachers of physiology have found them useful. The publication has found interested subscribers all over the world - from Pakistan to Uganda.

It is hoped that members of the Society will either subscribe themselves or make the publication known to their friends. Subscription rates are $3.00 per year, January through December, prepaid.

SPECIAL APS PROGRAMS AT THE SPRING MEETING

April 13-17, 1964

SYMPOSIA

"Circulatory Responses to Exercise" - E. H. Wood, Chairman

"The Relaxing Factor of Muscle" - J. Gergely, Chairman

"Arctic Biology: Effects of Extreme Changes in Light and Cold" - D. R. Griffin, Chairman

"Transport of Gases Across the Placenta" - C. A. Villee, Chairman

"Enzymic Activation of Blood Clotting" - J. H. Ferguson, Chairman

"Physical and Biochemical Aspects of Oxygen Transport and Utilization" - E. P. Radford, Jr., Chairman

TEACHING SESSION

"Innovations in the Teaching of Physiology" - R. E. Forster, Chairman

THIRTY-MINUTE INTRODUCTORY TALKS

Control of Respiration - F. S. Grodins

Sweating - S. Robinson

Renal Tubular Function - G. H. Giebisch

Gastric Secretion - B. I. Hirschowitz

Neuroendocrines - J. A. F. Stevenson

Smooth Muscle - D. F. Bohr

TASKS OF PHYSIOLOGISTS*

E. F. ADOLPH

Every generation conceives its sciences differently from its predecessors. The physiology of twenty five years ago is not our physiology, and properly so. We are adding to the old; but we are also transforming the old. Like modern physics, which I understand, relates only as cousin to classical physics, physiology has new concepts to work with. And still newer concepts are surely on the way.

How shall we prepare for a continually self-renewing science? Inasmuch as the science itself develops unpredictably, we evidently need a nonspecific preparation. We must prepare to invent concepts that will fit the climate in which we work. To invent them we shall need to cultivate the craft of concept-making to a greater degree than in the past. Whereas we often reached new realms of physiology by the force of a special laboratory technique, in the future we shall rely to a greater degree on our imaginations. How shall we enlarge our imaginations? The only method known seems to be by use of them.

In the physiology of the past generation one could trace, for instance, the concept of Clearance and its influences. This concept began to take shape from Ambard's rule for urea excretion. Then it spread to excretion of all substances. Later it could be generalized to include all translocating and transforming metabolic events. Its recognition did not depend on new techniques. But the concept generated new techniques and new types of experiments.

No one starts out to discover a particular concept, it seems. Rather, examination of phenomena suggests a general statement about them, a statement that usually has to be revised and revised before it corresponds to reality. But, the scientist can be receptive to concepts or theorems. He can ponder, instead of doubling his data. He can intentionally search for meanings, for relationship to other known phenomena.

How shall the cultivator of concepts get started? At present no one can recommend a better preparation than the intensive study of a few phenomena by means of planned experiment. Thereafter two courses are open: the scientist can improve the quality of his effort by narrowing his gaze, or he can relate his special phenomena to other groups of phenomena. He will rarely profit by a global review of the data of physiology until he has some specific concepts that he wants to test. Eventually a man who cultivates concepts has a chance to become a man of new mind.

What I am suggesting is that there may be an endless number of patterns in physiological thinking. Not just an endless number of phe-

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nomena and of relationships among them, but actually an endless number of constructs that can be made about them. Each of us may add to an edifice of physiological science if we wish to do so, by placing a joist or a stud that will support something instead of assuming that the joists and studs are already in place.

He who would raise a significant part of the grand edifice of physiology needs to decide early or late not to spend his life doing little researches. He needs a sizable concept, one bigger than he yet knows how to handle. He shuns attractive problems that offer easy solutions. He has faith that his powers in conceptual thinking will develop in step with the intricacies that challenge him.

There must be a wide range among future physiological concepts, for, no one can foresee what types of concepts will satisfy future physiologists. Minds must be open to recognize new types when they occur to someone. For example, the study of physiological adaptations today attracts a certain amount of thought and experiment. But there are almost no general concepts as to which adaptations are available, when they operate and how they evolve. No one has predicted where the insights will emerge that can open the floodgates of physiologists' interests and efforts in studying them. No doubt, messenger RNA and mediators at all levels of function are tools of adaptational processes. Still, we await the unorthodox spark that will illuminate the subject.

It seems to me that most physiologists' imaginations today are stereotyped to the exploration of physicochemical "mechanisms". Why not look as frequently at coordinations, origins, or consequences? I suggest that any one type of concept never does justice to a group of phenomena under study. Will poets and artists be imported to spur our imaginations? So long as education in our science consists predominantly in surveys of facts, how can anyone enter physiology with his imagination untarnished?

What I hope to see is a variety of effort. I would like to divorce us from gadgetry, and to strengthen the art of having ideas. I expect to secure to the individual a free choice of endeavor, not an endeavor limited to what his chief taught him. I quote:

> "Darest thou now, O soul,
> Walk out with me toward the unknown region,
> Where neither ground is for the feet
> Nor any path to follow?"

Walt Whitman was no physiologist, but he recognized that what the world needed was to discover laws for creations. Such discovery is a large order, for to date we know almost no rules about creative minds, except that practice helps them. Nevertheless, it may be possible to explore the unknown region and still keep the feet on the ground. I for one have faith this task can and will be done.

ORGANIZATION AND COMMUNICATION OF SCIENTIFIC COMMUNICATION*

HALLOWELL DAVIS

When I last spoke before this society as retiring Past-President I discussed, among other things, the population explosion. Today I want to examine a closely related problem that casts its shadow over all of science, namely, the information explosion. Both the increase in population and the increase in information will make great difficulties in the future. In the case of population there is a limit in terms of means of subsistence. For information, there is an equally definite limit in the possibility of assimilation. To control the situation we don't want censorship of scientific publication any more than we want enforced family limitation. The way to adjustment in each case is, I believe, through self-discipline which is the responsibility of the individual.

Each scientist must make his own decision as to the most efficient division of his effort between intake of information from the scientific literature and the development of new information in his laboratory. Furthermore, it is too obvious to need further comment that some organization of the raw information is essential. Some may be done by writers of reviews and textbooks, but proper organization must begin with the original publication.

At the present rate of increase of scientific discovery, due to the proliferation of new laboratories and the training of new investigators, the scientific world will some day be saturated with information. This will occur when it becomes cheaper and quicker to go into the laboratory and do an experiment than to search the literature to determine whether it has been done before and if so to read and evaluate the details. Improved techniques of retrieval of information, already discussed by Maurice Visscher, will postpone this evil day, but in any case both the saturation and the techniques of retrieval of information are concerned with the hard, detailed facts. I want to distinguish between the retrieval of such information and the development and exchange of ideas.

Ideas must be based on facts. They represent syntheses of facts in the forms of models and hypotheses which generalize and, more or less successfully, predict. Such organization of knowledge is the ultimate object of our research. When we have a good model we believe that we understand. Actually I believe that the most effective form of interchange of scientific information in the future will be in this form of organized information; namely the idea or the model and not the detailed facts on which the ideas are based. However, effective communication will always require a clear distinction between the original facts of observation and the hypothesis or model into which they are incorporated.

The task of gathering specific scientific facts can be delegated to many

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workers and the facts can be published for all to read and be grouped by computers according to index codes. However, the tasks of arranging facts, and particularly of drawing inferences and developing ideas, go on in single human brains. One of the hard, inescapable facts of biology is that the content or capacity of each human brain for facts is definitely finite; and some of our brains seem to be rather more finite than others!

Each scientific investigator must impose practical limits on his input. He must limit his problems to some extent and not try to know everything about everything. All of us have been selecting our input for many years. Several times I myself have happily but incidentally avoided detailed reading of bulky literature by moving into a new area. I would then make friends with the other kindred spirits who moved in with me, exchange information and ideas and techniques with them as rapidly as possible, and let the rest of the literature go by or read it only in second-and third-hand distillations and elaborations. Specifically my areas have been axonology, electroencephalography, the electrophysiology of the ear, and now human cortical evoked potentials. But in each case the relief has been only temporary.

Personal correspondence, laboratory "progress reports", informal man-to-man discussions, visits to laboratories and, more recently, our selected and highly organized symposia are all important means of communication. They supplement the traditional "corridor conversations" of our society meetings. Discussions are the best stimuli for the arranging of one's ideas, for selecting among them and for "trying them for fit" with the ideas of colleagues. I suggest that getting together, whether formally or informally, in small, congenial groups to discuss particular problems or techniques, should be included in the rationing of time and the planning of activity of every creative scientist. Of course, if one lives and works in a major scientific center such contacts are easy to develop and little time is spent in travel. The danger, on the other hand, in a large center is a surfeit of symposia, leading to either a retreat into isolation or complete mental lethargy or to frenetic and repetitive perpetual motion.

Nevertheless, however valuable the discussions in the "in-groups" may be, they bring with them another danger to effective communication, the danger of an overspecialized laboratory slang. Such jargon may greatly facilitate the exchange of information and the development of ideas within the group which knows it, but it utterly obscures ideas and their significance for the outsiders whom we must also reach. Each group must take the trouble to translate its laboratory language into a broadly accepted scientific vocabulary. Scientific communication is hampered enough by existing language barriers without creating new ones! More than this, each author must write his sentences efficiently for rapid assimilation by readers who skim. He must also provide an effective abstract and he must write a title that will lead to correct indexing for ultimate retrieval.

Here are some of my final words of advice to young investigators, to department heads and to laboratory directors alike.

1) Welcome opportunities to talk and visit and exchange ideas with scientific colleagues. "Lone wolfing" is out of style and inefficient.

2) Explain your experiments and ideas to elementary students or to friends who are not working in the same specialty. When you can get your ideas across to such students or friends with little specialized background, you will find you have stripped away most of your laboratory jargon and are ready to talk to or write for any audience, whether it be the American Physiological Society or the Scientific Community in general.

3) Write in moderation but write efficiently. Don't feel you must publish a paper every year or perhaps every six months in order to keep pace with annual reports and grant renewal requests. Build your papers around ideas. Get criticism of your manuscript from competent colleagues who know something but not too much about your work. Your friends may be more helpful and more synpathetic than the referee editors of the journals!

4) Participate in symposia, (within reason). They are particularly useful for the development and exchange of ideas as opposed to detailed facts.

5) Do your share of writing reviews. Make your reviews selective and synthetic, not merely catalogues of titles like a stack of IBM cards.

6) If you ever have an opportunity to contribute to the Handbook of Physiology, drop everything else and give it your utmost efforts. The Handbook series, advancing in a gigantic spiral through time and across one area of physiology after another, represents our best and most helpful single effort toward organized and systematic communication from one specialty to another and from one generation to another. To write a chapter in the Handbook is to ensure a bit of immortality. It is also a great responsibility because inclusion or omission in the Handbook may determine the survival of many an idea or even the body of information from which it was fashioned.

Now, to summarize my summary, I say, "It is the duty of each of you to organize your facts into ideas and to package your output well and put good handles on it."

COURSE FOR PHYSICIANS

Every other year the American Physiological Society and the American College of Physicians co-sponsor a refresher course for physicians.

This year the course will be given in Atlantic City, April 2-4, 1964 under the co-direction of Drs. D. H. Simmons and C. R. Kleeman. Following is a schedule for the course entitled:

"Current Concepts in the Physiology of Respiration, Circulation, and Electrolytes."

Thursday AM, April 2
- Opening remarks - D. H. Simmons
- Control and regulation of the vascular system - L. H. Peterson
- Adaptability of the heart - S. J. Sarnoff
- Regulation of extracellular fluid volume and the formation of edema - A. C. Guyton
- Panel discussion - Drs. Peterson, Sarnoff, and Guyton

Thursday PM, April 2
- Pulmonary circulation - A. P. Fishman
- Coronary circulation - D. E. Gregg
- Cerebral circulation - S. S. Kety
- Panel discussion - Drs. Fishman, Gregg, and Kety

Friday AM, April 3
- Interdependence of lung structure and function - N. C. Straub
- Surface properties and lung function - E. P. Radford, Jr.
- Mechanisms underlying tests of ventilatory capacity - J. Mead
- Panel discussion - Drs. Straub, Radford, and Mead

Friday PM, April 3
- Regulation of respiration - A. B. DuBois
- Neurological abnormalities and human respiratory regulation - F. Plum
- Gas transport - L. E. Farhi
- Panel discussion - Drs. DuBois, Plum, and Farhi

Information concerning registration for the course can be secured from Dr. E. C. Rosenow, Jr., Executive Director, American College of Physicians, 4200 Pine Street, Philadelphia 4, Pa.

(See Enclosure for Announcement)

EIGHTH BOWDITCH LECTURE

Transport of Large Molecules Across Capillary Walls

EUGENE M. RENKIN

The capillary wall forms the barrier between our closed circulatory system and the tissues which it serves. By its selectively restrictive permeability, it functions to retain the fluid volume of the blood, yet still allows the numerous components of the circulating fluid to pass across in amounts appropriate to their roles in the economy of the body. The mechanisms by which transport of materials takes place and the special permeabilities of this membrane which enable it to function adequately have long been the subject of physiological study.

It was in the laboratory of Carl Ludwig - Bowditch's teacher - that the basis of our present understanding of the transport of materials across capillary walls originated. Ludwig realized the importance of ultrafiltration as a transport process, and of solute osmotic pressure in regulating this process, and initiated the experimental study of lymph as a means of getting information about what went across the capillary wall. Bowditch was in Ludwig's laboratory when work in this field was being pursued, but did not take an active part in this project. He was sufficiently impressed by the potentialities of this work, however, to read a paper before the American Academy of Science in Boston in 1873 (3), describing some experiments of others in Ludwig's group which established connections between the lymphatic vessels and what we should call today interstitial spaces in connective tissue. It remained for Ernest Starling to solve the problem by recognizing the distinction between total osmotic pressure and colloid osmotic pressure as the force regulating fluid balance across the capillary membrane, and to establish the simplest description of capillary membrane restrictivity - free permeability to crystalloids and water, relative impermeability to colloids (21, 22).

Starling's Hypothesis accounts for the maintenance of continuous circulation in a vascular system whose capillaries must be permeable to the bulk of the constituents of the circulating fluid. Its very simple description of capillary permeability to small and large molecules is entirely adequate for this purpose. One need only add, as a second order correction, that impermeability to plasma proteins is not perfect, and that the very small quantity of proteins which leaks from the capillaries is returned to the blood stream by the lymph.

But to expand our knowledge of the mechanisms of material transport across capillary walls, we must seek a more detailed description of the permeability of the capillary membranes to molecules of different properties. What are the relative permeabilities to a graded spectrum of molecules? What general laws determine molecular permeabilty? How can one predict transport from permeability? For small molecules, which make up the greater part of materials exchanged, these questions have been given at least provisional answers by the work of Pappenheimer and his associates (17, 18, 19, 20). In my presentation today, I shall be concerned principally with the transport across the capillary membranes of

large molecules, those with molecular weights greater than 10,000.

Transport rates of these substances are exceedingly slow, compared with those of the smaller molecular species. Chinard and his co-workers used isotopic tracers to demonstrate that for such small molecules as water nearly 100 percent can exchange with tissue fluid in the course of a single circulation through the capillary network (4). Since circulation time for the whole body in man and mammals is of the order of one minute, it follows that a quantity of water equivalent to all that present in the blood can pass across the capillary walls in one minute. In contrast to this, Wasserman and Mayerson found the exchange rate of radioactive iodinated serum albumin to be only one thousandth part per minute of the total amount present in the blood (23, 24).

Two mechanisms are known to participate in transport of materials across capillary walls: diffusion, and ultrafiltration or osmosis. For small molecules diffusion is by far the more important of these, while ultrafiltration is primarily important as the mechanism underlying shifts of fluid volume. As molecular size increases, the contribution of ultrafiltration to solute transport becomes increasingly large (17) and filtration is believed to play a major role in lymph formation and the turnover of plasma proteins by way of the lymph (21, 26). Both these processes are passive. Transport always takes place in the direction of the free energy gradient, and no energy contribution by the capillary endothelial cells is necessary.

More recently, a third transport mechanism has been proposed: pinocytosis, or cytopempsis: material is transported from one surface of an endothelial cell to the other in minute vesicles (1, 14, 15, 16). The movement of the vesicles must require energy expenditure by the cell, therefore we classify vesicular transport as an active process. But whether transport can take place against concentration gradients is unknown. Much has been written about the prevalence of vesicular transport through capillary endothelial cells, but what role it plays in material transport, if any, remains to be established. It appears safest to evaluate possibilities of active membrane transport only after exhaustive consideration of passive transport processes. Let us examine the transport of large molecules through the capillary membrane by passive processes and if anything is left unexplained, we can return to pinocytosis and see what it might contribute.

First I should like to review transcapillary diffusion of small molecular species. The steady state transport rate of a given solute, M_D, is described by Fick's Law:

$$M_D = (C_1 - C_2)\ P \qquad (1)$$

where C_1 and C_2 are the solute concentrations (or activities) in the capillary plasma and interstitial fluid, respectively, and P is a permeability coefficient, equal to the D_S ($As/\Delta x$) of Pappenheimer et al. (19). D_S is the free diffusion coefficient of the solute and ($As/\Delta x$) is the effective diffusion area per unit path length in the membrane. Since the total capillary surface in a given mass of tissue is very difficult to estimate,

a large source of error is eliminated by expressing P per unit weight of tissue. To solve for P, one must measure M_D and (C_1-C_2). For relatively small molecules diffusion is very rapid, and C_1 falls considerably as the blood moves along the capillary from arterial to venous end. Under these conditions, M_D can be measured accurately as the product of the arteriovenous concentration difference and blood flow. However, the mean difference between blood and interstitial fluid solute concentrations cannot be obtained by direct measurement. Pappenheimer and his colleagues solved this problem by measuring the osmotic effect of solute added to the circulating blood, and calculating mean (C_1-C_2) by van't Hoff's Law. There are certain theoretical objections to the use of van't Hoff's Law in this circumstance, but the application of theoretical refinements to this problem has not yet been fruitful (7, 11). Pappenheimer's original list of permeabilities is still the best guide we have to capillary permeability to small molecules. It is reproduced in modified form in Table 1.

Substance	Mol.Wt.	D cm^2/sec	P $\frac{cm^3/sec}{100\ gm}$
(Water)	18	3.20×10^{-5}	3.7
Urea	60	1.95	1.83
Glucose	180	0.91	0.64
Sucrose	342	0.74	0.35
Raffinose	594	0.56	0.24
Inulin	5500	0.21	0.036
Myoglobin	17000	0.15	0.005
Hemoglobin	68000	0.094	0.001
(Serum Albumin)	69000	0.085	0.000

Table of Capillary Permeabilities
Cat's hind leg Pappenheimer et al. 1951

The molecular species studied are listed in order of increasing molecular weight. In the third column are the free diffusion coefficients of these substances in water at 37° C. The last column lists capillary permeabilities in cm^3/sec per 100 grams tissue. Permeability to water was not measured directly but was obtained by extrapolation of the other permeabilities to the molecular weight of 18. The permeability to serum albumin is given arbitrarily as zero to three decimal places, and represents the limit of sensitivity of the method.

The table illustrates one of the fundamental conclusions reached by Pappenheimer et al., namely that there is graded restriction to the passage of molecules through the capillary wall with increasing molecular size. If transcapillary diffusion were not restrictive, we should

expect P to decrease in parallel to the free diffusion coefficient, D. The observed decrease is much greater, and this indicates some kind of mechanical hindrance within the capillary membrane to the penetration of molecules.

Molecular size is not the only property which determines capillary permeability to different substances. All molecular species in Table 1 are lipid-insoluble. Substances which are appreciably soluble in lipids penetrate the capillary endothelium more rapidly than lipid-insoluble substances of comparable molecular size (20).

The method used by Pappenheimer and his associates loses precision as solute molecular weight increases and transport rate goes down, because the arteriovenous solute concentration difference becomes vanishingly small. As a rough guess, the reliability of the tabulated permeabilities to the largest molecules in the table is no better than two units in the third decimal place. The presence of serum albumin in lymph from leg lymphatics indicates that there is a finite capillary permeability to this substance, but we shall need a different method to measure it.

The key to the accurate measurement of capillary permeability to substances with molecular weights greater than 10,000 is found in the lymph. Lymph collected from different regions of the body contains water and low molecular weight solutes in essentially the same concentrations as in plasma, and high molecular weight solutes in lower but still very appreciable concentrations. The source of the lymph is the plasma. Isotopically labeled plasma constituents and foreign solutes covering a very wide range of molecular sizes have been shown to penetrate into the lymph (5, 9, 10, 14, 16, 25, 26). Characteristic plasma: lymph exchange rates of the plasma proteins and other high molecular weight constituents of plasma have been measured by a number of workers (2, 8, 9, 23, 24). Of specific usefulness for present purposes, penetration of dextran molecules of graded sizes from plasma to lymph in various organs and tissues has been subject to extensive study by Wasserman and Mayerson and their associates (14), and by Grotte (10).

The initial step in lymph formation is ultrafiltration through the capillary wall (19, 21, 26). There is a drop in hydrostatic pressure within the capillary network as blood moves from arteriole to venule, and consequently an excess of hydrostatic pressure over colloid osmotic pressure in some areas and a deficiency in others. A small quantity of fluid leaves the "arterial capillaries" and percolates through the interstitial space from which it is removed partly by back-filtration ("reabsorption") into the blood in the "venous capillaries" and partly by drainage from the tissue as lymph. The quantity of fluid filtered is only a small fraction of the plasma flow; and only a small part of it becomes the lymph.

Drinker did not believe that lymph could be simply a capillary ultrafiltrate (26). In lymph collected from leg lymphatics, lymph: plasma concentration ratios of the plasma proteins as high as 40 per cent are frequently observed, and in lymph from other regions of the body, the ratios may be still higher. Landis (12) and later Pappenheimer and Soto Rivera (18) demonstrated that the effective osmotic pressure of the plasma

is approximately 95 per cent of the osmotic pressure measured with a completely protein-impermeable membrane. Since back-filtration might be expected to show the same restriction to return of protein to the circulation as was shown in the original outward filtration, Drinker concluded that the relatively high plasma protein content of lymph was due to two successive ultrafiltration processes, one from arterial capillary to interstitial space, the other from interstitial space to venous capillary, and that the lymph drained from an organ was representative of at least part of the interstitial fluid of that organ.

Recently, Creese, D'Silva and Shaw collected minute samples of interstitial fluid from muscles by inserting fine glass capillaries parallel to the fibers. They found the albumin content to be about 40 per cent that of plasma (6).

The analysis which follows is based on Drinker's theory of lymph formation by filtration and back-filtration. Since the rate of lymph drainage from the interstitial space is relatively slow, it is necessary to make allowance also for the diffusion exchange of materials between the capillary blood and the provisional lymph. Figure 1 is a diagram representing these processes as they apply to the steady-state transport of a large molecular weight solute from plasma to lymph.

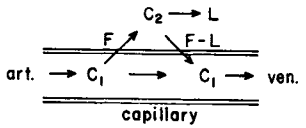

Fig. 1. Diagram illustrating lymph formation and the transport of a large molecular species from plasma to lymph. See text for details.

C_1 represents capillary plasma concentration of a high molecular weight solute. Diffusion transport of large molecules is very slow and there is no appreciable change of solute concentration from arterial to venous end of the capillary. At the arterial end, ultrafiltration takes place at F cm^3/sec. The quantity of solute transport per unit time in the provisional ultrafiltrate,

$$M_F = \frac{C_1 F}{K} \qquad (2),$$

where K is a constant which characterizes the extent of molecular sieving of the solute by the membrane. It is the ratio of effective membrane diffusion area for the solvent (water), Aw to that for the solute, As (17, 19).

At the venous end of the capillary, fluid moves back into the bloodstream at (F - L) cm^3/sec, the difference between filtration rate and lymph flow rate. The quantity of solute carried back into the blood per

unit time, M_{-F} is given by the same principle as above:

$$M_{-F} = \frac{C_2 (F - L)}{K} \qquad (3),$$

where C_2 is the concentration of solute in the interstitial fluid or lymph and K is the same as in equation (2).

Since C_2 is less than C_1 along the entire length of the capillary, net outward diffusion of solute takes place. The quantity transported per unit time, M_D, is given by Fick's Law:

$$M_D = (C_1 - C_2)\ P \qquad (1),$$

where P is the capillary membrane permeability to the solute, equal to D_s (As/Δx).

The total transport of high molecular weight solute from blood to lymph, M_L, is the algebraic sum of these three processes

$$M_L = M_F - M_{-F} + M_D \qquad (4).$$

M_L is also given by the relation

$$M_L = C_2 L \qquad (5).$$

Substitution of equations (1), (2), (3) and (5) in equation (4) yields the following relation:

$$C_2 L = \frac{C_1 F}{K} - \frac{C_2 (F - L)}{K} + (C_1 - C_2)\ P \qquad (6).$$

This is readily solved for the lymph: plasma ratio, R.

$$R = \frac{C_2}{C_1} = \frac{F + PK}{L(K-1) + (F + PK)} \qquad (7).$$

In this equation, R is a function of four independent variables: lymph flow L, filtration rate F, capillary permeability P and the reciprocal sieve coefficient K. For a limited range of molecular sizes, however, it is possible to simplify equation (7) and arrive at an equation which relates the lymph: plasma concentration ratio to lymph flow and capillary permeability alone.

For large molecules, As is much smaller than Aw, and therefore K is much greater than one. This makes it possible to replace (K - 1) in the denominator of equation (7) with K alone. Also, the product PK will be much greater than F, provided P is not exceedingly small. This makes it possible to replace (F + PK) in the denominator of equation (7) with PK alone.

$$R \cong \frac{PK}{LK + PK} = \frac{P}{L + P} \qquad (8).$$

The K's cancel, to give an approximate relation between R and L and P. Solution for P yields an approximation for capillary permeability in terms of two measurable quantities, lymph flow L and lymph: plasma concentration ratio R.

$$P \cong L\left(\frac{R}{1 - R}\right) \qquad (9).$$

The dimensions of L and P are the same: volume per unit time, both for a given weight of tissue. P represents that volume of plasma which gives up its contents of a particular solute to the interstitial fluid per unit time. The simplifications made in going from euqation (7) to equations (8) and (9) are equivalent to assuming that the principal mechanisms of transport of high molecular weight solutes from capillary to interstitial space is diffusion. The filtration component acts chiefly to provide the fluid volume into which the solute diffuses.

Experimental data suitable for analysis by equation (9) are available in the literature. Mayerson and his associates (14) and Grotte (10) collected lymph from diverse organs in anesthetized dogs after intravenous injection of dextran molecules representing a range of molecular weights from 10, 000 to 400, 000. They measured the rates of lymph flow from each organ studied, and the steady-state lymph: plasma concentration ratios for dextran molecules of sizes graded between the two extremes.

Figure 2 illustrates the calculation of a spectrum of molecular permeabilities from the results of two sets of experiments by Grotte (10). Three anesthetized dogs were given intravenous injections of a mixture of dextrans representing molecular weights between 10, 000 and 22, 000. The kidneys were tied off to prevent excretion of these in the urine, and thus to stabilize plasma dextran levels. Lymph was collected from superficial lymphatics of the hind leg. Samples of lymph and plasma were taken at hourly intervals and analyzed for dextran fractions of narrow molecular weight ranges by a method of fractional alcohol precipitation. Three to five hours after the injection of dextran, the lymph:plasma dextran concentration ratios became constant. Grotte's data for one dog are indicated on the upper graph by open circles. The values for the other dogs were closely similar. The ordinate is R, the lymph:plasma concentration ratio; a value of 1 indicates equality of lymph and plasma concentrations. The abscissa is molecular weight on a logarithmic scale, to facilitate representation of a wide range of values. The points for this curve represent molecular weights of 10, 12, 14, 16, 18, 20 and 22 thousand. There was a progressive fall in the lymph:plasma concentration ratio with increasing molecular size in this range. Lymph flow in this experiment was 1.0×10^{-3} cm^3/sec; the weight of the tissue from which the lymph was collected is not given. It must be about 50 to 100 grams in dogs of the size used.

The upper end of the molecular size spectrum was covered in experiments on another three dogs. These were given intravenously a sample of high molecular weight dextran representing molecular weights up to 300 thousand. The preparation and analysis were as before, except that the kidneys were not tied off, and the dextran was given 24 hours before lymph collection was begun. Since the dextran molecules below 60, 000 were eliminated in the urine during this period, a gap is left in the mo-

lecular spectrum between this point and the upper end of the molecular weight series. The mean values for three experiments were reported, and are illustrated here as open triangles. Lymph flow in these experiments was also 1.0×10^{-3} cm^3/sec.

After control values were established in both sets of experiments, venous congestion was produced by inflating a pneumatic cuff around the leg to 50 mm Hg. Lymph flow increased by a factor of 2.0 in the first experiment and 1.7 in the second. The venous congestion data are represented by the filled circles and triangles. Steady-state lymph: plasma concentration ratios fell, but not by the same proportion for all molecular sizes.

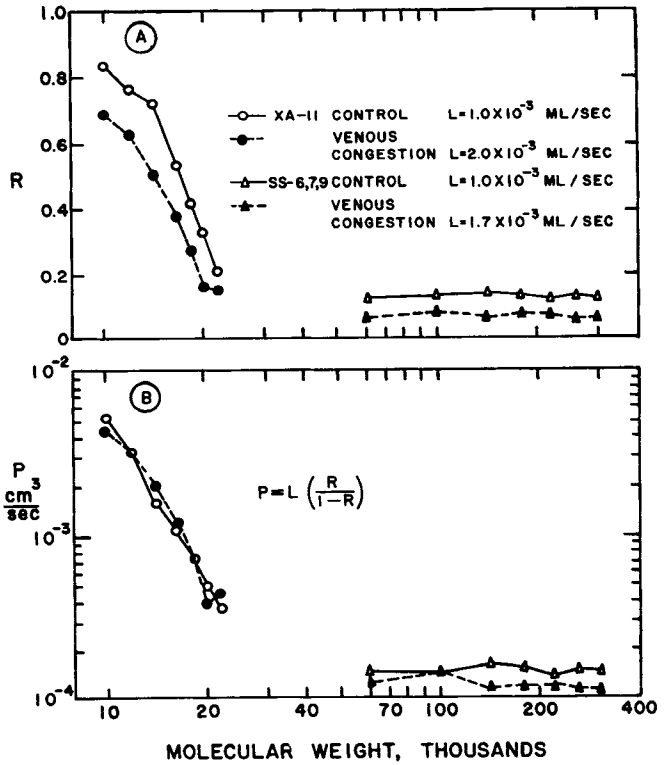

Fig. 2. Calculation of a spectrum of capillary permeabilities from data on lymph flow and composition.

A. Concentration ratios, lymph/plasma of dextran molecules of graded sizes in leg lymph of dogs. Data of Grotte, 1956.

B. Permeability of capillary walls to dextrans of graded sizes calculated from data above. See text for explanation.

The lower graph shows the capillary permeabilities calculated from the data above. The ordinate represents permeability in cm^3/sec on a logarithmic scale, the abscissa, molecular weight in thousands also on a logarithmic scale. Despite the large difference in lymph:plasma concentration ratios in the control and congested preparations, the calculated permeabilities are nearly the same. Permeability falls rapidly as molecular size increases, from 5×10^{-3} cm^3/sec at a molecular weight of 10,000 to 4×10^{-4} cm^3/sec at 22,000. Between 60,000 and 300,000 however, it becomes constant at about 1.3×10^{-4} cm^3/sec. In other experiments there is a slight fall in permeability in this range.

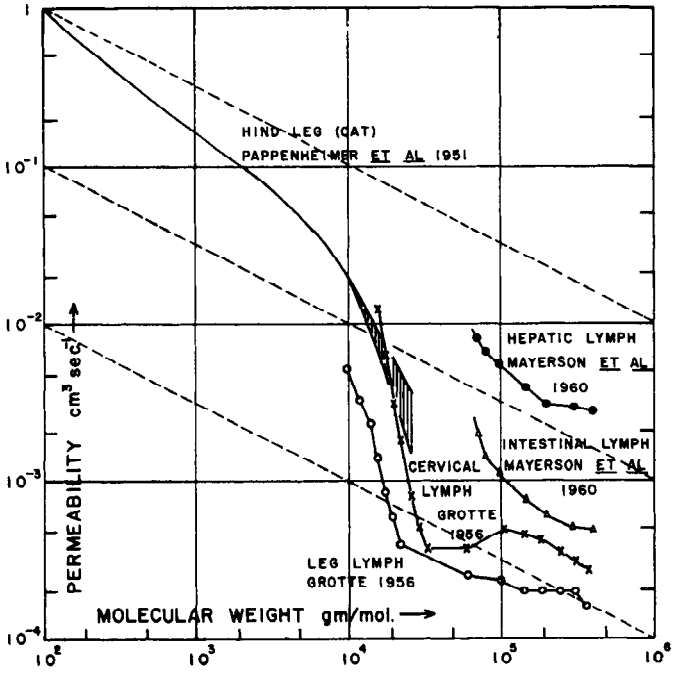

Fig. 3. Capillary permeability to lipid-insoluble molecules of graded sizes. Comparison of the results of the present calculations with those previously published by Pappenheimer et al. (19).

The third figure is a composite graph on a compressed scale, and represents capillary permeability to a wide spectrum of inert, lipid-insoluble molecules. The abscissa is molecular weight in grams from 100 to 1,000,000 on a logarithmic scale. The ordinate represents permeability in cm^3/sec from 1.0 to 0.0001, also logarithmic. The four curves with symbols on them represent capillary permeabilities calculated from lymph:plasma concentration ratios and lymph flows. The lowest curve is from data of Grotte (10) on leg lymph. The second

curve is also from Grotte's data and represents cervical lymph. The next two curves are from the data of Mayerson et al. (14) and represent intestinal lymph and hepatic lymph respectively.

The smooth curve extending into the low molecular weight region is a plot of the data of Pappenheimer and his associates describing permeability of the capillaries in the isolated, perfused hind leg of the cat (19). (The same data is represented in Table 1). The shaded area above a molecular weight of 10,000 shows the estimated limits of experimental accuracy. The curve is terminated at 17,000, the molecular weight of myoglobin. Where the two methods overlap, the permeabilities are of the same order of magnitude for cat's hind leg, dog leg, and dog cervical region capillaries, and the steepness of the fall in permeability with increasing molecular size is roughly the same. The permeability of the capillaries of liver and intestine to large molecules appears to be distinctly greater.

It is necessary, in analyzing the relation between these curves, to consider separately the relative permeabilities over a range of molecular weights and the absolute permeabilities at any given molecular weight. The permeabilities for the cat's hind leg are represented in cm^3/sec per 100 grams tissue weight. The other permeabilities are given in cm^3/sec for whatever mass of tissue was drained by the lymphatics cannulated. Tissue weights were not reported in any of the experiments available. Allowing about 50 grams for the weight of tissue other than bone drained by the lower leg lymphatics of a 15 kilogram dog, the leg lymph curve can be raised by a factor of two, or three tenths of a decade on the logarithmic scale, for comparison with the low-molecular weight permeabilities of Pappenheimer and co-workers. This makes them closely similar. Liver weight in dogs of this size is about 450 grams. Lowering this curve by two-thirds of a decade to represent liver capillary permeabilities per 100 grams of tissue brings them closer to the leg capillaries, but still distinctly higher.

Much more important information may be obtained from these curves without reference to their position along the vertical axis of the chart, by comparing their slopes in different molecular weight ranges. The molecular weight scale is, of course, the same for all curves, and the regions of steepest fall of permeability indicate the molecular weight ranges of greatest restriction to molecular transport. The dashed lines running diagonally downwards with a slope of -1/2, represent the diminution of transport to be expected on the basis of free diffusion. The free diffusion coefficient is inversely proportional to the square root of molecular weight. Any slope declining more steeply than this indicates additional restriction to transport, presumably by geometrical features of the membrane.

The curve of permeabilities for cat's hind leg capillaries shows moderate restriction in the molecular weight range between 100 and 10,000. At 10,000 the permeability is twenty per cent of what would be expected on the basis of free diffusion. Above 10,000, the curve turns more sharply downward, indicating greater restriction. If the origin of the restriction is a system of pores of 30 Å radius, as proposed by Pappen-

heimer and his associates, the curve should fall to zero at a molecular radius of 30 Å, corresponding to a molecular weight of 90,000.

The leg lymph curve shows severe restriction to permeability in the same molecular weight range, but somewhere between 22,000 and 60,000, the fall is broken. Above 60,000, the curve falls slightly or not at all. The region of steepest fall for cervical capillaries is shifted somewhat in the direction of larger molecules, and shows the same break and levelling. Both intestinal and hepatic curves show what looks like the final portion of a steep slope in the 50,000 molecular weight range, followed by a smaller slope extending to 400,000. In all cases, the slope of the high molecular weight "tail" on the permeability curve is not steeper than - 1/2, the slope characteristic of unrestricted diffusion.

It has been known for a long time that the rapid fall-off of lymph: plasma concentration ratios with increasing molecular size was limited to the smaller large molecules. Above a certain molecular size, no further reduction in lymph concentration relative to plasma is observed, at least up to the size of the largest molecules normally present in plasma (26). Mayerson and his colleagues (14) and Grotte (10) proposed that this could be explained in terms of two transport systems in the capillary wall: a system of small pores or openings of 30 Å radius, essentially as proposed by Pappenheimer et al. (19), which would account for the rapid fall in permeability between 10,000 and 60,000 and a less extensive system of very large openings or "leaks" which would account for the high molecular weight tail of the lymph:plasma concentration curve. Mayerson also suggested that the relatively high concentration of very large molecules in lymph might be due to vesicular transport.

The calculation of capillary permeabilities from the data of Mayerson and Grotte makes it possible to examine these hypotheses more closely. The part of the permeability-molecular-weight curve which falls most steeply can be accounted for by a system of pores through the capillary wall of 25 Å radius in the leg, 30 Å radius in the cervical region and not more than 40 Å radius in intestine and liver capillaries. Above 100,000, the curves fall more or less parallel to the theoretical slope for unrestricted diffusion. If a second system of pores exist, its dimensions must be very much larger than the size of the molecules in this range, at least 250 Å radius.

Since the curve of permeability falls sharply when the size of the small pore system is exceeded, it is possible to estimate the total cross sectional area of the large pores from the magnitude of the drop. At a molecular weight of 100,000, all of the permeability in leg capillaries must be due to the large pores. At 10,000 both large and small pores contribute to the permeability. The contribution of the large pores can be calculated by drawing a line from this point with a slope of -1/2 (the unrestricted diffusion slope) back to the 10,000 coordinate. The vertical displacement between this intersection and the experimental point represents the ratio of small to large pore transport at molecular weight of 10,000. In this case it is 8 to 1. However, at a molecular weight of 10,000 there is already considerable restriction to diffusion through the small pore system. Unrestricted small pore permeability can be estimated only by

extrapolating the curve into the low molecular region, and making the comparison at the molecular size of water. This leads to a ratio of more than 100 to 1 for small to large pore areas. In capillaries of the region drained by the left cervical lymphatic duct, the ratio is about the same. The data available for intestinal and hepatic capillaries do not extend to sufficiently low molecular weights to permit estimation of relative contributions to transport of the two hypothetical pore systems.

Another possible mechanism for the residual transport of large molecules above the restriction at molecular weights 10,000 to 60,000 is active transport of proteins through the endothelial walls by pinocytotic vesicles. We may imagine that the vesicles take up whole plasma from the inside of the capillaries, transport it unchanged through the cytoplasm and deposit it outside. Mayerson has called this cytopempsis to distinguish it from pinocytosis which refers properly to vesicular transport into cells (13). The dimensions of the vesicles observed in electron micrographs of capillary endothelial cells by Palade (15) and others (1) are large enough to rule out the possibility of steric restriction in the molecular weight range shown in Fig. 3.

The relation of permeability to molecular weight in this "residual" range should permit us to distinguish between free diffusion and vesicular transport. If transport occurs by free diffusion through a small number of very large pores, the permeability coefficients will continue to fall with increasing molecular weight, in proportion to the diminution of their free diffusion coefficients. In the logarithmic coordinates of Fig. 3, the slope of the fall is - 1/2, parallel to the broken lines. If transport is by cytopempsis, there will be no fall with increasing molecular weight, until the size of the molecule or particle is nearly that of the vesicle. I am assuming no other selective process operates. The curve of permeability vs. molecular weight should be horizontal.

Most of the experimental curves seem to flatten out to a slope less then - 1/2 above a molecular weight of 200,000, but it is difficult to be certain. In some cases - that illustrated in Fig. 2, for example - the curve for capillaries of the region drained by leg lymphatics is almost perfectly horizontal. In other instances, as for liver and intestinal capillaries, the curve falls with a slope of -1/2, and only at the extreme high end is there a suggestion of flattening. The way to a satisfactory solution is shown by the graph. It is necessary to extend the measurements into the millions decade of molecular weights. It will be difficult technically, but there is no reason why it should not be possible. The investigation will be well worth the effort, because if transport of these molecules occurs by diffusion, it will yield information about the nature and dimensions of the diffusion pathway, and if transport is mediated by vesicles, it will yield an absolute measure of the rate of vesicular formation and movement.

Vesicles have been observed in capillaries in many tissues (1), and it has been amply demonstrated that they are capable of taking up molecules or agglomerates of molecules large enough to be visible in electron micrographs (15, 16). It seems entirely reasonable to conclude that these vesicles can and do contribute to transport of materials across

capillary walls. The extent to which they contribute - what substances are transported, and how much - remains to be determined. From the calculated permeabilities to the largest molecular species studied by Mayerson and by Grotte, it is possible to make an estimate of the maximum possible contribution of cytopempsis to transport of materials across capillary walls.

Let us assume that the largest dextran molecule is transported solely by cytoplasmic vesicles. For the capillaries of the dog's leg, the calculated permeability to this molecule is 1.6×10^{-4} cm^3/sec. This figure represents the volume of capillary plasma which exchanges its content of this particular molecular species with lymph or interstitial fluid every second. If transport occurs by inclusion within vesicles, this figure represents the volume of plasma taken up by the vesicles and deposited outside the capillaries. Therefore a maximum estimate of the rate of cytopempsis in the capillaries of the dog's leg is 1.6×10^{-4} cm^3/sec. Lymph flow in these preparations was 1.2×10^{-3} cm^3/sec, thus the volume of fluid transported by the vesicles was no more than 13 per cent of that which appeared in the lymph. Assuming a tissue weight of 50 grams, the plasma flow through these capillaries must have been at least 30×10^{-3} cm^3/sec. Lymph flow was thus less than 4 per cent of plasma flow, and the volume of fluid transported by cytopempsis less than 0.5 per cent of the plasma flow. The contribution of cytopempsis to transport of small molecules must therefore be minute, since it has been shown by direct measurement that nearly 100 per cent of the plasma content of small molecules can be exchanged in the course of a single circulation (4). The functional importance of vesicular transport must be limited to plasma solutes with molecular weights above 10,000.

Most studies of vesicular transport have been carried out with the electron microscope. It is possible to count the vesicles present at any instant and to observe their content of macromolecular material, but one can infer the time course of events only from inspection of sections prepared at given intervals. It is possible to find a common ground for comparison of such necessarily static measurements with kinetic measurements of transcapillary exchange? From the estimate I made of the maximal rate of vesicular transport we can derive a rough figure for the average turnover time or "lifetime" of the vesicles. A few anatomical assumptions are necessary - but these can be obtained directly from electron micrographs.

The internal radius of a capillary is about 4 microns, and wall thickness about 1 micron. The relative volume of wall to lumen is 50 per cent. If one per cent of the weight of the dog's leg represents blood in the capillaries, then 0.25 cm^3 is the volume of the capillary endothelium in 50 grams of tissue. In some electron micrographs, the vesicles appear to make up twenty per cent of the volume of the capillary wall, 0.05 cm^3 per 50 grams of tissue. The rate of vesicular transport in dog's leg capillaries is less than 1.6×10^{-4} cm^3/sec per 50 grams. Dividing the total volume of the vesicles by the volume transported by them per second, we obtain the average lifetime of a vesicle: 300 seconds or 5 minutes. Due to the many approximations, this figure is valid only

as an order of magnitude, but it tells us to expect vesicular lifetimes of the order of a few minutes, rather than a few seconds or hours. Such lifetimes are consistent with Palade's electron microscopic observation on appearance of colloidal gold in the vesicles of muscle capillaries (16), and with Lewis' direct observations of the rate of vesicle turnover in tissue culture cells (13).

The same analysis can be applied to other tissues for which appropriate permeabilities are available. In the liver, the maximal rate of vesicular transport is greater than the measured lymph flow, 2.8×10^{-3} compared to 2.0×10^{-3} $cm^3/sec.$, but still only a minute fraction of the plasma flow, 1.7 $cm^3/sec.$ In this organ also, it appears that vesicular transport, can contribute significantly only to the transport of very large molecules.

To summarize: capillary permeabilities to inert lipid-insoluble substances graded in molecular weight from 10,000 to 400,000 have been calculated from published data on lymph flow and lymph composition relative to plasma. Comparison of these permeabilities with those for small molecules indicate that the sharpest restriction to transport occurs in the molecular weight range of 1,000 to 20,000 for capillaries of the leg and cervical regions, somewhat higher for the capillaries of the intestine and liver. Above the range of sharp restriction, molecular transport still takes place, but a greatly diminished rate, and little or no further restriction is encountered at least up to 400,000.

The region of sharp restriction of permeability is equivalent to that which Pappenheimer and his associates (17,19) attributed to a system of pores with radii of about 30 Å in the cat's hind leg. Pore radii close to this figure are consonant with calculated permeabilities for leg and cervical region capillaries, but somewhat larger radii, perhaps 40 Å, must be assumed for intestinal and liver capillaries.

The residual transport for molecules larger than these capillary pores must represent diffusion through a bigger set of pores, as suggested by Mayerson and his associates (14), and by Grotte (10), or to transport by cytoplasmic vesicles, alternatively proposed by Mayerson. These two processes can be distinguished by the slope of the relation between the logarithm of the permeability coefficient and the logarithm of molecular weight. For diffusion through pores, the downward slope must be 1/2 or greater. For vesicular transport, the slope should be zero. The data available do not run to high enough molecular weights to make a clear distinction possible, but in most cases the final slopes are less than - 1/2 suggesting that vesicular transport is at least partly responsible for transport of molecules larger than the small pore system.

If transport of large molecules is by diffusion through very large pores, the pore size must be much greater than that corresponding to a molecular weight of 400,000, since there is no evidence of restriction below this size. The ratio of large pore area to small pore area is about 1 to 100.

If transport of large molecules is by endothelial cell vesicles, the volume of plasma carried across the capillary wall by the vesicles is

only 13 per cent of the lymph flow and about 0.5 per cent of the plasma flow through the capillaries of the dog's leg. In the dog's liver, the rate of vesicular transport is a little larger than the lymph flow, but still a minute fraction, 0.2 per cent, of the plasma flow. These figures make it clear that vesicular transport cannot contribute significantly to transcapillary exchange of substances of molecular weight below 10,000. However, it is fully capable of accounting for a large part of the transport of larger molecules. For the transport of large molecules at the rates observed, a vesicular turnover time of a few minutes is indicated.

In conclusion: the capillary wall has two transport systems: one for small molecules, one for large. The small system - probably an array of openings some 30 Å in radius - permits extremely rapid exchange of very small solutes such as those important in tissue metabolism and ionic balance. It sharply limits the penetration of molecules larger than 20,000, and thereby permits maintenance of fluid balance across the capillary wall by the mechanism proposed by Starling.

The large system - either a passive transport system of a few very large pores or an active transport system of cytoplasmic vesicles - permits very slow transport of large molecules, not to support metabolism or to maintain material balance, but to provide for distribution of special chemical substances: hormones, antibodies and others still unknown. Much remains to be learned about both transport systems, about the substances transported by them and their rates of transport. Following Bowditch's example, I wish to direct your attention to what is still - after 90 years - an exciting and attractive field of research.

REFERENCES

1. Bennett, H. S., J. R. Luft, and J. C. Hampton. Morphological classification of vertebrate blood capillaries. Am. J. Physiol. 196: 381-390, 1959.
2. Bennhold, H., and E. Kallee. Comparative studies on the half life of I^{131}-labelled albumins and non-radioactive human serum albumin in a case of analbuminemia. J. Clin. Invest. 38: 863-872, 1959.
3. Bowditch, H. P. The lymph spaces in fasciae. Proc. Am. Acad. Sci. 8: 508-510, 1873.
4. Chinard, F. P., G. J. Vosburgh, and T. Enns. Transcapillary exchange of water and other substances in certain organs of the dog. Am. J. Physiol. 183: 221-234, 1955.
5. Courtice, F. C., and D. C. Garlick. The permeability of the capillary wall to the different plasma lipoproteins of the hypercholinesteraemic rabbit in relation to their sizes. Quart. J. Exptl. Physiol. 47: 221-227, 1962.
6. Creese, R., J. L. D'Silva, and D. M. Shaw. Interfibre fluid from guinea pig muscle. J. Physiol. (London) 162: 44-53, 1962.
7. Crone, C. Does "restricted diffusion" occur in muscle capillaries? Proc. Soc. Exptl. Biol. Med. 112: 453-455, 1963.
8. Fink, R. M., T. Enns, C. P. Kimball, H. E. Silberstein, W. F. Bale, S. C. Madden, and G. H. Whipple. Plasma protein metabolism - normal and associated with shock. J. Exptl. Med. 80: 445-475, 1944.
9. Flexner, L. B., G. J. Vosburgh, and D. B. Cowie. Capillary

permeability: rate of transcapillary exchange of iron added to plasma as radioactive ferric beta-1-globulinate. Am. J. Physiol. 153: 503-510, 1948.
10. Grotte, G. Passage of dextran molecules across the blood-lymph barrier. Acta Chir. Scand. Suppl. 211: 1-84, 1956.
11. Kedem, O., and A. Katchalsky. Thermodynamic analysis of the permeability of biological membranes to non-electrolytes. Biochim. Biophys. Acta. 27: 229-246, 1958.
12. Landis, E. M. Micro-injection studies of capillary permeability. II. The relation between capillary pressure and the rate at which fluid passes through the walls of single capillaries. Am. J. Physiol. 82: 217-238, 1927.
13. Lewis, W. H. Pinocytosis. Bull. Johns Hopkins Hosp. 49: 17-23, 1931.
14. Mayerson, H. S., C. G. Wolfram, H. H. Shirley, Jr., and K. Wasserman. Regional differences in capillary permeability. Am. J. Physiol. 198: 155-160, 1960.
15. Palade, G. E. Fine structure of blood capillaries. J. Appl. Physics 24: 1424, 1953.
16. Palade, G. E. Transport in quanta across the endothelium of blood capillaries. Anat. Record 116: 254, 1960.
17. Pappenheimer, J. R. Passage of molecules through capillary walls. Physiol. Rev. 33: 387-423, 1953.
18. Pappenheimer, J. R., and A. Soto Rivera. Effective osmotic pressure of the plasma proteins and other quantities associated with the capillary circulation in the hindlimbs of cats and dogs. Am. J. Physiol. 152: 471-491, 1948.
19. Pappenheimer, J. R., E. M. Renkin, and L. M. Borrero. Filtration, diffusion and molecular sieving through peripheral capillary membranes. A contribution to the pore theory of capillary permeability. Am. J. Physiol. 167: 13-46, 1951.
20. Renkin, E. M. Capillary permeability to lipid-soluble molecules. Am. J. Physiol. 168: 538-545, 1952.
21. Starling, E. H. The influence of mechanical factors on lymph production. J. Physiol. (London) 16: 224-267, 1894.
22. Starling, E. H. On the absorption of fluids from the connective tissue spaces. J. Physiol. (London) 19: 312-326, 1896.
23. Wasserman, K., and H. S. Mayerson. Exchange of albumin between plasma and lymph. Am. J. Physiol. 165: 15-26, 1951.
24. Wasserman, K., and H. S. Mayerson. Dynamics of lymph and plasma protein exchange. Cardiologia 21: 296-307, 1952.
25. Wasserman, K., L. Loeb, and H. S. Mayerson. Capillary permeability to macromolecules. Circulation Res. 3: 594-603, 1955.
26. Yoffey, J. M., and F. C. Courtice. Lymphatics, Lymph and Lymphoid tissue. Cambridge: Harvard Univ. Press, Chap. 2, 1956, pp. 53-120.

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RETRIEVAL AND EVALUATION OF INFORMATION*

MAURICE B. VISSCHER

The span of life of the American Physiological Society also covers the period of an exponential rise in volume of published reports of studies in the physiological sciences. The Society was organized to promote direct personal oral communication between its members. It was in fact reluctant to accept responsibility for supporting mechanisms for communication by means of the printed word. Witness, for example, its reluctance to accept the American Journal of Physiology as a gift from its prime sponsor, Dr. William T. Porter, who established its editorial and economic integrity as a private venture before generously offering it to the Society. Times and attitudes have changed. In fact, attitudes have almost reversed. Today, the American Physiological Society is proud to be the publisher, not only of three major journals of primary publication, the major review journal, and a house organ, but also of the Handbook of Physiology which is intended to serve the needs of physiological scientists in the area of systematic exposition of the present state of physiological knowledge in all areas of its field.

The retrieval and evaluation of information in any scientific field becomes difficult with some power function of the amount of information available. The numerical value of the power can be reduced by improvements in the mechanisms employed by the scientific community for storage and retrieval. Every scientist who complains about the difficulties in "keeping up with the literature" should lend a hand in helping. It will not do for us either to bemoan the passing of the good old days when it was easy to search the old and the new literature for information in one's field of interest, or to resign ourselves to allowing ourselves to be ignorant of the world's store of knowledge. The sensible approach is for scientific societies to take responsibility for improving the old and developing new mechanisms in this important area. The American Physiological Society in the past accepted some of these responsibilities. I predict that in the future it will find itself compelled to accept others. Every time a new journal is started or an old one is expanded, the problem becomes more acute. The Handbook of Physiology is one of our current answers to the problem of evaluation and interpretation. The problem of information announcement, storage, retrieval, evaluation, correlation, and interpretation is not one to be turned over to documentalists or information specialists, although they can be very useful in carrying out certain parts of the process. The large body of working scientists must participate in the intellectual effort of making information available, intelligible, and useful. I urge our members and our officers to continue to explore and exploit feasible methods for improving our own information systems in physiology.

*Address given at the Convocation celebrating the 75th Anniversary of APS, August 27, 1963, Coral Gables, Florida.

NATIONAL SOCIETY FOR MEDICAL RESEARCH AND ANIMAL RESEARCH LEGISLATION

Dr. B. J. Cohen, (official APS representative to the Council of the National Society for Medical Research) reports on the action of the Council meeting in October.

Dr. Hugh Hussey, Director of Scientific Activities of the AMA reported on the recently organized AMA Task Force which is working actively to support the scientific community in dealing with the animal research legislation problem. The Task Force is made up of representatives of the AMA; American Hospital Association; American Veterinary Medical Association; Association of American Medical Colleges; American Dental Association; Association of State Universities and Land Grant Colleges; and the National Society for Medical Research. Its functions are to consider the animal research legislation problem, to combat restrictive legislation, insure proper testimony at hearings, and stimulate the preparation of a manifesto showing that federal regulation of animal research is not needed. The Task Force adopted the following five-point "consensus" for its guidance:

1. The use of animals in research is essential.
2. For research to be effective there must be good care and proper use of animals, and an extension of educational programs related thereto.
3. Care of animals is generally good and can be improved where necessary by voluntary actions that entail setting of standards, surveys of facilities and care procedures, and accreditation of laboratories utilizing animals.
4. Provision for animal welfare is incorporated in all state and many local laws.
5. Federal regulatory legislation in any form is not needed and would be harmful.

Dr. Hussey indicated that the Task Force is considering, with the Animal Care Panel, the implementation of a voluntary accreditation program for laboratory animal facilities. He also indicated that the Task Force has endorsed the "Guide for Laboratory Animal Facilities and Care" prepared by the Animal Care Panel.

Dr. Visscher, vice president of the National Society for Medical Research (NSMR) presented a careful analysis of the possible utility of having the scientific community sponsor affirmative legislation. After some discussion the Council adopted the following resolutions:

1. It is the consensus of the NSMR National Council that the public interest would be harmed by federal regulation of the use of animals for scientific study.
2. It is the consensus of the NSMR National Council that it would be contrary to the public interest for the Congress to pass new legislation setting up additional authority for federal agencies

to regulate the housing and care of animals in scientific research and teaching programs in non-federal institutions.

3. It is the consensus of the NSMR National Council that affirmative legislation, in the spirit of the "Joint Resolution" now being circulated, be supported for introduction in the Congress at an appropriate time.
4. The President and the Board of Directors of the NSMR are informed that the National Council wishes such legislation to be introduced at such time as it seems strategically desirable to the Board of Directors.
5. The National Council instructs the Board to draft a bill in the spirit of the "Joint Resolution," and distribute it to the Council for revision or approval by January 1, 1964.

The "Joint Resolution" in its present form is an affirmative declaration of the importance of animal experimentation to the public health and welfare. It also affirms ethical and moral obligations to provide humane and effective care, transportation, handling, and treatment of laboratory animals. Further, it authorizes the Surgeon General and the Secretary of Agriculture to conduct and support research and training related to adequate care, treatment and utilization of laboratory animals. Finally, the Resolution proposes that the Congress request the President of the National Academy of Sciences to establish a National Academy of Sciences Committee on Laboratory Animal Care. The Committee would consist of leaders in the field of laboratory animal care and use, and of representatives of federal agencies.

A representative of the Academy indicated that the present wording of the Resolution, as it relates to the National Academy of Sciences is not appropriate to the Academy's function as an advisory agency. For example, it is not within the purview of the Academy to "promote the coordination of efforts of various federal agencies to provide adequate care, treatment, and utilization of laboratory animals...". It was agreed that the problems of wording could be resolved. The wording of the bill to be prepared by January 1 is to be revised to meet the Academy's requirements.

Two points of view were brought out at the meeting. The Medical Research Association of California (MRAC) supports the view, shared by the New York Society for Medical Research that legislators need something "to be for." They are under considerable pressure "to vote against cruelty." What they would like is a piece of legislation acceptable to the scientific community which they could vote for as a "vote against cruelty." The MRAC has prepared a non-regulatory legative proposal authorizing the Surgeon General to support research, training, construction, and dissemination of information in the field of animal care. This bill may soon be introduced by a member of the House from California. The New York State Society for Medical Research also has a bill in preparation.

The other point of view, presently held by the NSMR Board of Directors, is that no substantial benefit is to be gained by pressing for legislation to authorize activities that already are legal. The scientific

community's program is to seek more support for research, training, construction, and dissemination of information in the field of animal care; and to encourage education and voluntary accreditation programs such as the Animal Care Panel Animal Facilities Accreditation Program. No additional legislation is needed to implement these activities. However, the Board recognizes that political pressures may force the Congress to hold purposeful hearings (hearings in which it is clear a bill will be reported to the floor). This may not happen, in which case no legislation need be introduced; but if it does, it is necessary to have a bill ready which is acceptable to the scientific community. Such a bill should be in final form shortly after January 1, 1964.

Progress is being made toward a successful resolution of the legislative problem. However, it is clear that the issue may be with us for some time to come. We should not interpret the fact that affirmative legislation has not yet been introduced as inaction on the part of NSMR. The fact is that our representatives are fully aware of the legislative problems, and are doing all in their power to assure a successful outcome.

B. J. Cohen

TRAVEL TO CONGRESS IN JAPAN

Maurice B. Visscher, Chairman
U. S. National Committee for the IUPS

Members of the American Physiological Society and others intending to participate in the XXIII International Congress of Physiological Sciences in Tokyo, Japan in early September 1965, are urged to give early consideration to the problem of financing their travel to that Congress. The U. S. National Committee for the International Union of Physiological Sciences hopes to have some funds for support of participants in the Congress, but it considers it very unlikely that it will have sufficient funds to provide travel awards for the great majority of persons who will wish to attend. Consequently, the Committee strongly urges that all persons whose research programs will be benefited by their participation in this Congress consider at this time the desirability of requesting authorization for travel from the agencies supporting their research. Such authorization should be requested at the time of grant applications for the fiscal year during which September 1965 will occur.

TEACHING OF PHYSIOLOGY TO MEDICAL STUDENTS DURING THE FIRST HALF OF THE 20th CENTURY*

A. C. IVY

At the Semicentennial of the American Physiological Society in 1938, the primary concern was physiological research. Today, I am primarily concerned about the teaching of physiology. This is because research and adequate funds are here to stay, and I doubt that the brains of first year medical students will be any better prepared in the future than they are today.

Most teachers of physiology in 1938 were quite satisfied with their student product. They believed their product was as well prepared for the study of clinical medicine and surgery as the time allotted to physiology permitted. The chief complaints were the lack of research funds and that less than 10 per cent of the students had an aptitude and a desire for graduate study and a career in teaching and research.

The objective of most every teacher of physiology in 1920 was to assist in the production of physicians by enlightening the technicalities of the practice of medicine and surgery. The teacher's first function was to "keep school." It was found by various trials that a disciplined plan of instruction was superior to the laissez faire plan because the former promoted better study habits. The second function of the teacher was to stimulate the students to like their work. It was found that this was best achieved by indicating to the student how various items of physiological information were related to the cause, prevention, diagnosis and treatment of disease. The third function of the teacher was believed to be to stimulate the students to think logically and usefully in terms of physiology. This was difficult to achieve because past training had primarily cultivated the student's ability to memorize.

Such pedagogical ideals have paid large dividends. Thirty five years ago physiology was frequently viewed as a hurdle to be cleared in order to study medicine and surgery. Today physiology has been extended into every branch of medicine and surgery. Physiological laboratories have been established in many sections of the Armed Forces, and in numerous governmental agencies and industrial concerns.

My chief concern, today, regarding the teaching of physiology to medical students is a growing trend to eliminate the applied aspects from the instruction in preclinical physiology and to reduce the hours allotted to the teaching of basic physiology.

This trend is due to a number of factors, some of which are the following: 1) A great increase has occurred in the knowledge of physiological processes. 2) The degree of specialization of teachers of

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physiology has increased because more emphasis has been placed on research. Consequently fewer teachers with broad interests and the inclination to relate their subject matter to the concerns of physicians, exist. 3) This trend has been greatly enhanced by government grants. 4) As clinical departments have expanded their research program, the services of personnel trained in physiology have been employed. The teaching of applied physiology has been taken over by clinical instructors. As a result, teaching hours in clinical subjects have been increased and the hours in preclinical physiology have been decreased.

This trend toward the reduction in the hours allotted to preclinical physiology is not sound. Teachers of preclinical physiology should indicate the practical applications in order to make their subject more interesting and valuable to medical students. And, they should "hold the line" on the hours allotted. However, the major portion of the applied physiology should be added as a part of the teaching program of the clinical years. This is sound because the years of internship and residency have been added to teach the technicalities of the clinical subjects.

The importance of the applied features of physiology has developed during the past 30 years. It will develop more during the next 25 years, provided its growth is not made at the expense of instruction in preclinical physiology.

G.I. GROUP ANNUAL DINNER

Dr. C. F. Code will be the speaker at the annual dinner of the gastrointestinal group of the American Physiological Society on Thursday, April 16, 1964 during the Federation Meetings. His topic will be "Physiology of the Gastro-Duodenal Junction."

PHYSIOLOGISTS IN WORLD WAR II*

D. B. DILL

In 1950 I wrote an article for "Science" on "Biologists in Military Service." This dealt chiefly with post-war events. At the end of the war there was a rapid exodus of scientists in uniform: they felt compelled to return home to mend their fences. In this brief talk I am going to reminisce about some experiences of "physiologists in World War II."

At the meeting of the Federation in Chicago in April 1941, I commented on the need for more physiologists to enter the uncharted field of applied physiological research as related to military physiology. Some had already reoriented their research and many others did so during the next year. As Comroe has pointed out, the end result of the greatly increased emphasis on such fields as environmental physiology, exercise physiology, nutrition, and pharmacology not only had great practical value to our country; there were major gains in fundamental knowledge in these fields.

An early beginning had been made at what was then called Wright Field, near Dayton, Ohio. The following account of the beginning of the Aero-Medical Laboratory there has been supplied by Maj. Gen. Harry G. Armstrong MC (Ret.):

> "On 15 September 1934 I was assigned to duty at Wright Field as a "Consultant" to the Equipment Branch of the Engineering Section. This proved not to be very productive and I was able to have the next budget include an aeromedical research laboratory. In Washington this request was referred to the Air Surgeon (then Maj. Grow) for Staff action and it was approved at that level and funded.
>
> "When I arrived at Wright Field the World War I altitude Chamber was there and I used it for my initial experiments. For the new laboratory I needed a bigger and better chamber and thought it would expedite matters and reduce cost if I could get the plans for Drinker's high pressure chamber and modify them as necessary. Drinker gave me a copy of the specifications for their chamber and also allowed me to recruit Dr. Heim who joined me in June 1936."

It was my privilege to spend a few days in this laboratory in 1937 and to take part in one of the first experiments conducted in the new chamber. At that time J. F. Hall, Jr., and E. A. Pinson had joined the staff. Two years later Armstrong's book was published: it became a well-known classic.

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In 1940 Armstrong was succeeded by O. O. Benson, Jr.; the latter divided the summer of 1940 between the Mayo Clinic and the Fatigue Laboratory. At Rochester he profited greatly by association with Boothby, Baldes, and Lovelace. The major contributions to the solution of military problems of the latter three continued through the war, the first two as civilians, the third as a medical officer. At the Fatigue Laboratory, Benson sought my help in persuading scientists to join him at the Aeromedical Laboratory. F. G. Hall and I joined him in January 1941 and not long after Gagge and Guillemin arrived. I wish there were time to trace the war-time history of that laboratory. I'll add one note about an early incident. Shortly after my arrival one of the sergeants came to me confidentially to say that virtually all planned research had been completed prior to our arrival. He feared the increased staff would find little to do.

I left the Fatigue Laboratory in capable hands and with a climatic laboratory including an altitude chamber under construction. It was shortly fully devoted to military research. Among those who played a major role in that program under the benevolent eye of L. J. Henderson were W. H. Forbes, R. E. Johnson, H. S. Belding, S. M. Horvath, R. C. Darling, and Sid Robinson.

Physiologists were not always received by senior officers with open arms. During 1940 I proposed to the Army Quartermaster Corps a modest scientific study of footgear. This was rejected on the grounds that the small areas of uncertainty about military footgear would be resolved by practical field trials. Then I understand that the first proposal for establishing the Naval Medical Research Institute was rejected on the grounds that medical research required by the Navy was provided for already in the Naval Medical Center.

Once we were in the war attitudes changed rapidly. Committees of the Office of Scientific Research and Development, NAS-NRC, mobilized the resources of civilian research centers on the one hand and sought out unsolved military problems on the other. Senior scientists were sought as advisors by the armed services, -- Bronk by the Air Force, DuBois and Ivy by the Navy, Siple and Talbott by the Army to mention only a few. Among physiologists who served as line officers, one of our Councillors, James D. Hardy, commanded combat vessels in the war zone.

Military medical laboratories were established. What was first called the Armored Medical Research Laboratory was built at Fort Knox and staffed with a distinguished group of scientists including Willard Machle, Ted Hatch, Bill Bean, Bill Ashe, Steve Horvath, and Norton Nelson. The Air Force expanded its School of Aviation Medicine at Randolph Field to include research in aviation medicine. The Naval School of Aviation Medicine at Pensacola embarked on a research program under the direction of Ashton Graybiel, formerly associated with the Fatigue Laboratory, and with collaboration in the early phases with Ross McFarland and later, Dick Riley.

As time went on demands for physiologists burgeoned especially after

the Air Force decided to buy 80 pressure chambers for indoctrination of air crews. When this happened I am told that Gen. Grant, the Air Surgeon, called on his advisor, Det Bronk, for a roster of physiologists. He was at once furnished a copy of the Federation Directory. "Recruit 100 of these physiologists to train air crews in our altitude chambers," he was ordered.

Midway in the war I was transferred to the Research and Development Division of the Quartermaster General's office. This was then headed by master craftsman George Doriot, borrowed from the Harvard Business School and once a runner on the Fatigue Laboratory treadmill. During this period I was fortunate in being able to learn first-hand of many physiological problems still unsolved. I had two months in North Africa and Italy in 1943 and two months in the South and Central Pacific areas in 1944.

General Doriot had recruited prima donnas from all fields of exploration to staff his Special Forces Branch. Included were Paul Siple, F.W. Wulsin, Bestor Robinson, Bob Woodbury, and Sir Hubert Wilkins. Gen. Doriot and Paul Siple with advice from Will Forbes had set up the Climatic Research Laboratory at Laurence, Massachusetts, under the direction of John H. Talbott, formerly of the Fatigue Laboratory. This Army laboratory in association with the Fatigue Laboratory tackled and solved a great many problems in applied physiology.

In closing I must emphasize that I have given a biased account colored by my own experiences. Everyone at this table was involved directly or indirectly in war-time research. Perhaps we should pool our experiences and compose a balanced documentary account of the roles of, "Physiologists in World War II."

REFERENCES

Dill, D. B. Biologists in military service. Science 111: 675-676, 1950.
Armstrong, H. G. Principles and Practices of Aviation Medicine, Baltimore: Williams & Wilkins, 1939.

PERSONAL RECOLLECTIONS AS TO THE AFFAIRS OF THE SOCIETY FROM 1921 - TO DATE*

W. F. HAMILTON

The first meeting of the society which I attended was in New Haven, 1921, at which insulin was announced. The society was very small then and the congeniality and kindness of the older men gave me a most favorable impression of the group. After a heart-rending deferral, I was admitted to membership in 1924 and have had the good fortune to be able to attend at least one meeting per year ever since. About twelve years after I joined the society I was asked by Dr. Hooker to be a consulting editor of the Journal. I remained active in publication matters from about 1936 until some time in the future when the Handbook on Circulation will be finished.

The only policy matter that I concerned myself with in these years was the matter of Exhibits at the annual meeting. The group was getting too big to meet on campuses and hence demonstrations were being given up. Other groups were attracting commercial exhibitors so I wrote to a few of their secretaries and to a few exhibitors and received encouraging replies. Dr. Hooker, however, due to failing health, could not implement the project. When after the war, Milton Lee took over the Federation, he saw this correspondence and followed it through much to our scientific and financial profit.

In 1942 I was elected to council. The meetings were cancelled in 1943, 1944, and 1945, over my bitter protests. Transportation was available for button collectors and sundry sales conventions and I thought we were selling our national importance inexcusably short by not having serious professional meetings during the war years.

A council meeting in 1945 was held in Rochester at which we selected new members and did routine business. We were exasperated by the fact that only one copy of the applications for membership was available. The conservatism of council in those days was such that they voted 6-1 against my motion that applications be submitted in quadruplicate, a rule which has since gone into effect.

My stint in council lasted from 1942 to 1949. I had been active in society affairs for so long that I felt rather let down but was much gratified to find that I had been appointed to the Board of Publication Trustees from 1949-1954.

Among the larger policy matters that were decided during this period were: consolidation of the function of the Board of Trustees as an independent trusteeship capable of entering into long term contracts with business and with personnel and consequently being able to get supplies and services

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in a rising market at better advantage than if their autonomy were less secure.

Tightening up the security of long term policy control in the hands of the trusteeship had been given impetus by a stampede of membership and council to present funds to the supposedly war-pressed publications group of the British Physiological Society. It turned out that they did not need the money and it was returned.

A symptom of this tightening up was manifest in 1952 when council proposed to divert a sizeable sum from publication funds to the support of various ventures which "needed to be done." This caused the threatened resignation of certain trustees and the projects died aborning. The status of the Board as real trustees seemed to be confirmed.

During the period 1949-1954, the project of publishing the Handbook was launched. Maurice Visscher is to be credited with the energy and foresight that developed this project. Council gave a rather grudging consent based to some extent on the theory that the project might deplete publication funds which were of such size as to overshadow the general funds of the society.

Various members with editorial and administrative experience were circularized about the Handbook. John Field came up with a detailed plan for management of the Neurophysiology Section and was empowered to set up a committee to work out details. Field was appointed Editor-in-chief and Victor Hall, Executive Editor. When it came out in 1959 "Section I Neurophysiology" was an unqualified success financially, typographically, and most important, scientifically. Other sections are underway and projected.

The headquarters of the Society and of the Federation were posing an acute problem. Other needs more directly concerned with the activities of N. R. C. had forced this body to terminate their hospitality to our offices and we rented a suite in a downtown office building. Considerable discussion came up in council as to whether society headquarters should be in Washington or in the central states. When, however, it seemed apparent that nearly all national organizations of our sort had headquarters in Washington and that NIH, N. S. F., and N. R. C. would be the source of funds, of talent, and of background for organization, the opposition to a Washington office was dropped.

To find a location in Washington for a permanent society home or preferably one for the Federation as a whole, proved a discouraging task. It had become a fetish among society executives that headquarters should be located downtown within easy taxi ride of the Union Station (or airport?) and with this restriction all that our realtor could show us was a discouraging array of exorbitant dumps with no parking and limited access.

I take credit for making the query about the possibility of finding a home near NIH and the Naval Hospital. I urged that in the near future such a location would be a cynosure for Biomedical investigators from

all over the world and that cheap land and plenty of it could be found.

Our realtor had access to the Hawley estate. At first it was touch and go as to whether we could get it zoned for our activity and whether the Roman Catholic Bishop would get it first for a school. These difficulties were surmounted with the help of our realtor and as a result of the devoted struggles of Milton Lee.

We found that some of the land could be sold off for a subdivision, making our investment relatively small and still leave us with more land than we could then see the use of. It was also found that the Federation would purchase the property from APS in case it should be decided that this would be the best course. This final consideration caused the last objection on the part of the more conservative members of the board to evaporate and the Hawley estate was purchased.

We then cast about for a name of our headquarters. I urged that Beaumont was most appropriate. Not only did the word fit the beautiful lay of the land but Beaumont himself was a dedicated contributor to physiology before the discipline became compartmentalized into Biochemistry, Pharmacology and so on. The name was adopted and now we have Beaumont House, owned by the Federation. My Boston Congress Bronze Medal with Beaumont's features in relief, adorns the door of the old house and a replica of it in cast stone the entrance to the new building.

Much to my amazement, I was elected President in 1954. On my President-Elect tour I found sentiment among members in favor of sectionalizing the big American Journal by topic. I still hope this may be done.

During this year the biophysicists split off from the APS in spite of the efforts of many members to extend hospitality in the parent organization.

R. G. Daggs was appointed permanent Executive Secretary of the society. The mythical poor instructor living in a garret prevented raising dues to pay him and support from evanescent overhead from NSF contracts could not be counted upon. Recently, dues were raised and the society became self-supporting.

Through the helpful energy of Louis Katz, the fall meeting lectureship was funded. I had the honor of suggesting that the lectureship be named after our first president and of appointing John Pappenheimer first Bowditch lecturer.

In the last decade the Board of Publication Trustees has evolved into a body of senior members of the society who, by common consent, perpetuated the highest traditions of financial and editorial management. They exemplified the mechanism that is adopted by all responsible state governments in running their universities, hospital systems and highway systems. By following the trusteeship principle, it is possible for a democracy to run a permanent project. Trustees can enter into long

term commercial contracts and can employ personnel on terms satisfying to high grade professional people, who wish to spend a life time in the development and management of a worth while project.

In the 1960 business meetings the by-laws were changed. After a confused hassle, which would never have been tolerated by a less casual assembly, the new and very ambiguous by-laws were voted down. The consensus of the confusion seemed to be that the matter was of sufficient importance to be put to a mail vote of all of the membership.

The opposition rested on its oars and was taken aback when the question was brought up again before a very small business meeting. After an eloquent disparagement of the trustee principle and an even more eloquent support of the principles of democracy, a motion was put over allowing a council committee to write a pre-approved set of by-laws. These by-laws, which have never been formally considered by membership, are found in the directory. In them:

1. The trusteeship principle is eliminated.

2. The publication's project has become schizophrenic in that financial and editorial parts of this function are split.

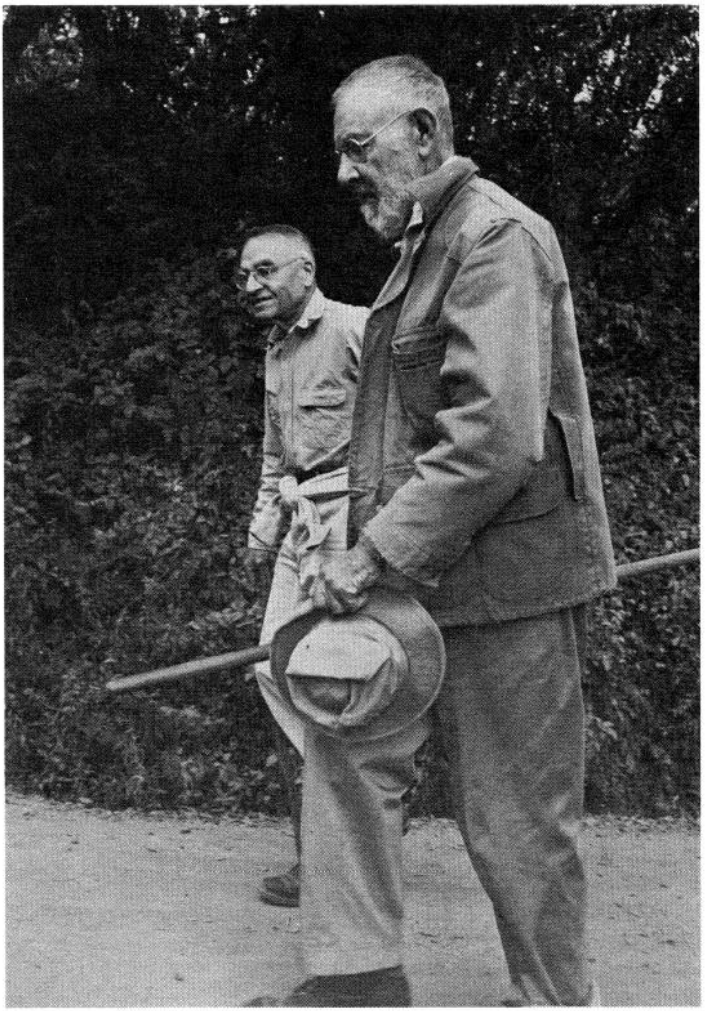
3. No provision is made in the by-laws to report to membership the financial status of the publications project or the changes in editorial policy.

NATIONAL REGISTER OF SCIENTIFIC AND TECHNICAL PERSONNEL

In late March the Federation will again assist in circularization of Questionnaires for the National Register of Scientific and Technical Personnel for 1964. It is strongly urged that everyone who receives a FASEB Questionnaire complete and return it promptly to permit the coding and analysis of the information to be completed and ready for report by the National Science Foundation in December 1964.

NEWS FROM PERCY DAWSON

It was Dr. Dill who suggested that I send him a photo of my hiking pal and me, and that I write something to go with it. So I am going to answer some possible questions which my picture and my name might be expected to call forth.



Doubtless it will be asked how I came to ride the cycle ergometer at the age of ninety. This is the story.

As a boy I played lacrosse and cricket and made frequent excursions for collecting insects and fossils. In 1889 I matriculated at McGill. I had been handicapped from childhood by respiratory troubles during the winter months, and my attacks became so severe that I withdrew from McGill, went south and entered Hopkins. While there I played (point and counterpoint) for four years on the lacrosse team. For the latter my training was an all year process which I continued with more or less strictness all the rest of my life. The result was that, for a person with a sedentary occupation, I could do remarkable feats of endurance, nothing Olympic but things out of the ordinary in hiking over the mountains and plains.

In addition to these hygienic habits, I for many years rode strenuously a cycle ergometer in my laboratory. With this apparatus I made researches and I also used it in teaching - with every four students I rode once and then one of them rode once, and the four wrote up the two sets of results.

About fifteen years ago I had found hiking inconvenient and had given it up, although I still continued rope-skipping, deep knee bends and dumbbells. About twelve years ago at a Harvard dinner in Palo Alto, I ran across a retired geologist and mine promoter, who is a few years younger than I. In spite of his advantage in age and strength, he was willing to humble himself to my speed in hiking, and so we became an inseparable pair. We walk all year once a week on the mountain roads. At first it was eight miles, later only six - three up and three down. The cycle ride at Stanford was a magnification of one of these walks.

The second question is not professional but a matter of human interest to those who have known me personally. Why did I leave an associate professorship at the Johns Hopkins Medical School to become a graduate student at the Harvard Divinity School?

I was a promising young physiologist in 1904, but between 1902 and 1909 I gradually became more and more interested in more general problems of social welfare and spent more and more time and thought on social settlements, recreation centers, city governments, trade unions and so forth. I had not known the World before, and it came to me as a shock that, while Science is so splendid, Society is so awful! I thought to myself, "Science has been the growing point of our culture in the Nineteenth Century, but in the Twentieth Century it is Society that is to be straightened out and cleaned up or we shall all be lost!" Then I thought that if I left physiology for welfare work I would have to choose between some secular social service organization and the church. I thought that my intellectual and cultural equipment would be better suited to the church, and moreover, I knew pastors who had done fine work for social improvement. For a while matters drifted, then suddenly Dr. Osler asked: "Would you accept a professorship at McGill?" ... I went to Harvard, and later from there to a church in Ann Arbor, Michigan.

In 1913 I joined the physiological staff at the University of Wisconsin. I was an instructor at $1200 a year, but I was in splendid company. I found that the teaching of physiology to medics was not so progressive as at Hopkins, and was dissatisfied. But by a series of welcome opportunities, I arrived at a practically independent position, still teaching physiology but with only students of Physical Education to care for. I was at home in this atmosphere, for I had always regarded Physical Education as a most important branch of Preventive Medicine. Gradually I became as interested in the problem of teaching as in those of physiology, and with that Alexander Meikeljohn appeared on the scene to establish the Experimental College at the University of Wisconsin. Oh, how I longed to be in on this new pedagogical adventure! Then quite unexpectedly Meikeljohn offered me a position on his staff. I hesitated, then said, "I have an experimental college of my own which I cannot neglect but I shall accept a half-time job." Long after this he told me, " I wanted you. I heard you quote from Harold Joachim's "Nature of Truth" and said to myself, 'That's the sort of scientist I want."

I do not think that any more of my biography is called for on this occasion, so I shall end by telling what I am doing now. I am studying my own life and writing an autobiography. This is for me a difficult task, for I know enough of the canons of historical criticism and of psychology to make me very cautious, skeptical and critical of my memory and material, which is abundant. Also I need to be very insensitive for the proper debunking of myself.

A Note from D. B. Dill

Observations of Percy Dawson's performance on the bicycle ergometer last summer extended the laboratory record of his work tolerance to 49 years; his first paper published in the "American Journal of Physiology", Vol. 50, recorded measurements begun in 1914. It was my pleasure on July 27 to help Karl Wasserman of the Dept. of Medicine, Stanford University School of Medicine, make quite a complete record of Dawson's responses to a 30-minute ride in which he reached an oxygen consumption of 1.5 liters per minute. The results are being prepared for publication.

A word about his hiking pal, Augustus Locke. He was born in North Adams, Mass., 1883 and holds four Harvard degrees: B.A., 1904, S.B., 1905, E.M., 1909, and Sc.D., 1913. For his record in geology see Who's Who in America.