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THE AMERICAN PHYSIOLOGICAL SOCIETY

Founded December 30, 1887; Incorporated June 2, 1923

OFFICERS, 1962-1963

President - H. S. Mayerson, Tulane University, New Orleans, Louisiana
President-Elect - H. Rahn, University of Buffalo, Buffalo, New York
Past-President - H. W. Davenport, University of Michigan, Ann Arbor, Michigan
Executive Secretary-Treasurer - R. G. Daggs, 9650 Wisconsin Avenue, Washington 14, D.C.

STANDING COMMITTEES


REPRESENTATIVES TO OTHER ORGANIZATIONS

American Association for the Advancement of Science - R. E. Smith (1964), R. G. Daggs
American Institute of Biological Sciences - W. O. Fenn (1965).
American Documentation Institute - M. O. Lee (1964).
APS Members of the U. S. National Committee for International Union of Physiological Sciences - R. W. Gerard (1963), Chairman; M. D.
Visscher (1965), H. S. Mayerson (1967).


**Federation Advisory Committee** - H. S. Mayerson (1964).


**Federation Public Information Committee** - A. C. Guyton (1964).

**PUBLICATIONS**


Managing Editor - M. O. Lee

Executive Editor - Sara F. Leslie

Chief Editor of *Journal of Neurophysiology* - V. B. Mountcastle

Editor of *The Physiologist* - R. G. Daggs

Associate Editor of *American Journal of Physiology* and *Journal of Applied Physiology* - R. L. Zwemer

Associate Editor of *Physiological Reviews* - R. G. Daggs

**EDITORIAL BOARDS**

American Journal of Physiology and *Journal of Applied Physiology* -

Section Editors - M. B. Visscher (Circulation), Hermann Rahn (Respiration), W. D. Lotspeich (Renal and Electrolyte Physiology), H. W. Davenport (Gastrointestinal Physiology), Jane A. Russell (Endocrinology and Metabolism), L. D. Carlson (Environmental Physiology), Knut Schmidt-Nielsen (Comparative and General Physiology), Elwood Henneman (Neurophysiology).


*Physiological Reviews* - C. F. Code (1964), Chairman; J. E. Rose (1965),
THE PHYSIOLOGIST 239


PAST OFFICERS


Executive Secretary-Treasurer - 1948-56 M. O. Lee, 1956 - R. G. Daggs.

CONSTITUTION AND BYLAWS

Adopted at the 1953 Spring Meeting

CONSTITUTION

ARTICLE I. Name
The name of this organization is THE AMERICAN PHYSIOLOGICAL SOCIETY.

ARTICLE II. Purpose

The purpose of the Society is to promote the increase of physiological knowledge and its utilization.

BYLAWS

(Amended April 1961)

ARTICLE I. Membership

Section 1. The Society shall consist of members, honorary members, associate members and sustaining associates.

Section 2. Members. Any person who has conducted and published meritorious original research in physiology and/or biophysics and who is a resident of North America shall be eligible for membership in the Society.

Section 3. Honorary Members. Distinguished scientists of any country who have contributed to the advance of physiology shall be eligible for proposal as honorary members of the Society.

Section 4. Associate Members. Advanced graduate students in physiology at a predoctoral level, teachers of physiology, and investigators who have not yet had the opportunity or time to satisfy the requirements for full membership shall be eligible for associate membership in the Society provided they are residents of North America.

Section 5. Sustaining Associates. Individuals and organizations who have an interest in the advancement of biological or biophysical investigation, may be invited by the President, with the approval of Council, to become sustaining associates.

ARTICLE II. Officers

Section 1. The management of the Society shall be vested in a Council consisting of the President, the President-Elect, the Past-President for the previous year, and four other members. The terms of the President and of the President-Elect shall be one year. The terms of the four additional Councilors shall be four years each and they shall not be eligible for immediate reelection except those who have served for two years or less in filling interim vacancies. A person may serve only one term as President, except that if the President-Elect becomes President after September 30 he shall continue as President for the year beginning the next July 1st.

Section 2. Nomination and election of a President-Elect and Councilor(s) shall be by ballot at the Spring meeting of the Society. They shall assume office on July 1 following their election.

Section 3. The President-Elect shall serve as Vice-President and Secretary. Should he have to function as President prematurely, the Council shall select from among its own members a Secretary.

Section 4. The Council shall be empowered to appoint and compensate an Executive Secretary-Treasurer who shall assist it in carrying
on the functions of the Society, including the receipt and disbursement of funds under the direction of the Council.

Section 5. The Council may fill any interim vacancies in its membership or vacancies on any Board or Committee of the Society, unless otherwise provided.

ARTICLE III. Dues

Section 1. The annual assessment on members and on associate members shall be determined by the Council and shall be due in advance on July 1.

Section 2. A member whose dues are two years in arrears shall cease to be a member of the Society, unless after payment of his dues in arrears and application to the Council, he shall be reinstated at the next Spring meeting by special vote of the Council. It shall be the duty of the Secretary to notify the delinquent of his right to request reinstatement.

Section 3. A member who has retired from employment because of illness or age may, upon application to the Council, be relieved from the payment of the annual member assessment.

ARTICLE IV. Meetings

Section 1. A meeting of the Society for transacting business, electing officers and members, presenting communications, and related activities, shall be held in the Spring of each year, with other member Societies of the Federation of American Societies for Experimental Biology, except that under exceptional circumstances the Council may cancel such a meeting.

Section 2. A Fall meeting of the Society shall be held at a time and place determined by the Council, for presenting communications and for transacting business except the election of officers.

Section 3. Special meetings of the Society or of the Council may be held at such times and places as the Council may determine.

Section 4. Regional meetings of the Society, for the purpose of presenting scientific communications, may be authorized by the Council.

ARTICLE V. Publications

Section 1. The official organs of the Society shall be the American Journal of Physiology, the Journal of Applied Physiology, Physiological Reviews and such other publications as the Society may own.

Section 2. A Publications Committee composed of three members of the Society appointed by the Council shall be responsible for the management of all of the publications of the Society; the Managing Editor, Executive Secretary and President of the Society shall be members ex-officio, without vote. The Committee shall have the power to appoint a Managing Editor and editorial boards for the Society's publications. The term of each member of the Publications Committee shall be three years; a member may not serve more than two consecutive terms. The Council shall designate the Chairman of the Committee who shall be an ex-officio member of the Council, without vote. The Committee shall present an annual report on publications and policies to the Council for approval and an
ARTICLE VI. Committees and Representatives

Section 1. The Council may appoint such special and standing committees as it deems necessary or that are voted by the Society.

The Council may name members of the Society as representatives to other organizations whenever it deems such action desirable.

Section 2. A Finance Committee, composed of three members of the Society appointed by the Council, shall receive budget proposals annually from the Committees, the Council and the Executive Secretary of the Society and shall determine the annual budget, reserve funds, and investments of the Society, subject to approval by the Council.

The capital fund of the present Board of Publication Trustees (defined as the investments and unencumbered funds of that Board as of April 1, 1961) shall be a reserve fund for publications and may be used by the Publications Committee to finance new or established publications without authorization of the Finance Committee (though subject to approval by Council). The Finance Committee shall not approve the expenditure of any of this capital fund for nonpublication purposes without the consent of the Publications Committee. The Finance Committee shall be responsible for the separate investment of the reserve fund for publications; any capital gains from such investment shall accrue to the fund (capital losses will, however, reduce the value of it). Annual income from the investment of the fund may be used for any of the activities of the Society including publications.

The term of each member of the Finance Committee shall be three years; a member may not serve more than two consecutive terms. The Managing Editor, the President, and the Executive Secretary shall be ex-officio members, without vote. The Council shall designate the Chairman of the Committee who shall be an ex-officio member of the Council, without vote.

ARTICLE VII. Standing Rules

1. Election to Membership. Two members of the Society must join in proposing a person for membership, in writing and with a statement of his qualifications. The Council may, from the persons so proposed, nominate candidates for election to membership. Nominations shall be presented at Spring and Fall meetings; a two-thirds majority vote of the members present and voting at the next following Fall or Spring meeting shall be necessary for election.

If a Spring or Fall meeting of the Society is not held, the procedures of nomination and/or election of new members may be effected by mail.

The names of the candidates nominated by the Council for membership and statements of their qualifications signed by their proposers shall be available for inspection by members during the Society meetings at which their election is considered.

2. Election to Honorary Membership. The proposal of an honorary member shall be made by two members of the Society to the Council in writing. The Council may, from the candidates so proposed, make nominations to the Society at a Spring meeting. A two-thirds majority vote of the members present shall be necessary for election.
Honorary members shall have the privilege of attending business sessions of the Society but shall have no vote. They shall pay no membership fees.

3. Election to Associate Membership. Associate members shall be proposed, nominated and elected in the same manner as full members. Associate members shall have the privilege of attending business sessions of the Society but shall have no vote. Associate members may be nominated for full membership.

4. Presentation of Papers. At a Spring meeting of the Society, held in conjunction with the Federation meetings, a member or honorary member may present orally or by title, be co-author of, or introduce not more than one scientific paper, except upon invitation of the Council. An associate member or a non-member may present orally one scientific paper only if sponsored by a full member of the Society. At a Fall meeting, a member, honorary member, or associate member may present orally not more than one paper, except upon invitation of the Council. Upon invitation by the Council, a member may contribute papers to specially designated sessions of the Society without forfeit of his privilege of presenting a regular scientific communication.

5. There shall be a Committee on Membership appointed by and advisory to the Council.

6. There shall be a Program Advisory Committee appointed by the Council.

ARTICLE VIII. General

Section 1. Amendments. These Bylaws, except Article VII, may be amended at any Spring meeting of the Society by a three-fourths majority vote of the members present. The Standing Rules of Article VII may be amended by a majority vote of the members present at either a Spring or Fall meeting of the Society.

Section 2. Quorum. At all business meetings of the Society fifty members shall constitute a quorum.

Section 3. Parliamentary Authority. The rules contained in Roberts Rules of Order shall govern the conduct of the business meetings of the Society in all cases to which they are applicable and in which they are not inconsistent with the Bylaws or special rules of order of the Society.
APS MEMBERSHIP STATUS

OCTOBER 1962

Regular members 2141
Associate members 164
Retired members 133
Honorary members 16
Total membership 2454

SUSTAINING ASSOCIATES

Abbott Laboratories
Ayerst Laboratories
Beckman Instruments, Inc.
Burroughs Wellcome and Co.
CIBA Pharmaceutical Products, Inc.
Ethicon, Inc.
Gilford Instrument Laboratories, Inc.
Gilson Medical Electronics
Grass Instrument Co.
Harvard Apparatus Co.
Hoffman-La Roche, Inc.
Lakeside Laboratories
Eli Lilly and Co.
Merck Sharp and Dohme Research Laboratories
The Norwich Pharmacal Co.
Chas. Pfizer and Co., Inc.
Precision Scientific Co.
Riker Laboratories, Inc.
A. H. Robbins Co., Inc
Sherman Laboratories
Smith Kline and French Laboratories
The Squibb Institute for Medical Research
Tektronix, Inc.
The Upjohn Co.
Warner-Lambert Research Institute
Wyeth Laboratories

DECEASED MEMBERS

The following deaths were reported since the 1962 Spring meeting.

George Bachmann (R) - November 28, 1959
Clyde Brooks (R) - January 1962
A. J. Goldforb - April 17, 1962
E. L. Porter (R) - April 14, 1962
L. W. Roth - June 22, 1962
The following, nominated by the Council, were elected to membership in the American Physiological Society at the Fall meeting, 1962.

**FULL MEMBERS**


ARMSTRONG, Bruce W.: Asst. Prof. Surg., Univ. Maryland

ARMSTRONG, George G.: Assoc. Prof. Physiol., Univ. Mississippi

ASCHEIM, Emil: PHS Postdoctoral Fellow, New York Univ.

BACANER, Marvin B.: Assoc. Prof. Physiol., Univ. Minnesota


BEDELL, George N.: Assoc. Prof. Internal Med., State Univ. of Iowa

BERMAN, Alvin L.: Asst. Prof. Neurophysiol., Univ. Wisconsin


BIANCHI, Carmine P.: Assoc., Pharmacol., Univ. Pennsylvania


CLEGG, Moses T.: Assoc. Prof. Animal Husb., Univ. California, Davis

CLOWES, George H. A., Jr.: Assoc. Prof. Surg., Western Reserve Univ.

COLE, Harold H.: Prof. Animal Husb., Univ. California, Davis


DUKES-DOBOS, Francis N.: Environ Physiologist, PHS

EPSTEIN, Alan N.: Asst. Prof. Zool., Univ. Pennsylvania


FORD, Donald H.: Assoc. Prof. Anat., State Univ. of New York


GREEN, James W.: Prof. Physiol., Rutgers Univ.

HAGIWARA, Susumu: Res. Prof. Zool., Brain Res., UCLA


HARPER, Alfred E.: Prof. Nutrition, Massachusetts Inst. Technology

State Univ.


HETENYI, Geza J.: Asst. Prof. Physiol., Univ. Toronto

HOLM, Louis W.: Prof. Physiol., Univ. of California, Davis


KANEKO, Jiro J.: Asst. Prof. Clin. Pathol., Univ. of California, Davis


KLAIN, George J.: Biochem. Dept., Arctic Aeromed. Lab., USAF


LANGSTON, Jimmy B.: NIH Postdoctoral Fellow & Instr., Univ. Mississippi


LORENZ, Frederick W.: Prof. Poultry Husb. & Poultry Physiol., Univ. California


McCANN, Frances V.: Asst. Prof. Physiol., Dartmouth Univ.

MESCHIA, Giacomo: Asst. Prof. Physiol., Yale Univ.


NADEI, Jay A.: Assoc. Staff Member, CV Res. Inst., Univ. California

NAIMARK, Arnold: Res. Fellow, CV Res. Inst. Univ. California


NYE, Robert E., Jr.: Asst. Prof. Physiol., Dartmouth Univ.

PARTRIDGE, Lloyd D.: Asst. Prof. Physiol., Yale Univ.

POCHUND, Robert S.: Space Physiologist, Aerospace Corp., Los Angeles


REYNOLDS, Robert W.: Asst. Prof. Psychol., Univ. California, Santa Barbara

ROSENBERG, Edith E.: Asst. Prof. Physiol., Univ. Montreal

ROSENZWEIG, Mark R.: Prof. Psychol., Univ. California, Berkeley


SCHEDL, Harold P.: Res. Asst. Prof. Med., State Univ. of Iowa

SEARS, Dewey F.: Asst. Prof. Physiol., Tulane Univ.
SEGUNDO, Jose P.: Res. Anatomist & Teacher, UCLA
SLATER, Grant G.: Res. Physiol. Chemist, UCLA
SMITH, Harold M.: Assoc. Prof. Physiol., Univ. Arkansas
SMITH, Karl U.: Prof. Psychol., Univ. Wisconsin
SONNENDLICK, Edmund H.: Investigator, Lab. CV Physiol., NHI
SWENSON, Edward W.: Cardiopulmonary Lab., VA Hosp., Coral Gables
TEITELBAUM, Philip: Assoc. Prof. Psychol., Univ. Pennsylvania
WARE, Frederick: Asst. Prof. Physiol., Pharmacol., Univ. Nebraska
WEBER, Annemarie: Asst. Member Inst. Muscle Disease, New York
WEBER, George: Prof. Pharmacol., Indiana Univ.
WILSON, Wilbor O.: Prof. Poultry Husb. & Poultry Physiol., Univ. California

ASSOCIATE MEMBERS

AULSEBROOK, Kenneth A.: Asst. Prof. Physiol., Univ. Arkansas
CRISTOFALO, Vincent J.: Res. Fellow, Univ. Delaware
DAHL, Dennis R.: PHS Postdoctoral Fellow, Univ. Kansas
DAHL, Nancy A.: PHS, Predoctoral Res. Fellow
GINN, H. Earl., Jr.: Cl. Invest., VA Hosp., Oklahoma City
GOETSCHE, Dennis D.: Assoc. Prof. Physiol. & Pharmacol., Oklahoma State Univ.
HUTT, Bruce K.: Res. Assoc., Cl. Physiol., Univ. Tennessee
ISAACSON, Allen: Res. Assoc. Physiol., Inst. for Muscle Disease
KOCHE, Thomas I.: Res. Physiol., NIH postdoctoral Fellow, Univ. California
MACHEWICZ, Paul P.: Assoc. Prof. Biol., Univ. Dayton
Physiology as a science is facing new challenges. At one time physiology along with botany and zoology represented the life sciences. With the rise of the chemical sciences 50 years ago, biochemistry split from physiology and became a separate unit. Within the last 10 years we have seen the impact of the physical sciences on physiology with the formation of a new interdisciplinary effort in biophysics. At the present time, theoretical engineering is making an impact on physiology with the advent of biomedical engineering. Some physiologists are beginning to question whether physiology exists as a separate discipline or whether it should be splintered into many areas of interest beginning perhaps as a split in the applied and basic aspects of the science. This would presuppose that an individual could choose his area of research and become an expert in cellular physiology, mathematical biology, a particular organ system, or some other area of the whole discipline. Such an idea would greatly influence the type of training in both undergraduate and graduate departments. To examine the present status of physiology and determine its path toward the future, the Physiology Research Training Committee of the National Institutes of Health held a major conference of program directors in June, 1962. In a two-day meeting, some 50 directors of training programs representing the larger part of all students training in physiology, discussed many matters concerned with physiology as a science and with the training of physiologists in the past and the future. Several interesting ideas came from the meeting.

The meeting as planned was relatively simple in order to allow time for discussion and comment. On the first day a discussion of training at the pre- and postdoctoral levels was conducted by individuals stressing the training of medical students, postdoctoral students, predoctorals, and the M.D. from the standpoint of their contribution to physiology. On the same afternoon a series of short papers on developments in the area of physiology was presented and this was followed by discussion of each paper. These papers included discussions of biomedical engineering, psychology, veterinary physiology, and comparative physiology. On the second day, a group discussion of topics related to recruitment, standards of training, and the advisability of courses in undergraduate physiology, was presented with introductory talks by the session leaders.

Sentiment at the meeting revealed that many prominent physiologists think that physiology is not progressing to the same degree as biochemistry or biophysics. This may be due to the fact that physiology has not had the sudden spurts of knowledge brought about by electronmicroscopy in histology, DNA in biochemistry, and engineering in biophysics.

For many years physiology was taught by essentially homeopathic methods. The student took the first two years of medical school along with the medical students, did a problem in some phase of organ physiology and received the Ph.D. That this is not the current approach is
demonstrated by the fact that many of the current M.D.'s receive exactly the same training as a part of the medical school function in the Medical Student Research Training Program and yet these individuals are not considered to be qualified physiologists.

The distinguishing feature of the graduate program was the seminar. This was the sauce spread over the entree of medical school subjects. Seminars have ranged from a purely domestic venture in which the graduate students, good and bad, presented work of their own interest and were questioned in a cursory manner. From this beginning the seminar may range up to the full scale lecture by a visiting scientist complete with visual aids and polite questions by the faculty with no student participation. These are usually unrelated in topic and often sparse in content. There is another type of seminar called a study seminar which does merit some respect. This will be discussed later. Examinations in the graduate program vary from polite oral examinations, in which the departmental staff carefully whitewash the inadequacies of the graduate students, to reasonably good written quizzes.

Research was the one thing that distinguished the Ph.D. training from M.D. training. Now the medical student's opportunities for research in the summers during elective time, and drop-out years, is growing so rapidly that we cannot point to the thesis as the great crowning glory of the Ph.D. degree. The Ph.D. degree which resembles an M.D. degree or fraction thereof is not adequate for research training in years to come.

There are solutions to some of these problems. One is to obtain graduate students who have a B.A. training superior to the premedical training. The students who have Bachelor of Science degrees rather than diffuse premedical type of degrees, and who are trained in disciplines other than biology which can contribute to physiological research such as chemistry, physics, engineering, and psychology are particularly important. Secondly, training should be required in the university disciplines. There is no training in medical schools that cannot be done by some university department. Thirdly, many physiologists agree that there should be some structured teaching. This is necessary with the growth of graduate schools. A structured teaching program in which the university disciplines are used to take the student beyond the level of that which is familiar to the medical school courses requires an able and dedicated faculty. The physics and chemistry departments do this routinely, but in the average medical school physiology department this is not done.

Still another problem arises in the training of postdoctoral students. Two methods are in general use. One which might be called a "structured" approach outlines a study program, perhaps formal course work, and a definite research project for each student. The second method, which may be called an "unstructured" program allows the student to decide for himself what is necessary to make up his deficiencies. Otherwise, students work along with a member of the staff on a project of interest to the staff member. Physiologists today may be either an M.D. or Ph.D.

It may be useful to review some of the characteristics of M.D. train-
ing in physiology. In 87 medical schools in America practically all re-
quire organic or inorganic chemistry, but none physical chemistry. Only
half require general biology. All require introductory physics. Math-
ematics is essentially not required at all. Small wonder that when the
medical schools reported weaknesses in medical preparation, the weak-
nesses were led by mathematics and communications skills.

The M.D. has been selected for admission to medical school on some-
what different grounds than has the college student who attends a graduate
department to study for a Ph.D. The M.D. considering a career in physi-
ology has assets and deficiencies. His assets include a medical education.
However, such a plethora of facts or current opinions are taught that they
may dampen or extinguish a spirit of inquiry that might have flourished
over the same years in a graduate department of physiology. The essen-
ce of physiology may not be the tools, but rather a certain point of view
of science.

One of the real recruiting grounds for physiology in the past has been
the M.D. and will continue to be so, and it is our job to cultivate this
field very thoroughly. The individuals who have gone into physiology have
all had experience in physiology which have brought them into it. A suc-
cessful research experience during medical school is one of the determin-
ing factors.

A measure of specialization is a necessary consequence of a graduate
training program. If many university disciplines contribute to physiology
a student cannot be expected to obtain 4 degrees. If graduate training is
on a sufficiently high level, it follows that if a man comes from psychology,
he cannot handle the work of a biophysicist. In point of fact, the middle
of the road physiologist can not handle the work of a biophysicist. It is
obvious that a number of pathways must be established leading to the Ph.D.
degree.

It is possible to arrange a structured program in physiology. At one
school in the second year after a medical course in physiology, two sub-
stantial courses running throughout the year are offered, one which covers
in a seminar the whole field of physiology, but covers it from the litera-
ture where every student reads and discusses the same topic. The second
kind of structured course would be one which begins with physics and ends
with instrumentation, and the application of the physical principles to
physiological systems. The third kind of structure is a study seminar
where all students read the same papers, and the papers are of such
critical nature and such difficulty that the instructor can step in where
the student leaves off and carry the topic further for a greater depth of
understanding. Many of these seminars may be given at two levels, one
for people who know something about the subject, and one for those who
do not.

Time must be found for the new knowledge and the physiology depart-
ments must assume a greater and greater role in teaching fundamental
or basic physiology. This may lead to a situation where the clinical de-
partments acquire people trained in clinical investigation who can teach
the applied or human physiology. We must counteract the tendency in
our medical schools to place more and more emphasis on general education and to accept more and more students who are not well prepared in science.

More and more physiology of man—circulation, digestion, etc. is being carried out by people who are in the clinical departments. In the Annual Review of Physiology about 30% of the chapters reviewing the fields of physiology are written by people who have titles in the clinical departments. Some institutions have capitalized on this by bringing into the physiology department staff who are in the clinical departments. However, the control of the course remains in the hands of the professional physiologist. Furthermore, the presence of the clinical staff in the basic department participating in the seminars is a scientific advance for the clinician. The medical faculty is taught through this technique, and secondhandedly it keeps the medical student abreast of the important recent developments. This has a bearing on the training program since the medical students who have an interest in becoming part time physiologists can get training, so as they continue in the clinical departments they can return to reinforce the activities of the physiology department.

Engineering can contribute greatly to physiology. Engineering approaches are essentially approaches which implement biological interpretation and investigation. Analogs of membranes and sodium pumps are essentially engineering problems. The study of the aortic pulse, of vessel or lung compliance, and control of the digestive tract, all involve engineering approaches to the biological system. In all these examples the fundamentals of physics and of matter have essentially been shaped by engineering into the applicable techniques for the biologist. There is an approach which the engineer uses with respect to the application of physical principles and mathematics, which essentially makes it easy for him to think about biological systems.

One of the methods to obtain competence in this area is for physiology departments to recruit from engineering departments people who have interests in the biological fields. The mathematics and physics that the biomedical engineer may use have been shaped by engineering to those things that apply to systems and system control. If such people with different backgrounds are placed together in a graduate student laboratory, terminology is exchanged, the biologist helps the engineer, and the engineer helps the biologist. An interesting end product is obtained.

We may turn our attention to the veterinarian in physiology. There are essentially three types of veterinarian who go into graduate training programs. There is one who is interested primarily in the basic science discipline. There is the veterinarian in a graduate training program who is interested in the field of laboratory animal medicine and who aspires to go into a situation in which he divides his time between this area and basic research. Then there is the category of individual in graduate training who aspires to go full time into laboratory animal medicine. Veterinarians whose careers are full time in laboratory animal medicine contribute more largely to a medical school than the individual who aspires to go half time into a basic science discipline and half time into
Comparative physiology is an important and often neglected area. Physiology may be classed into 3 general types: cellular physiology, that dealing with functions common to most organisms; the physiology of special groups, which includes all medical physiology; and comparative physiology. The unique feature of comparative physiology is that it uses kinds of organisms or in some cases kinds of tissue as one of the experimental variables in a situation. A comparative physiologist asks how different organisms solve their life problems and by comparing the modes of solution in different organisms is able to throw light upon mechanisms which may be very vague in some organisms.

Comparative physiology can contribute to medical physiology in its philosophical approach. The comparative approach puts man in his proper biological perspective. In the first place, most comparative physiologists come into the field with a zoological background, and one of the weaknesses that keeps recurring is in the physical sciences. One of the big problems is the supplementation of a zoological background with appropriate physical training.

To be a good comparative physiologist, a person must know something of the kinds of animals that exist, of their morphology, and particularly of their embryology. The fact is that most comparative physiologists have come through zoology and need to have a background which will help them to appreciate the kinds of animals that are available for experimental work. Insect physiology, for example, has expanded at a tremendous rate. The same will be true for fish physiology and for physiology of parasites in the near future. There is a very real need for the introduction of more comparative physiology in medical school physiology departments. One approach which is almost essential for the experimenter is to know the animals in their natural habitat. Comparative physiology, unlike other kinds of physiology must combine field and laboratory approaches.

The traditional training program has been for a student to major in physiology and take a minor in another subject. Often the person minoring in a subject is a second class citizen in it, and does not receive the kind of training that he should in order to really be able to handle the problems of both areas. There is another approach which involves developing a really joint program between two different departments. This is entirely different from a major or minor arrangement. This has operated at one university where the departments of psychology and physiology actually cooperate to produce an individual who is extremely well trained in this generally gray, overlapping area. The reasons why joint programs are set up are that recognized areas of overlap exist in two departments. The students or the individuals are working on the same problems, but they are using different techniques.

Another more fundamental and practical reason for starting a joint program is that people educated in two areas cannot take a Ph. D. in physiology and then a Ph. D. (for example) in psychology. Too many years are invested for the expected return. There are usually peripheral courses which do not contribute directly to the program. There is
the possibility for the development of new ways of thinking and handling problems and a spontaneous generation of new outlooks now presenting these people the core courses in both disciplines. In research there is obviously a need for such individuals.

One of the main problems in a joint program is having the correct intellectual environment. It is necessary to have a long history of cooperation between two departments. The physical environment is important. To weld a medical physiology department in a medical school to a basic science discipline requires a nearby university and optimal proximity.

Instead of having two departments cooperate, it is possible to have a middleman in the form of a research center. For example, one such research center is called the Communications Center where electrical engineers, psychologists, neurophysiologists, cyberneticists, information theorists, etc., come together to do research and graduate teaching. This center belongs to no department, but has perhaps as many as 6 different departments collaborating. For example, within such a center there is offered a course in information theory and feedback mechanisms of the central nervous system, which carries graduate credit in the department of electrical engineering as well as graduate credit in the department of biology. A neurophysiologist, for example, would get the rigorous training of a physiologist but do his research in the Communications Center. His opposite number would be a student getting a Ph.D. in electrical engineering with a minor in communications problems of the central nervous system.

In addition to the question of the type and quality of training there are several questions of mechanics which arise in every training program. One of these concerns the setting of standards of graduate education. It is acknowledged that the American Chemical Society has set standards for the chemistry departments and that the engineering societies have set standards in engineering, and these have raised the quality of instruction. There is agreement, however, that such standards should not be set in physiology, especially at the graduate level. It was generally agreed that a department deciding to set up a graduate or undergraduate program in physiology should have the benefit of expert advice and this should come through the American Physiological Society. Considerable pressure has been exerted by the program directors to have the APS poll the group to determine what standards are placed upon new departmental members, and therefore what training is considered by the majority to be acceptable.

Considerable question was raised about the examination of graduate students. It was generally agreed that this was a necessary part of training and such examinations should be of relatively difficult nature. Solutions to the problem of "easy" examinations were many and included having the individual rated by someone outside the school, giving a preliminary, qualifying, and final exam, using written as well as oral exams, using the Master's degree as a "cutoff" point, and excluding the major professor from the room during the examination.
It was agreed that universities set their own standards of training, and that many of these are set by the graduate school over which the department has no control. The major emphasis should be upon research training and it was agreed that course work was not sufficient to give understanding of a science. Most program directors felt that every student should have human physiology as a part of training, although a few felt that cellular physiology would be satisfactory.

**SUMMARY OF IMPORTANT REQUIREMENTS**

The requirements below were determined by program directors to be the material which a graduate student should have upon graduation. Much of the material may be obtained at the undergraduate level, and in fact, most of the participants specifically stated that every effort should be made to encourage the prospective graduate student to take any or all of the courses listed below before entering graduate school.

1. **Physics Requirements**

   The majority preferred that all students have two years of physics. One of these should be general physics and the second should be electronics engineering, electricity, or some similar course. Many expressed a desire to see students take nuclear physics, atomic physics, etc.

2. **Chemistry Requirements**

   All participants believed that the graduate student should have general, organic, and physical chemistry as a minimum. Many others desired, in addition, physical organic, advanced organic, etc.

3. **Biology Requirements**

   Most of the group felt that two years of biology was sufficient. None thought four years of biology was necessary. Some (5-6) thought no biology was necessary for a physical scientist entering physiology. The group expressed themselves vigorously as being in favor of the "new" biology rather than classical forms.

4. **Mathematics Requirements**

   All members were in favor of every student having calculus. A very high percentage agreed that students should have differential equations or other higher math courses.

5. **Foreign Language Requirements**

   Ninety percent of the group felt that one foreign language was enough and only 5 would like to see two languages as at present. Many persons expressed the desire to see the requirement for a foreign language made the entrance requirement for graduate school.
6. **Training Requirements**

Most of the group felt that the qualifying examination was a good method of testing students and should not be abandoned. About 50% of the group felt that a published paper should be accepted in lieu of a thesis, and about 1/4 felt that both should be required. About 1/3 of the group felt that a training program should be launched which would train teachers in preference to investigators for smaller schools. The opinion was evenly divided on whether a structured or unstructured program should be the method of choice.

7. **Other Requirements**

About half of the group felt that they would accept an engineer or physicist into the physiology graduate program without prior biology and would consider him an excellent candidate.

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**CHANGE IN RULES FOR PRESENTATION OF PAPERS**

As was stated in the May issue of THE PHYSIOLOGIST, the Society, at its business meeting in April 1962, voted the following:

"A person's name can appear only once."

"A member has only one of three choices - give a paper; be co-author of a paper; or sponsor a non-member."

The rules will be strictly enforced for the 1963 Spring meeting. The deadline for receipt of abstracts is January 15, 1963. Detailed instructions and abstract forms will be mailed to members the first of December.

Since the deadline for receipt of abstracts has been set as late as possible there will be no time for communication with authors who do not strictly follow the new rules. Abstracts not following the rules will not be accepted.

**PLEASE FOLLOW RULES CAREFULLY**
AAAS

Sunday, December 30, 1962, 9:00 AM. Penn Center Room, Sheraton Hotel, Philadelphia

Symposium: Space Biology and Life Support Problems of Manned Space Flight

Joint Programs of the American Physiological Society, NASA, and the American Society of Zoologists

Arranged by Freeman H. Quimby, William A. Lee, and Orr E. Reynolds, NASA, and Robert Smith, UCLA

PART I

"Space Biology"

Freeman H. Quimby, NASA, Presiding


3. An Integrated Model of Abiogenesis. Sidney Fox, Florida State University.


5. Space Radiation Biology. Cornelius A. Tobias, University of California.

PART II (2:00 PM)

"Life Support Problems of Manned Space Flight"

Stanley C. White, NASA, Presiding

6. NASA's Manned Space Flight Programs. William A. Lee, NASA.


8. Space Suits. James Correale, NASA.


10. Acceleration and Weightlessness. Edward McLaughlin, NASA.
COMPARATIVE PHYSIOLOGY OF URINARY EXCRETION

BODIL SCHMIDT-NIELSEN

In the present discussion I shall emphasize the comparative aspects of nitrogen excretion, and I shall try to elucidate the handling of urea in the kidney through a discussion of the physical chemical properties of urea and its behavior in biological systems.

In the majority of living creatures the kidney plays a minor role in nitrogen excretion. In aquatic animals, with the exception of certain secondary invaders of aquatic habitats, 80 to 90% of the total nitrogen excretion takes place extrarenally, i.e. through gills or body surface, where it is excreted in the form of ammonia. As shown by Goldstein and Forster (10), ammonia is formed in the gills of the Sculpin from glutamine and glutamic acid through the action of glutaminase and glutamic acid dehydrogenase. Thus, because of the high intracellular content of NH₄ at the site of production, ammonia can leave the body through the gills by simple diffusion despite a low blood NH₄ concentration.

In animals that have become partly independent of water, urea has become the major end product of nitrogen metabolism. This phenomenon can be seen most clearly in the life cycle of the frog. During the tadpole stage the concentrations of the urea cycle enzymes in the liver are very low. At metamorphosis, when the animal prepares to spend part of its time out of water, the concentrations of the urea cycle enzymes increase considerably (2), and urea becomes the major nitrogenous waste compound. The kidney takes over the excretion and at the same time the ability of the kidney to secrete urea actively is initiated (9).

Certain amphibians, i.e. Xenopus and the spotted newt, return to a completely aquatic environment either immediately after metamorphosis or at a later stage. After the return to water, ammonia excretion again becomes more dominant (6,23).

While the tolerance to ammonia in the blood is very limited, the tolerance to urea is remarkably high. Ammonia in concentrations higher than 0.2 mM is not well tolerated. Consequently, the shift to urea production is important for the survival of the animal that leaves its aquatic environment.

When a frog is out of water there is a decrease in the glomerular filtration rate (32) and an increase in the reabsorption of water and urea from the renal tubules and from the bladder (20). Thus, the urea concentration in the blood must rise during such periods, but this does not cause any ill effects since the tolerance to elevated plasma urea concentrations is considerable. In the lungfish, which estivates in mud cocoons in drought periods lasting as long as three to five years, the blood urea

*Taken from the introductory remarks given at the session on Renal Concentrating Mechanisms at the 1962 Federation Meetings.

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concentration may rise to about 1000 mM (34). In marine elasmobranch fish the body fluids are maintained isotonic to the sea water through an elevated plasma urea concentration of about 350 mM (35). A similar mechanism for tolerating sea water is used by the crab-eating marine frogs (11). In these also the plasma urea concentration is around 350 mM.

Neither fish nor amphibians can produce a urine more concentrated than the blood. In the frog, Rana catesbeiana, urea is excreted by active tubular secretion and plasma urea concentration is normally maintained around 0.2-5.0 mM/liter. The urine urea concentration varies between 5 and 100 mM/liter (32). Obviously, since the urine is never hypertonic to the plasma, the urine urea concentration must under all circumstances be somewhat lower than the plasma osmolality.

Neither fish nor amphibians have any need for conserving water steadily, because when they return to water the supply is unlimited and the accumulated urea can be rapidly excreted in a hypotonic urine.

For true terrestrial forms, the situation is quite different. The supply of water is rarely unlimited. Consequently, water must be conserved at all times. For these animals the evolution has taken two directions. On the one hand, we have the mammals in which urea has become the major nitrogenous waste product and in which the ability to produce a hypertonic urine has fully evolved. On the other hand, we have various invertebrates, birds, and reptiles in which the excretory product may vary with the habitat and in which nitrogen can be excreted as uric acid when water is limited. Thus, in aquatic insects ammonia is excreted. This is true also of some aquatic reptiles, for example the alligator, where ammonia is excreted predominantly (5). In turtles urea or uric acid excretion may alternate even within the same animal (15). This change in nitrogen excretion is probably brought about in response to a change in the availability of water. In birds, and adult insects, uric acid is excreted predominantly.

Among the uric acid excretors, only the birds and the insects can produce a urine that is hypertonic to the blood, and this is usually to a rather limited extent*. As shown by K. Schmidt-Nielsen and collaborators (28, 31), the ability to excrete salt extrarenally is found in birds as well as reptiles, and thus the need for producing a hypertonic urine is not really present since nitrogen is excreted in the highly insoluble form of uric acid.

In the urea excreting mammals on the other hand, the ability to concentrate the urine is fully developed and salt excretion is completely taken over by the kidney. In the mammal, urea is always the major

* In a few species of birds the ability to concentrate salt is much greater. It has recently been shown by Poulsen and Bartholomew (26) that a Savannah sparrow can produce a urine with an osmolality four times that of the blood. How nitrogen is handled in these birds is not yet known nor is the structure of their kidneys well known.
nitrogenous waste product regardless of whether the habitat supplies them with an unlimited amount of water, as is the case for the beaver, or whether it provides them with no water at all, as is the case for the desert inhabiting rodent. Instead of varying the nitrogenous end product according to the availability of water, the efficiency of the countercurrent system in the kidney varies.

It appears that a kidney operating as a countercurrent multiplier system is not very well adapted for uric acid excretion. As the tubular fluid becomes concentrated in the loops of Henle in the distal convolutions and in the collecting duct due to reabsorption of water, one would expect uric acid to precipitate out, and this would probably plug the tubules. In the uric acid excretors the major reabsorption of water takes place in the cloaca and not in the renal tubules themselves. The birds possess an incomplete countercurrent system with only part of the nephrons having a loop of Henle and the rest of the nephrons being of the reptilian type (36). It is possible that uric acid secretion does not take place in the nephrons with a loop of Henle but only in the nephrons of the reptilian type.

On the basis of this reasoning, I will venture to suggest that the countercurrent system is specifically designed for the urea excretors with a need for water conservation. Although the countercurrent system is very efficient in concentrating salt, it does not seem to have developed to fill the need for producing a urine with an electrolyte concentration higher than that of the blood, since in fish, reptiles, and birds a hypertonic electrolyte solution can easily be produced by organs other than the kidney, i.e. gills or salt gland. However, once an animal has lost the enzymes necessary for making most of the nitrogenous waste into uric acid, it can only excrete nitrogenous waste with a minimum of water if it can make a urine that is hypertonic to the blood.

Physical Chemical Properties of Urea

The urea molecule is a dipole which very easily forms hydrogen bonds with other urea molecules, with water, and with protein molecules. Urea dissolved in water forms an exceedingly ideal solution (27). This means that urea and water molecules act as if they are quite indifferent to whether water or urea molecules are next to them.

The strong tendency of urea and water molecules to form hydrogen bonds causes them also to break hydrogen bonds easily. It has recently been shown (18) that the tendency to break hydrogen bonds is no stronger for urea than for water. The denaturing effect of urea solutions is not due to a specific hydrogen bond breaking ability of urea, but to the fact that urea for unknown reasons causes globular proteins to unfold (37). The nonpolar groups of the protein molecules seem to be less ureophobic than hydrophobic. The denaturing effect of urea to proteins becomes evident at a concentration around 4 molar, which, incidentally, is the maximum urea concentration ever observed in mammalian urine.

Urea can be actively transported in some biological systems. According to our current thinking active transport requires some kind
of specific binding between the transported substance and an organic carrier molecule. However, at the moment we know of no firm binding of urea to a protein molecule. Urea can, however, be very loosely bound to protein molecules. Kay and Edsall (13) have shown that mercaptalbumin doubles its volume in urea solutions. This is due to a greater urea density around the molecule. The finding that the urea space exceeds the water space in muscle (1) and in erythrocytes (25) can probably be explained on the basis of the higher urea density around the protein molecules.

**Movement of Urea Through Biological Membranes**

Urea easily penetrates plasma membranes, readily distributing itself throughout the total body water. The low oil/water partition coefficient for urea, 0.00015 (4), indicates that urea when penetrating the plasma membrane moves through aqueous pores rather than through the lipid-protein membrane itself.

Various membranes show large differences in their permeability to urea as shown in Table 1. The uterine membrane of the dogfish has a very low permeability to urea (A. Hogben and B. Schmidt-Nielsen, unpublished). The low permeability prevents the loss of urea from the body fluids, with a concentration of approximately 350 mM, to the uterine fluid, with a urea concentration of about 2 mM. As shown by Maffly et al (20), the permeability of the toad bladder to urea is also very low. However, when antidiuretic hormone (ADH) is added to the membrane the permeability increases approximately 10 fold. The permeability increase is the same in both directions, and it is not influenced by the urea concentrations. This indicates that the urea transport through the toad bladder is entirely passive, and is not facilitated through binding to a carrier. It was further shown that the permeability to thiourea

<table>
<thead>
<tr>
<th>Tissue</th>
<th>Permeability coefficient cm sec⁻¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dogfish uterine wall¹</td>
<td>10 x 10⁻⁷</td>
</tr>
<tr>
<td>Toad bladder²</td>
<td>26 x 10⁻⁷</td>
</tr>
<tr>
<td>Toad bladder + ADH²</td>
<td>261 x 10⁻⁷</td>
</tr>
<tr>
<td>Ox Erythrocytes³</td>
<td>780 x 10⁻⁷</td>
</tr>
<tr>
<td>Water 30μ thickness⁴</td>
<td>45670 x 10⁻⁷</td>
</tr>
</tbody>
</table>

1. Unpublished data by A. Hogben and B. Schmidt-Nielsen. 2. Data from Maffly et al (20). 3. From Davson, Textbook of General Physiology, p. 230, Little, Brown & Co., 1959. 4. Calculated from the diffusion coefficient for urea in water (136 x 10⁻⁷ cm² sec⁻¹) as if the biological membrane was substituted by a layer of water 30 μ thick.
is not increased by ADH, while the permeability to acetamide is increased almost as much as to urea. Thus, the increased permeability to urea appears to be related to the structure of the molecule rather than to its size alone.

The above mentioned data show that there are large differences in permeability to urea of various membranes, and furthermore that the permeability of a membrane to urea can change by hormonal action. Both of these facts are of considerable interest to the understanding of the handling of urea by the mammalian kidney.

Active Transport of Urea

In two organisms we have conclusive evidence of active transport of urea. One is the elasmobranch fish, and the other the bullfrog.

In the kidney of the elasmobranch urea is actively reabsorbed. Urea concentration in the glomerular filtrate is the same as in the plasma, around 350 mM, but the urine urea concentration is as low as 40 mM. According to Kempton’s data (14) it appears that water reabsorption roughly follows the reabsorption of urea. There is no clear-cut evidence for a tubular maximum for reabsorption of urea (14), and the mechanism is not blocked by the administration of probenezid (8).

For the frog kidney there is clear evidence of tubular secretion of urea, as first shown by Marshall (21). The urea clearance is normally 5 to 6 times the glomerular filtration rate (32). Secretion is limited by a tubular maximum, i.e. the amount of urea secreted by the tubules increases with the load until a maximum is reached at a plasma urea concentration of approximately 3 mM. The tubular secretion of urea in the frog is completely inhibited by 2, 4 dinitrophenol and by probenezid. When secretion is inhibited the urea clearance falls to values lower than the filtration rate indicating back diffusion of urea in the renal tubules (7).

Back diffusion was also shown by Lovc and Lifson, in the double perfused frog kidney. Perfusing the renal arterial circulation with one urea isotope and the renal portal circulation with another they found a transfer of urea into the tubules of 2.9 mg/kg/hr, and an outflux of 2.1 mg/kg/hr (19).

It has been suggested, although not definitely proved, that the secretion of urea takes place primarily in the proximal tubules (39). The secretory process seems to be associated with accumulation of urea in the tubular cells. The urea concentration in the kidney of the frog is higher than in the blood, and almost as high as in the urine (22). The concentration is higher in the dorsal portion of the kidney, where the proximal tubules are located, than in the ventral portion which contains the distal tubules. In in vitro studies (24), it has been found that frog kidney slices retain a higher urea concentration than that of the medium. Furthermore, the dorsal part of the kidney retains more urea than the ventral part. This retention can be inhibited by 2, 4 dinitrophenol.

As mentioned earlier, the ability to secrete urea by the frog kidney,
develops during metamorphosis at the same time as arginase becomes available in the liver (9). It is possible that arginase may play a role in the active transport of urea.

**Urea Excretion in Mammals**

In the present discussion I shall not deal in detail with the behavior of urea in the mammalian kidney since this was discussed in the introductory talk last year by Dr. Berliner. I shall only mention that the accumulation of urea in the renal papilla of the mammalian kidney can be explained as being due to diffusion of urea out of the terminal collecting duct. The urea delivered to the region through diffusion is recirculated, and conserved by the vasa recta and the loop of Henle, both acting as countercurrent exchange systems. For the kidney to operate in this manner, we must assume that various parts of the nephron and collecting duct have different permeability coefficients to urea. As discussed above, this assumption is not unreasonable, since there is good evidence that different biological membranes can have very different permeability to urea.

Renal regulation of the urea clearance occurs with dietary change in the intake of nitrogen (29), furthermore, at low nitrogen intake the concentration of urea in the renal papilla equals that of the urine, while at high nitrogen intake the concentration of urine may be 500 to 1000 mM greater than at the tip of the papilla (33). These changes may be explained on the basis of a change in the permeability of the distal convoluted tubule and of the collecting ducts to urea (30). As mentioned above a change in permeability to urea could be brought about by hormonal action. In this case, however, antidiuretic hormone could not be responsible as suggested by Jaenike (12) since the data mentioned above were obtained during antidiuresis at both levels of nitrogen intake.

Whether or not urea is actively secreted or possibly produced (3) in the mammalian kidney is still an open question. On the basis of micropuncture data (17, 38) and microcatheterization studies (16), it seems most likely that secretion, if it takes place, is located in the early part of the distal tubule.

**REFERENCES**

Because of the enthusiastic reception given the Postgraduate Courses in Physiology designed for practicing physicians, given in connection with the American College of Physicians, the American Physiological Society's Publications Committee and the Council have decided to start publication of a small journal designed to interpret physiology for physicians. The journal will emphasize the contributions of physiology to clinical medicine and surgery. It will be designed for the physician who wants to know how, why and when to use physiological tests in diagnosis; how drugs and hormones act; and why and how symptoms and disease develop. The journal will have a format similar to that of Current Concepts of Cardiovascular Disease (which allows 4 to 6 pages of printed material), will contain only one article per issue, and will be published monthly. The journal will have a low nominal subscription rate, to partially cover costs, with the hope that medical students, interns and residents may subscribe to it as well as practicing physicians. It is believed that the APS has neglected its responsibility to several hundred thousands of practicing physicians and medical students and that we can do a very effective job through the medium of this small publication.

The Editor-in-Chief of the new publication is Julius H. Comroe, Jr. Members of the editorial board at present are F. L. Engel, M. I. Grossman, I. London, I. H. Page, R. F. Pitts, and S. Wolf. Each editor will be responsible for articles in his field of speciality. Suggestions and comments should be sent to the Editor-in-Chief.

The first issue will be distributed free to several hundred thousands of physicians and to all members of APS sometime in January 1963. There will be a tear-off reply slip for those who wish to subscribe - subscription rate is $3.00 per year. It is felt that many APS members who are not physicians may wish to subscribe and have the journal sent to their personal physician, a physician friend, a medical student or intern.
PAST-PRESIDENT'S ADDRESS

HORACE W. DAVENPORT

HUMAN VOICES

The President of this Society shares one characteristic with Charles II who never said a foolish thing and never did a wise one; his words are his own, his acts are his Council’s. Each President having, like Tallyrand, survived his year in office is charitably allowed 30 minutes to address members as he will. This is as much public reward as he can expect for whatever he has done for the Society, and his failures can be forgotten. It is not the custom for the Past-President to review his stewardship; rather he delivers himself of a tragical-comical-historical-pastoral survey of physiology. I shall not depart from this custom, but I do want to thank those 150 or so members who, voting at a business meeting, entrusted the office to me. I was raised to this bad eminence at a moment when a long-needed revolution in the structure of the Society put an especially heavy burden on its officers. Although this crushed any pleasure I might have taken in the office, I know it is a great honor to be for a year the official head of American physiology.

Alas, high office in the American Physiological Society does not certify that its holder is scientifically preeminent. If you count over the 36 men who have been your President and the hundred who have served on Council you will recognize some of them as the best physiologists of their time, but you will also recognize that many, like me, have displayed only respectable competence. This is proper, for a man is elected to do the business of the Society, not to be as Hooke was for the Royal Society a practicing scientist. The way you vote shows that you understand the qualities required of your officers, for election often lights on the man who has conspicuously served the Society rather than on the man who has done the best experiments. The pride an officer may take is that as a man he has the confidence of his fellow members. The work of the Society is for the most part done out of sight, and I wonder how well you know what the boys in the back room do. I have observed over the eleven years it has been my privilege to sit on Council that each officer brings to the Society some one distinctive quality: one is effectively devoted to education, another understands finance and makes the Society solvent, a third starts a splendid publication venture, and a fourth gives serene and balanced judgment. (Each also brings some idiosyncrasy which in six solid days of meeting may become a bit tiresome, but at the end all annoyance is washed away with ethanol.) Collectively your officers should have the practical wisdom which is the mark of a good administrator who creates the atmosphere in which research can flourish, and collectively your officers have had the right qualities.

Our admirably succinct constitution says that the "purpose of the Society is to promote the increase in physiological knowledge and its utilization." Science is essentially a private and lonely accomplishment, and the true increase in physiological knowledge is generated in the mind. On the other hand, the purposes of the Society are public ones: to do what we can to make conditions most favorable for productive thought and, once
the creative act has occurred, to make its fruits most generally available. The Society, being a voluntary and amateur organization, is not efficient, but over the years it has served physiology well. You will find an astonishing total when you add up all the things our Society does for physiology, and each one of these is the contribution of someone you did the honor to elect to your Council.

There are some things the Society can do poorly or not at all. It is a weak political pressure group. I wish those frantic members who seize the lapels of an officer and shout: "You must get a law passed against anti-vivisection!" would remember the definition of a congressman and the means of influencing him which Henry Adams gives somewhere in the Education. I had intended to quote Adams, but after reflecting that most of us depend for all our research support and a large fraction of our salaries upon the good will of Congress I decided that hinting at the imperfections of its altruism might be impolitic. We do not exert political pressure; we are its objects. Neither are we a labor union. We cannot command the pay, prestige or working hours of a bricklayer. You have frequently been told that our salaries and our status are too low. Before asking whether we are using the wrong measuring stick, I shall tell you about a colleague of mine who frequents the Pentagon. Being a mild and polite gentleman, he always stands back to allow generals and colonels and even majors to precede him into the conference room. Recently the chief of protocol took him aside and said in effect: "Look, doc, you are making us intolerably nervous. When you are here as a consultant you have the rank of a lieutenant general. You damn well go through that door in front of a major general!" So three stars glitter invisibly from the shoulders of one biologist, at least if he is a Michigan department chairman and the Past-President of his professional society. A great advantage of academic life is that we live outside the ordinary status structure, and we can, as Charlie Gray observed, wear a tweed coat to lunch at the Yale Club. It would be wrong to give up this freedom in order to compete with funeral directors for the rewards they seek.

I am about to say something nasty about money, and I know from experience that I must preface my comments with an oath of allegiance to the dollar. My problem will be familiar to all of you who sit on administrative boards in medical schools. You will recognize the moment when it becomes necessary to tell your clinical colleagues that the sole purpose, the be all and end all, of a medical school is not the care of the patient, that in a university, teaching and research have paramount claims. When I reach this point I draw a deep breath and deliver a five minute speech to the effect that although I am only a poor bastard of a Ph.D., I really do understand the importance of patient care. I agree that the quality of patient care in a university hospital must be the best, but... likewise, I really do understand the importance of money, but I must say that as professional men and women we have obligations and rewards which are totally outside the value system of money. By definition, a member of a profession has a confidential relation with a subordinate, and that is why there are only four professions: the law, medicine, the priesthood, and teaching. The Church tries to assure itself that candidates for ordination have a true vocation, and I think we should be as strict.
Supplied with training grants we are enticing into physiology every prospective graduate student who can count to twenty without removing his shoes although we assure each other that knowledge of differential equations is the absolute minimum for a modern physiologist. (Would there be a place for Harvey or Cannon or Bernard today?) Sometimes when offering a stipend or negotiating a salary I am overcome by the memory that I got my first job (not in physiology) in November of 1929. Those entering physiology now are better off by an order of magnitude than we were before the war, but I suspect that training grant stipends or the salary of an assistant professor (there are no more instructors) are paid in faerie gold. It buys the wrong things. As one who belongs to a generation which settled its career before marrying, I think the wrong thing is polyphiloprogenitivity and that the intense domesticity which is the fashion today eats up the years which were better spent on study and scientific, as distinct from biological, productivity. I move annually in our faculty that we deny admission to married students and that we dismiss any who marries. No one ever seconds my motion. Alternatively, I suggest that instead of dependency allowances, we give continence allowances. By an irresistible train of thought I am driven to remembering my introductory lecture on gastric motility. I describe the methods used to measure movement of the stomach, and I contrast the accurate records obtained using modern transducers with the old, misleading ones given by an 8 cm balloon. I conclude by telling my students: "The condon has a place in physiology, but that place is not the stomach."

Science and art are the two creative activities distinguishing man from other animals; all the rest of his business merely keeps the machine of life running. Although the greatest art equals the greatest science on any scale of value, it is more satisfactory for those of us who do not own the highest genius, to be scientists rather than artists. As an occupation, science has one important advantage over art; science is subjected to a generally accepted set of external controls. Neglecting the extremely rare, and usually fictitious, unappreciated innovator, we can say that the general body of contemporary scientific opinion is, if not correct, at least facing in the right direction. Science is eager to correct itself on good evidence. We usually approach truth by successive approximations, and even in those instances in which the jump is a radical one, the scientific community reacts with glee rather than with dismay. A physiologist knows how his work fits into the body of his science, and he can make a reasonably accurate estimate of its value. In the terrible night of self-doubt which comes in middle age the physiologist can at least reassure himself that he has added something to the shape of truth. This means, I think, that science has a place for the second rate. Art does not, and all art except that minute fraction which is the very best, is quickly and properly swept into the ash can. It is the sense of having made some lasting contribution which is the real reward of science. One's contribution may be very small indeed. A life of work may end as half a sentence in a textbook, and there is no name mentioned. A better man may leave a small paragraph, and the work of only the best may inform a whole chapter. The value of this comes into better perspective when we remember how many millions have lived, are living and will live, leaving behind no trace whatever. I would guess that of the nearly 200 million Americans
now alive only a few thousand will leave anything of lasting meaning behind them. Of these thousands most are probably members of the elite professional societies, and I conclude that a substantial fraction belongs to the American Physiological Society and is here tonight.

In promoting the increase and exchange of physiological knowledge our Society has encountered formidable problems in its meetings and publications. You know better than I what these problems are, and you also know that none of the proposed solutions has much chance of success. At the risk of startling you with its brilliance I want to outline a new solution. This is to combine three well-known techniques: the method of inventory control used by mail-order houses, the data analysis methods used by seismologists to distinguish earthquakes from explosions, and the stock market ticker. We will abolish the American Physiological Society and the Federation. In their place we will erect an enormous computer with a capacious memory, and we will connect it with each physiological laboratory. All present knowledge will be stored on the memory drums, and by working the appropriate controls a physiologist may ask the machine to print out on his own receiver, information on any subject. At the end of each working day the physiologist will feed into the machine his current results, or he may arrange to have his analytical instruments connected directly to the outgoing lines. The machine will integrate the results into the corpus of physiological knowledge and make the revised information available to any inquirer. Publication will no longer be necessary. When a physiologist has made an important contribution, importance being judged by the number of bits revised and added to the memory drums, a bell will ring in his laboratory, and when five of these events have occurred a light will flash in his dean’s office, signifying that he is now eligible for promotion. If, however, the results are neither correct nor novel a red light will turn on and a horn will emit a Bronx cheer, and when this has occurred some predetermined number of times, say three, a trap door will open precipitating the investigator into a vat of boiling oil. This is the equivalent of encountering Ajax Carlson or Carl Wiggers while giving a poor paper.

The principles are clear. Working them out is a mere engineering detail, yet I doubt my solution will be accepted. In the loathsome jargon of the day we say that we attend these meetings to promote communication in physiological science; at least that is what we write on our travel vouchers. The actual fact is that we are here because we are gregarious human beings. Certainly, we are attending this ceremonial dinner, not for any scientific purpose, but to renew our fellowship as members of the Society. The official portrait may display a group of dispassionate automatons, but the truth is that we do use our human qualities in being physiologists. Some of the qualities are unlovely ones: envy and calumny and hate and spite. A good bit of our work is driven by the will to prove some other member wrong and to demonstrate the fact in open meeting. Many a shaft is more barbed and hurled with greater force than if its aim were only scientific truth. Driven by hubris I myself have several times inflicted wounds which I have bitterly regretted. We deplore these failings, and we excuse them because we are only human. But we also display more amiable qualities. In growing up as scientists each of us finds a new father, and there are strong bonds of filial love reaching
back to the one who has formed us and reaching forward to those we ourselves are molding. Let us not be too strangled by Anglo-Saxon reticence to express this love when it can still be received. The obituary notice is too late. In science one can win a friend at a distance. We know a man's work and his scientific personality long before we see his face, and once meeting him there are no preliminaries to intimacy. We all have "meeting friendships;" there are many whom we count as true and close friends about whose personal life we know almost nothing. We may have nadders and pads among our members, but we have sweet, gentle, generous, and noble members too. Edward Adolph said that belonging to the Council of this Society gives one another family. This is also true of the Society at large, and it is better than a natural family in that we have chosen our own brothers. Let us admit, if only to our secret selves, that we are tied by more than scientific bonds, and as an example to you and at the risk of having human voices wake us and we drown, I want my last official words to this Society to be "I love you all."

HISTORY OF THE SOCIETY

A history of the Society with special emphasis on the last 25 years is being prepared by Professor Wallace O. Fenn. To assist him in this task he has requested all members of the Society to send him any anecdotes from Society events which seem worthy of a permanent recording. Any item of significance relative to the Society or its members will be welcome. If you have observed any changes or trends in the affairs of the Society please describe them. Amusing anecdotes from Society meetings deserve to be recorded. Events which occur in the corridor or "behind the scenes" are often particularly revealing. Informal photographs taken at Society meetings are also solicited.

There is of course no guarantee that any such material can be used for this must depend upon the judgment and discretion of the author. There is however much important information not included in the formal minutes of the meetings and it seems highly desirable that as much of this as possible be retrieved and put on record. Your assistance in this task is earnestly solicited.
BEHAVIORAL ASPECTS OF NEUROPHYSIOLOGY

ROBERT W. DOTY

Science now almost daily refines our picture of the universe, dissolving atoms into multiple submysteries, directly assaying the constructs of Copernicus and Einstein, and rearranging the chemistry of life. Yet our knowledge of reality can never exceed knowledge of the workings of the organ by which we know it. In this respect the task of neurophysiology in probing the nature of experience is uniquely important, but also uniquely difficult. Its ultimate object of investigation, the human brain, is the most complex in the known universe. With facts meager to the ambition of understanding this brain it is exceedingly helpful to realize that phylogenetic bonds are indissoluble, that mouse and man have the same types of neurons, and that in general the major principles of neural function vary but slightly in the mammalian series. Thus in the following selective summary what is implied for cat most likely holds as well for man; and that the vast detail of neural action manifest in the stalking of prey is only slightly less wondrous and complex than that subserving the writing of this sentence.

The functions of the nervous system are divisible into six categories: sensorial, effective, attentive, motivational, mnemonic, and, at least for higher primates, cognitive. The first four of these functions are related to portions of the nervous system which are to a considerable degree separable, while the latter two appear to be general, nonlocalizable properties of the brain.

Sensorial function involves analysis of the spatially and temporally encoded signals coming in all-or-none impulses from the external and internal worlds. It encompasses the classical sensory pathways and their respective thalamic and cortical stations. The effector system includes performe the motoneurons and neurons passing to glands (e.g. supraoptichypophyseal tract) and peripheral ganglia. In addition, the cerebellar-rubral- reticular system, pyramidal system, basal ganglia and interneuronal systems of the ventral horn must be included as participating in effector organization. Simplicity of schematization even at this level vanishes in the face of many complexities, among them the following: 1) Primary sensory fibers send branches directly to motoneurons, and hence could be classified as possessing an effector function. Similar difficulty in specifying where "sensoric" function ends and motor function begins will characterize most reflexes. 2) Electrical stimulation or ablation of cortical "sensoric" areas elicits or affects movement; and photic, auditory or somatosensory inputs can evoke activity in the classical "motor" cortex. 3) Systems described below as 'attentive' and 'motivational' are intimately involved with sensation and movement. 4) A learning factor is present in visual processes, and probably in other sensory and motor mechanisms.

* Taken from the introductory remarks given at the Session on Motivation, Learning and Behavior at the 1962 Federation Meetings.
Despite its being thus a gross oversimplification our classification can still serve to emphasize the principal functions identified for the centrencephalic and limbic systems.

The Attentive System

A single impulse in a sensory fiber can probably be detected as a sensation in the tactile system unoccupied by resting discharge. The central nervous system must receive thousands of such impulses each second, most of which remain without effect yet are potentially capable of eliciting sensation and reaction. We are unaware, for instance, of the pressure of our shoes, clothing, spectacles, the passage of air through the nose, saliva in the mouth, or of major portions of our visual or auditory environment unless "attention" is specifically directed towards some aspect of these continuing sensory inputs. The organism cannot effectively respond to the vast array of simultaneous signals impinging upon it; hence a major function of the nervous system must be the selection of the momentarily significant modality and pattern.

Exactly how this selection is accomplished is uncertain, but a number of suggestive and important facts are at hand. First, it is apparent that attention usually covaries with consciousness (although important exceptions exist) and must be closely related to whatever neural processes underly this indefinable condition. From this point of view it is thus not surprising that the systems of the brain controlling sleep and wakefulness should serve attention as well as awareness. Second, the central nervous system is able to modify or even initiate sensory input at or very close to the receptor level (e.g., at the first central synapse). This centrifugal control system appears to be directly related, in many instances, to the centrencephalic system (see below). Suppression of input is the major effect so far observed, but both suppression or enhancement are of obvious relevance to attentive processes. Third, stimulation of the centrencephalic system has been shown to influence the excitability of neurons in the "sensory" cortex. The centrencephalic system can thus augment or suppress sensory functions at the cortical level (as in turn the cortical systems play upon the centrencephalic system) and, of course, such control would also be expected in the "focusing" of attention.

The term "centrencephalic" was invented, almost from physiological and philosophical necessity, to describe a subcortical system integrating and capable of controlling the activity of the two cerebral hemispheres*. Evidence for the existence of such a system comes from the general bilateral synchrony of electrical activity in homotopic cortical areas, and from EEG arousal reactions, "recruiting" waves and "secondary" potentials, all of which have an exceedingly wide bilateral effect at the cerebral

* The original definition also included the explicit assumption that the "centrencephalic" system was the highest level of cerebral function. The extended definition which follows in this summary is thus a still more serious expropriation than it might seem at first since it omits from the functions ascribed to the centrencephalic system this role in the integration of conscious experience.
cortex and which involve principally midline neural systems for their transmission or elicitation. "Nonspecific system," "ascending reticular system" or "reticular activating system" are frequently used terms which I think could profitably be subsumed under "centrencephalic system." "Nonspecific" is a good term to describe the fact that this system is influenced by all sensory modalities, that many neurons therein can be discharged by several different sensory inputs, and that under some circumstances the outcome of activity in the system is a global, "nonspecific" one. Recent evidence, however, suggests a high degree of precision and discreteness in the physiological capacities of the medial brain stem system(s), so that while "nonspecific" may describe certain characteristics of this area of the brain, it is likely to be a serious misnomer for its function. Description of the system as "reticular" stretches the anatomical concept even for the lower brain stem, and its diencephalic ramifications possess definite nuclear groupings. The term "centrencephalic" thus seems the best at hand and indeed is most convenient in bearing both a functional definition and an anatomical connotation. I would like to enlarge the term to signify the subcortical systems, extending from obex to septum and constituting for the most part the central core of the brain stem, which are concerned with the functions of attention and awareness. Portions of the medulla and pons must be included in the system since it has been shown that the medulla influences the time course of EEG arousal reactions elicited by mesencephalic stimulation, that electrical activity in the pons signals the appearance of generalized low voltage, fast EEG patterns during sleep, and that exclusion of the lower systems by mid-pontine section produces a state of EEG "arousal" which lasts for days.

The Motivational System

Certain types of sensory input are capable of commanding the entire behavior of the organism to seek or avoid such stimulation. The systems of the brain which assign the input its approach or avoidance pattern can be called "motivational".

As usual, objections can be raised to any suggested classification. A limb withdraws from noxious stimuli even when controlled only by the isolated spinal cord, yet one would not wish to call this "motivated" behavior. The term is better restricted to the much more complex stimulus "evaluations" and responses involved in feeding, drinking, sexual and maternal activities, flight, aggression, gregariousness, grooming, etc. Responses to pain, warmth or softness (the infant monkey upon its cloth mother, the cat upon the sofa), general "discomfort" and restraint are hard to classify, but the stimuli eliciting them certainly have a motivational factor. There are phenomena in primates, such as curiosity and drug addiction, which are highly motivating in the sense that the individual will seek various stimuli most avidly, yet which cannot be easily accommodated in most schemes of motivation. Motivation often appears to be a central state eliciting and guiding instinctive behavior. The description of motivation in neural terms will thus be complicated by the fact that many motivating stimuli originate in the nervous system itself (either "spontaneously" or under chemical influence) and the motor activity of the organism is directed towards stimuli that will
alter the conditions of the relevant central neurons. There are no clues as to how motivating patterns of neural activity are to be distinguished from nonmotivating ones, nor how the motivational system commands the motor apparatus to achieve inputs appropriate to the motivational state.

In the face of such a diversity of effects and the lack of understanding of their nature it is encouraging to learn that neuroanatomy provides some unifying element in the picture. The major motivational effects, with the exception of pain, are controlled from the limbic system (and even pain is significantly under limbic influence). The limbic system is an outgrowth of the olfactory system, the rhinencephalon and its extensions. It is not difficult to understand how motivational effects came to be associated phylogenetically with the olfactory system. The end result of most motivation is preservation either of the individual or of the species. Throughout the earliest vertebrate series it was olfaction that was the principal link to this survival, in feeding, in escaping, and in mating. Among mammals it is still the olfactory cue which for prey and predator alike most often signals the requirement for "fight or flight" and evokes the concomitant changes in the autonomic and motor systems. Similarly the olfactory sense guides the mating behavior of most mammals, and a well-supported perfume industry bears familiar testimony to its lingering relevance in the sexual activities even of microsmatic man. The phylogenetic heritage of limbic system function survives seemingly unchanged in the face of diminished importance of the olfactory system per se.

In defining the term "limbic system" the emphasis must certainly be placed upon "system", for it is the massive richness of the interconnecting pathways that is one of its most distinctive anatomical features. The term "limbic" is taken from limbus (border) and signifies the structures bordering the medial aspect of the hemisphere which form the functional and anatomical hub of the system. This includes the piriform area, hippocampal gyrus (entorhinal area), fronto-temporal-insular, post orbital, cingulate and retrosplenial cortex. These structures have extensive interconnections, and they surround and send fibers into the hippocampal formation and the amygdala. The fornix carries fibers to and from the hippocampus, most of which arise or end in nuclei of the septal region, while the remainder distribute to the hypothalamus and mammillary nuclei. The fiber counts in man for one side of the brain are: 2,700,000 fibers in the descending fornix and 912,000 fibers in the hypothalamic portion. The corresponding figures for the macaque are roughly 500,000 and 110,000. These data suggest that the fornix system plays a proportionately larger role in the human brain than in that of the monkey. Compared to the five fold increase in fornix fibers in man versus monkey, the optic nerve input is the same in each, about $10^6$ fibers, while the pyramidal tract of man has but two times as many fibers as the macaque.

From the mammillary nuclei (principally the medial nucleus) fibers pass in the mamillothalamic tract (Vicq d' Azyr's bundle, about 100,000 fibers in cat) to the anterior nucleus of thalamus. The anterior thalamic nuclei in turn project to limbic cortex, thus forming a potential loop of
action: limbic cortex -- hippocampus -- mammillary body -- anterior thalamic nuclei -- limbic cortex. A peculiar relation exists among the last three of these structures since if the cingulate gyrus is removed in young rabbits not only do the anterior thalamic nuclei undergo retrograde degeneration, as expected, but so too does the medial mammillary nucleus; a retrograde "transynaptic" degeneration!

The major outflow from the amygdala is a diffuse one passing into the preoptic area, hypothalamus, nucleus of the diagonal band of Broca, olfactory tubercle and dorsal medial nucleus of the thalamus. (The latter structure onto the frontal cortex, was the main nucleus degenerated in cases of therapeutic frontal lobotomy, and receives important inputs from the medial septal nucleus, nucleus of the diagonal band, and the ventromedial tegmentum.) A prominent fiber bundle, the stria terminalis, leaves the amygdala and, similarly to the fornix, arches dorsally and anteriorly before descending into the septal area.

From the septal and preoptic areas two fiber systems take origin, one, the medial forebrain bundle, distributes throughout the hypothalamus and, along with some fibers from the fornix, the ansa lenticularis (from globus pallidus) and the dorsal longitudinal fasciculus of Schütz, carries the influence of the more anterior limbic system onto its mesencephalic portions in the central gray, ventral tegmental area of Tsai, the tegmental nuclei of Gudden and Bechterew, and mesencephalic reticular formation. The other system comprises the stria medullaris and its associated habenular nuclei giving rise to the habenulodendular tract (fasciculus retroflexus of Meynert) which passes to the interpeduncular nucleus. The fibers there execute a peculiar figure 8 of crossing the midline and returning prior to terminating. The interpeduncular nucleus projects generally into the dorsal tegmental area. A group of fibers from the entorhinal area also pass via stria medullaris into the region adjacent to the central gray. From these tegmental areas fibers project via the medial forebrain bundle and subthalamus rostrally into the septal area to influence the hippocampus and other anterior limbic structures.

This very cursory outline of the anatomy of the limbic system illustrates not only its challenging complexity but also its interdigitation and overlap with the centrencephalic system at certain points. Auditory, photic, somatosensory and olfactory impulses also reach the hippocampus and amygdala; and vagal influences pass to hypothalamic, preoptic and septal areas, and to orbital and cingulate cortex. The limbic system controls the endocrine and autonomic nervous systems and in addition commands a great variety of movement.

The latter point is particularly cogent if the basal ganglia (globus pallidus, putamen, caudate nucleus, claustrum, subthalamic nucleus (corpus Luysii) and substantia nigra) are to be considered part of the limbic system. There are several reasons for thinking this could be the case, but none of them are fully compelling. The globus pallidus is an extension of the nucleus of the diagonal band of Broca and the cells of these two structures are similar in appearance. The bed nucleus of the stria terminalis continues into nucleus accumbens which is a part of the caudate nucleus. Yet direct afferent connections from limbic
system to basal ganglia are not prominent. Motivation seems to be involved in some aspect of their function since self-stimulation can be obtained with electrodes in putamen, caudate nucleus or globus pallidus for monkeys or cats; and rats are aphagic after bilateral lesions in pallidofugal paths. It has also been pointed out that birds, whose complex behavior is guided almost exclusively by inherent motivational factors, have a highly developed striatum.

In any event, sensorial, effective and attentive functions are represented in the limbic system. How then describe it as the motivational system? The answer is apparent in the behavioral effects obtained by interference in the limbic system through ablation, disease, or artificial stimulation. These effects are strikingly different from those similarly produced from the neocortical systems.

Bilateral ablation of the amygdala makes the most savage animal docile, whereas destruction of the ventromedial nucleus of the hypothalamus converts a previously tame animal into a dangerously vicious one. In the male cat loss of the piriform cortex produces a "sexual athlete" that attempts to copulate with anything that moves or stands still. Destruction of the lateral hypothalamus destroys feeding behavior. Such an animal will die of starvation without touching preferred food, (though if it is force-fed through the first few postoperative weeks, it may recover feeding behavior to some degree).

Electrical stimulation of the limbic system of an unanesthetized animal, even in a highly restricted environment, can produce behavior overtly mimicking that produced by natural motivating stimuli. Stimulation of the amygdala, anterior hypothalamus in the vicinity of the fornix, or in the central gray can yield the complete defense-attack posture in cats i.e. piloerection, arching of the back, flattening the ears, pupillary dilation, exposure of claws, snarling and hissing. Stimulation of the deep temporal pole in a hound-type dog seems to produce an "hallucination" of the prey; the dog stands attentively motionless with head "pointing" while the nostrils quiver, searching the wind. Penile erection, ovulation, uterine contractions, grooming, changes in blood sugar, ADH and ACTH secretion, contraction of the stomach, gastric lesions, micturition and defecation in adequate posture, vomiting, food ejection responses, licking, chewing, and salivation, are among the effects observed upon excitation of various limbic structures.

If the environment is diversified or if the animal is allowed to choose whether stimulation should be applied or not, many of the foregoing effects gain new significance (and complexity!). If food is available to the animal, or water, it will eat ravenously when the appropriate zone is stimulated in its lateral hypothalamus, or drink to the point of bursting upon stimulation in the preoptic area. Violent attack may ensue upon objects present during stimulation which provokes a defense reaction, or the animal may flee if the opportunity is available.

By training an animal to press a lever to obtain food and then administering electrical stimulation of a relatively restricted portion of the nervous system with each lever-press, it is possible to determine whether
the animal seeks, avoids, or is indifferent to the stimulation. Several results obtained with procedures of this nature are unequivocal. First, the overwhelming majority of points in the nervous system from which stimulation is either sought or avoided lie within the limbic system. Second, except for some slight "curiosity" effect, animals are surprisingly indifferent to neocortical and cerebellar stimulation even when it produces violent movements. Third, the self-stimulation produced need not arise from a confusional effect, but rather can imitate closely, save for its insatiableness, the various properties of a naturally rewarding stimulus. Fourth, this abnormal engagement of the motivational system can be exceedingly powerful in capturing the animal's behavior.

Despite these important gains much remains to be learned about these phenomena. There are no details as to where the excitation must be conducted to produce the self-stimulation or avoidance, i.e., the neural steps and states between the stimulation and the next lever-press are unknown. (They are equally unknown for elicitation of feeding or drinking by central stimulation; the centrally elicited rage reaction is channeled principally, but not exclusively, through the central gray.) In the cat and monkey there are many "indifferent" points as far as limbic system stimulation is concerned and rather high stimulating currents are usually required to produce self-stimulation. The rat, on the other hand, responds well at very low intensities in almost any limbic area. This could mean several things. Perhaps the appropriate systems are discretely localized so it is unlikely for them to fall exactly under the stimulating electrode placed in larger brains, but can be reached by the field of high intensity currents. On the other hand the appropriate systems might be rather diffuse and require activation of a large proportion of the system to produce the self-stimulation effect. Self-stimulation not infrequently produces abnormal electrical discharges in the limbic system, (which is much more seizure-prone than the rest of the nervous system), yet this is not a necessary concomitant nor is it unknown for physiological stimulation. Thus, for instance, there is a protracted burst of bizarre electrical activity in the hypothalamic system of the female cat following coitus. Strangely, self-stimulation can be obtained with brief trains of pulses to areas that are strongly aversive to slightly longer pulse trains (e.g. 0.5 sec. versus 1.0 sec.). This indicates that activity in the same system can be attractive or aversive depending upon its temporal pattern. Finally, there is the problem that self-stimulation can occasionally be obtained from regions having no obvious connection with the limbic system, as for example, from the brachium of the superior colliculus.

Most of the data gathered for animals seem to be directly transferable to man, and are supplemented by many clinical observations supporting the idea that the physiology of emotion occurs in the limbic system. Pathological action of this system seems to be unquestionably present in the psychotic state. A man might suffer abnormalities of the visual system and see nonexistent objects, or, affected in the motor system, suffer violent bouts of movements; but if these processes should storm through his amygdala unchecked, or feed an incessant action through a circuit of the limbic brain, he would be most likely to suffer from rage,
unbridled fear or a similarly powerful, ineffable and mysterious dis-
arrengement in his appraisal of the world. In the latter circumstance
he is insane. The pathological processes cannot yet be identified, but
they are to be sought primarily in the limbic system.

Learning

Learning cannot occur without a mnemonic trace. There must be
several types of mnemonic trace; for instance: one which holds the
sensory input momentarily and keeps it accessible, almost as an after-
image, and is rapidly dissipated; another, which is experimentally but
not introspectively demonstrable, seems to hold past information "acces-
sible" for several hours in a rather fragile manner since the trace is
erased by anesthesia or electroconvulsive shock; and finally there must
be a permanent trace which endures despite continuing metabolic turn-
over and fluctuation of electrical activity. There are undoubtedly others,
but these few provide a sufficient number of problems. In the first place
we can say a mnemonic trace is "accessible", but accessible to what we
know not. The "read out" mechanism is as mysterious as the storage
process. Whatever the alteration is that maintains a representation of
past input, it must occur in the nervous system. It seems inescapable
that the change, in the last analysis, must be a chemical one, in neurons
or in their parts or glial relationships, which will alter the excitability
or responsiveness of the system. If so, what is happening in the chem-
ical relations of all the neurons which will store a lifetime of future
traces, and how many traces can be stored? Despite the folklore of
the hypnotized bricklayer remembering each brick of his long lifetime,
it seems extremely unlikely that all momentary traces are converted
into permanent ones or even that all "permanent" traces survive.

There are at least four neurophysiological phenomena which appear
to have some analogy to memory traces. First are well-known phenom-
ena of post-tetanic potentiation or depression in which the effects of
stimulation endure for several minutes, or for hours in special circum-
stances. Another type of effect is seen in the spinal cord. If a postural
asymmetry exists for 45 minutes or more following an ablation such as
hemicerebellectomy, the asymmetry persists for hours after severance
and isolation of the cord. Application of anodal polarization of about
5 to 20 uA to the cerebral cortex also produces a selective change in
its excitability, as is discussed below. Finally there is the permanent
increase in excitability of cortical neurons created in a "mirror focus".
If an epileptic zone is created on one hemisphere, after several weeks
abnormal excitability sometimes develops in the homotopic region of
the other hemisphere. This induced abnormal excitability seems to sur-
vive for at least several months even in a neuronally isolated slab of
this cortex. Whether any of the foregoing effects have significant re-
lation to normal processes is not yet known.

Even if the problems of the mnemonic trace were solved, learning
would not be fully explained. There are many forms of learning, but
all imply the association of one mnemonic trace with another. In possi-
ibly increasing order of complexity some of the types of learning are:
1) Habituation (negative learning, suppression of the inconsequential),
of which extinction of conditioned reflexes is probably one form; 2) Imprinting, and perhaps other subtle aspects of accumulating experience such as "learning to see"; 3) Classical or type I conditioning in which one stimulus follows another independently of the response to the first stimulus; 4) Instrumental, operant or type II conditioning in which the response to an initial stimulus controls the presence or absence of a subsequent stimulus. Other more complex types of learning can profitably be omitted at this stage.

Habituation is the decrease in effectiveness of a repeatedly presented stimulus. It is to be distinguished from fatigue upon proof that the stimulated system is still, in the habituated state, capable of full response and that the effect of the stimulus upon the receptors is unchanged. The latter stipulation excludes changes in pupillary aperture, stapedial tension, etc., from being relevant to the phenomenon of habituation and such factors must be carefully controlled in any reliable investigation.

The simplest form of habituation seems to occur in the isolated spinal cord. The later potentials evoked in the lateral column of the thoracic cord by mild electric shocks to the skin gradually disappear in up to several hundred presentations given at rates of 1 to 0.1/sec. A transient increase in intensity of the stimulus restores the potential to its original value (a result not expected were the diminution attributable to fatigue). In the intact unanesthetized animal a restoration of this evoked cord potential can be obtained by an added acoustic stimulus ("disinhibition"). Habituation of postrotatory optic nystagmus is present after mesencephalic destruction, but not after loss of the pontine tegmentum. Following lesions of the pons which may produce either continuous low voltage fast (LVF) or high voltage show (HVS) patterns of cortical activity, habituation is very difficult to obtain for light flashes presented at the rate of 1/sec. This is particularly striking in that potentials outside area striata, which are lost with only a few repetitions of the flash presented to an intact cat, are maintained for thousands of presentations after the pontine lesion.

These experiments, and others, suggest that the centrencephalic attentive system plays a prominent role in the phenomenon of habituation and indeed such action would serve admirably in processes of attention. To avoid becoming too enamoured of the electrical record, however, it is well to remember that despite the diminution or loss of the potential at early synaptic stations, there is still effective input to the nervous system. This is easily shown by establishing habituation to a given auditory stimulus S1 and then presenting S1 in combination with another effective stimulus S2. S1 becomes, through the process of habituation, an inhibitory stimulus, and when it precedes S2 the effect of the latter is greatly diminished. Thus S1, though "habituated", and perhaps eliciting no macroscopically apparent potentials in the cochlear nucleus, manages to attain some higher levels of the nervous system.

This is shown still further in studies on habituation of the EEG arousal reaction to tonal stimuli. A novel stimulus can evoke one of two complex responses, the "orienting reaction" or the "startle response". There is some argument as to whether the searching move-
ments of the orienting reaction may be a conditioned reflex (although it seems unlikely) but the EEG arousal reaction, the evocation of potentials in widespread areas of the nervous system, changes in respiration, cardiac rate and skin resistance, seem to be inherent reactions. Both responses are readily lost ("extinguished") following a few repetitions of the initially novel stimulus. There is evidence that the startle response cannot be habituated in the absence of the cerebral cortex. In the intact cat the EEG reaction to a novel stimulus is at first lost upon repetition even though each presentation is accompanied by a painful shock. In the sleeping cat it can be seen that the arousal reaction has two components, one of 10 seconds duration or less, and the other much more protracted. It is the protracted arousal which is lost during habituation, while the brief arousal persists to some degree even in the habituated state, i.e., there is some effect from the stimulus despite habituation. During the brief arousal some analysis of the input is probably performed. Thus, if the animal has been habituated to a 500 cycle tone and this tone is presented, there is only a very brief EEG arousal reaction, but a 1,000 cycle tone will produce a protracted response. Auditory cortical areas are not required for this distinction.

Passing now to the study of conditioned reflexes some general comments should be made. First it must be realized that in the usual training situation the conditional stimulus is not only the buzzer, flash or other phasic environmental change designated "CS", but rather includes the entire experimental setting. This can be dramatically illustrated by having an animal give different conditioned responses (CRs) to the same CS given in different rooms, or in the same room at different times of the day.

Motivation is an important factor in the formation of conditioned reflexes, and it has been convincingly argued that it is an essential one. However, directly applied cortical stimuli, which an animal neither seeks nor avoids, can be used in the temporal sense as conditional and unconditional stimuli (CS and US). In such circumstances the "cortical" CS can often elicit a CR similar to the movement produced by the "cortical" US and it can be concluded that such CRs, which have essentially all the properties of the more commonly established CRs, are established without motivation.

The required temporal relations of CS and US are particularly perplexing when considered in neural terms. This can be illustrated by considering the phenomenon of post-tetanic potentiation. If synaptic system "A" is tetanized for a few seconds it may show increased responsiveness for several minutes. The potentiation is limited to the activated system "A", but, if systems "A" and "B" share interneurons, then antecedent action in "A" may have a protracted effect upon the response of system "B". It is tempting to hypothesize a role for these relatively enduring effects in explaining phenomena of conditioning. In conditioning, however, it is the response to the antecedent stimulus, the CS, which is altered, and the US, which bears the temporal relation of "B" in the foregoing paradigm, remains unchanged. This is the temporal paradox of conditioning. Until it is understood why the response to "A" (CS) should change as a consequence of subsequent action in "B"
Finally, under general comments, the problem of localization of the neural alteration underlying conditioning or learning should be discussed. Much effort has gone into these localization attempts for it is obvious that the neural processes of learning cannot be adequately studied if the responsible neurons cannot be identified. A cat is able to learn somesthetetic discriminations with the left paw following section of the corpus callosum and removal of all cerebral cortex on the right save pericruciate and fronto-lateral areas; and it is unable to learn if only these latter regions are removed. It would thus appear that these frontal areas participate in this learning in some critical way. Yet because attentive and motivational factors are also present, it is not likely that the necessary neural alterations occur exclusively in this frontal cortex.

In the spontaneous passage of learned visual discriminations from one hemisphere to another through the corpus callosum in animals with visual input limited to one hemisphere (by section of the optic chiasm) it is at least possible that motivational and attentive factors might be absent. Were this so, one could look only to the pertinent visual area for the alteration. This is unlikely, however, since motor and attentive patterns plus motivational significance must also be present for performance. In one situation these complex factors are "transferred" or "rendered accessible" to one hemisphere from another by a single experience. A rat, trained to press a lever to obtain food while the activity of the right hemisphere is disrupted by spreading depression, gives no evidence of the learned habit when subsequently tested with the right hemisphere normal and the left subjected to spreading depression. The right hemisphere alone is able to sustain the habit if but one trial is given with both hemispheres in the normal condition. While it is conceivable that the entire engram "lever-pressing for food", which took many trials to learn, could be abruptly bestowed upon the "untrained" hemisphere by such concurrent action with the "trained" one, a more conservative interpretation might hold that patterns of excitation in the right hemisphere were merely augmented to reach a subcortical engram complex.

Assigning a critical role to a particular structure on the basis of ablation experiments is difficult since the lost function may be one of sensory analysis or performance rather than "memory". This point is strikingly illustrated with "reversible ablation" of the hippocampus by electrical seizure discharges. During such hippocampal seizures a cat is unable to make a leg flexion CR. Yet it can be trained to make such CRs even though all training trials are administered throughout a period of days only while hippocampal seizure activity is present bilaterally. Upon testing in the normal condition CRs appear immediately and for the first time. The "ablation" had deleted performance, but left learning undisturbed.

With this lesson in mind for the possibilities of misinterpreting experiments in which CRs fail to appear subsequent to ablation, and with consideration of the voluminous literature showing survival of CRs of varying complexity and perfection despite extensive destruction in any
prosencephalic structure, it seems safe to conclude that learning is a diffuse property of the nervous system. This view is reinforced by the fact that conditioned reflexes can apparently be elaborated in almost any species possessing a central nervous system, and can be obtained in the isolated spinal cord. "Spinal conditioning" in mammals is elusive and rather ephemeral, yet none the less real. In frogs the phenomenon is more stable. With "training" beginning six months after section (histologically confirmed) of the upper cord conditioned reflexes were established in 2000 pairings given at 1 minute intervals, 25-50 times per day. Application of a 0.07 mm diameter wire to one area of the skin served as CS. For the US a 0.11 mm diameter wire was applied to the skin at some distance from the CS. The CR was a scratching movement directed to the area of the US when the CS was applied. In two frogs the CR endured for periods of 73 and 103 days after cessation of "training."

Study of the electrical activity of the brain is beginning to give a much more detailed and significant picture of the neural processes subserving learning than anything heretofore possible with purely behavioral observations. The studies can be undertaken with or without reference to behavior itself.

In the former category are studies showing that repeated precedence of a light flash by a sound gives rise to a condition in which the sound alone can evoke a late ("secondary") potential similar to that evoked by the flash or can block the alpha rhythm of the EEG as would the light. If a slowly flickering light is used, it is sometimes possible for the sound to induce rhythmic potentials at a frequency similar to that of the flicker. This remarkable capacity of the brain to generate specific rhythms is also encountered occasionally in behavioral situations, as noted below. It can even be demonstrated at the level of the single neuron. If a series of flashed is given repeatedly at the rate of 3/sec. during anodal polarization of the visual cortex, isolated units continue to respond with bursts at 3/sec. to a single flash given 30 seconds or more after the cessation of the preceding rhythmic flashing.

In other instances anodal polarization of the cerebral cortex augments the excitability of the subjacent cells and has a peculiar, enduring effect in that the cells subsequently continue responding to stimuli presented during the period of polarization. For example, single cortical neurons, which fail to respond to ipsilateral or contralateral electrical pulses, during anodal polarization may respond to both. If during the polarization ipsilateral pulses are given repeatedly, the ipsilateral stimulation is able to elicit these responses for some 20 minutes after cessation of the polarization, whereas stimuli which were not "paired" with the polarization are ineffective. The effect can be observed grossly if it is the motor cortex which is polarized. In this case stimuli given during polarization continue to produce movements of the appropriate limb for some 20 minutes after removal of the polarization. Again, stimuli which are not repeatedly presented during polarization remain ineffective.

While electrically recordable phenomena are of undoubted interest for problems of memory and learning, their relation to these processes
is not yet adequately specific, and they often lack the required persist-
ency and reproducibility. Analysis of the electrical events during be-
havioral learning has not simplified the picture; but several important
principles have been established. The results, of course, depend upon
the method. Most studies show that there is a complex sequence of
changes in various parts of the brain at different states in the learning
process. Some of these, such as the increasing consistency of the EEG
arousal reaction to the CS as training proceeds, can be plotted as "learn-
ing curves" and precede the development of behavioral manifestations of
learning. The attentive process, which such EEG data suggest, is prob-
ably an essential part of learning. It is not an essential part of the per-
formance of learned acts, however. As training proceeds past the point
of initial learning, these cortical arousal reactions become localized to
the region of sensorimotor cortex, and may even disappear. A highly
trained but sleepy cat can make specific conditioned movements to the
CS while neocortex is in HVS activity. In such cases the CR is accom-
panied by LVF activity in the hippocampus and septum, and sometimes
mesencephalic reticular formation, and no CRs occur without such sub-
cortical transformation from HVS to LVF activity.

This and much other electrophysiological data emphasize again the
fact that "learning" is occurring throughout the brain. At present, the
various processes of attention, motivation, habituation, sensorial anal-
ysis and effector organization cannot be dissected in their respective
contributions to these electrical events. Surprisingly, it appears, in
some instances at least, that the electrical records are affected not so
much by the motivational setting of the experiment as by the type of
response the animal must give. If a series of clicks as CS is always
followed by the US regardless of the animal's performance, the poten-
tials evoked throughout the brain by the CS become augmented and it
makes no difference whether the US is an electric shock or sugar pellet.
If on the other hand the animal must make a specific movement to the
CS either to escape a shock or to receive a reward, then the potentials
evoked by this same auditory CS are greatly diminished.

Single units, apparently any place in the cerebral cortex of the mon-
key, can respond to light flashes even before they are used as a CS. The
evolution of the conditioned state among the population of neurons sampled
so far is evidenced mostly by suppression of these "inappropriate" re-
sponses to the CS. A significant change occurs in parietal areas, how-
ever, since cells here are more readily affected by the CS as it acquires
significance. The unit responses have no predictable correlation with
the EEG activity recorded from the cortical surface.

This latter result calls attention to the fact that the neurophysiological
significance, if any, and even the origin of the EEG remain obscure. It
is still entirely possible that the digital process of neurons discharging
or not discharging all-or-none impulses in statistical codes may be the
only integrative mechanism operative in the nervous system. At least
it is certain this mechanism must be present, as it is mandatory for
any immediate action at a distance exceeding a few millimeters. The
same certainty of significance cannot be assigned to EEG processes, and
if significance exists, it must ultimately be expressed in nerve impulses.
The DC potential across the cortical surface affects the excitability of cortical neurons, for instance as mentioned above, but normally these DC changes are probably diffuse and vary with the degree of wakefulness. The cases in which the slow electrical activity can be shown to have an "integrative" role, such as in synchronizing potentials in the two halves of the cut strychninized spinal cord or in the nicotinized frog brain, are grossly abnormal. Pyramidal cells in the hippocampus can remain silent during violent bursts of "EEG" seizure activity, and then discharge at high frequency during the absence of the surface oscillations.

It can probably be accepted that dendritic activity, which these slow potentials presumably represent, can set the threshold of the cells to which they are attached. The difficult question, however, is whether action in one cellular dendritic system has a significant effect upon the dendrites of the many neighboring cells with which it is intertwined. If it does, then this process is obviously important in neural integration. Recent knowledge of the organization of the cortical somatosensory and visual systems shows the cells to be arranged in highly precise, modality specific columns. The utility of such an arrangement is still problematical, but it is unlikely that the specificity of operation so gained should be defeated by crude interactions of dendritic masses.

Still there is some behavioral evidence that these slower potentials may be significant. A phase shift of the hippocampal rhythms occurs as an animal learns and performs a particular task. Also, as noted above, the brain is able to reproduce certain rhythms. When animals are simply brought into the experimental environment where they are being trained to a flickering light as a CS, waves similar to those induced by this CS may often appear in its absence. The strongest evidence favoring the view that the slow potentials carry information comes from experiments in which cats were trained to make response "A" to flash frequency 1 and response "B" to flash frequency 2. When such an animal made a mistake, i.e. made response "A" when it should have made "B", it was found that the rhythm then generated in the brain to frequency 1 was actually that expected upon presentation of frequency 2. Convincing as such findings are they must also be incorporated in the same body of knowledge which shows that large potentials can be evoked in the human cerebral cortex without the individual being aware of it.

Obviously many problems remain. Yet there must be those who think we have already gone too far, in showing how electrons and chemistry can delete or insert into the brain, and thus into the individual consciousness, a memory or a mood -- how physical properties govern the material of experience. In important respects the "a prioris" of the human mind, envisaged by Immanuel Kant, have been reduced to nucleic acid sequences in the genes which build the brain. It is the peculiarity of this genetic material, forged in the pitiless struggle for survival, that it has produced primate curiosity. As a consequence, we shall seek so long as this sublime chemistry endures.
GENERAL REFERENCES