THE PHYSIOLOGIST

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Cover: James Moultrie, Jr., first Professor of Physiology, Medical College of the State of South Carolina.

Reflections: A Lifetime Romance – A Labor of Love

On July 1, 1985, Martin Frank, Ph.D., will assume the duties of Executive Secretary-Treasurer of the American Physiological Society. Dr. Frank, who is currently with the National Institutes of Health, was selected by the Search Committee and Council. Biographical information about him will appear in a future issue of *The Physiologist.*

My own plan is to continue working for the Society on a volunteer basis to promote the Centennial Celebration culminating in 1987. Because I have received many inquiries from members, I have written this editorial to give some of the background for the change.

The American Physiological Society and its members have had a profound influence on my professional career beginning in 1942, six years before my election to membership in 1948. As a graduate student during World War II, I was interested in doing my thesis research in altitude physiology but found it a difficult field to enter.

Published experimental work was sparse, and it was rumored that much security-classified research was under way. Thus the subjects covered were not available to a graduate student lacking security clearance. Obviously, this was a dangerous area from which to pick a thesis topic without obtaining good advice from someone with access to classified information.

In my search for such advice, Louis B. Flexner of the Committee on Aviation Medicine of the National Research Council steered me to A. C. Ivy who, on leave from his academic post at Northwestern University, was Scientific Director of the Naval Medical Research Institute in Bethesda. Dr. Ivy was also immediate Past President of APS, having served as Secretary of the Society for the four previous years. I remember my astonishment to find such a prestigious and busy man spending time and mental energy advising a beginning graduate student, and in his friendly and collegial manner. A series of events generated by Dr. Ivy soon found me employed at NIH in the Altitude Physiology Unit of what was then the Laboratory of Industrial Hygiene, with permission to use NIH facilities for my thesis research outside normal working hours. He became my research advisor by arrangement with the University of Maryland.

My immediate supervisor was J. Newell Stannard, another APS member and a former postdoctoral fellow of Wallace O. Fenn. Through Newell, I became acquainted with Dr. Fenn and also Philip Bard, who served as APS President during the war years since a meeting to hold elections of new officers was not possible. Both Fenn and Bard showed the same unassuming and friendly attitude I had encountered in Ivy. At this point, I decided that this was a group of men with whom I would enjoy spending a lifetime association.

Toward the end of my subsequent Navy service in 1946, I became involved in the study of tooth pain occurring at altitude and was referred to Ralph W. Gerard at the University of Chicago for advice concerning a hypothesis I had about the phenomenon. Again I found a warm and helpful senior colleague. Gerard and I developed a close friendship that resulted in my election to APS membership in 1948.

On the night of Gerard's election as President-Elect in April 1950, we had dinner together after the business meeting. He was enthusiastic about his election and wanted to make his presidency count. He said he wished he knew what the young members of the Society wanted and asked me to conduct an unofficial inquiry in an attempt to determine the wishes of the "young members." With two other "young members" and the assistance of Milton O. Lee, recently installed as the first employed Executive Secretary of APS, many suggestions were collected. In pulling these together, I conceived the idea of forming a number of committees, including younger members, advisory to Council to perpetuate member involvment with Society affairs. Several of these committees were established by Council. Others were deferred pending further study. The "study" turned into a "Survey of Physiology." I was asked to help get the Survey started, and I complied, spending eight months in full-time work for APS as Director of the Survey of Physiological Sciences (*Mirror to Physiology,* R. W. Gerard, APS 1958).

In that capacity my contact with leaders in physiology was broadened and deepened. In retrospect it is hard to imagine relationships like this developing for a young scientist (I was 22 years old when I first met Ivy) in any other field of endeavor. Subsequent history of the leadership in physiology has shown that unpretentious collegiality among physiologists has been a remarkably universal quality. Perhaps the patterns of behavior were engendered by the early leadership of APS and its parent society, The (British) Physiological Society.

As physiologists continued to be my favorite associates during a career in government science administration, it was therefore not surprising that I applied for the position of Education Officer of the Society when it was established in 1970.

In 1973, Ray Daggs retired and I assumed duties as Executive Secretary-Treasurer. The Society has been an exciting place to work. During the time I have held the Executive Officer position, many changes have taken place:

- A Bylaw amendment to elect Officers and Council by mail ballot (increasing the referendum by an order of magnitude), *Physiologist* 17(1): 2-5, 1974.
- An increase of 300% in attendance at the Fall meeting
- Sectionalization of the *American Journal of Physiology, Physiologist* 18(4): 483-484, 1975.
- A threefold growth in pages published by our journals, including *The Physiologist.*
- Sectionalization of the membership into areas of interest, *Physiologist* 17(4): 419, 1974.

• Addition of two new membership categories, Corresponding for Foreign Members (*Physiologist* 17(4): 411–413, 1974) and Student (*Physiologist* 19(1): 11–12, 1976).

• Formation of a Task Force (1973) and, later, a Committee on Women in Physiology (1982) and a meteoritic use in the proportion of women members.

• Establishment of a Program Executive and Advisory Committees (providing representation for all sections), August 1976.

• Establishment of a Public Affairs Executive and Advisory Committees (providing for representation from each state of the U.S.) with much enhanced activity especially in the area of prevention of restrictions on animal experimentation, in April 1982.

• Use of computer for membership records, membership election, election of officers, meeting programming, manuscript control, statistical data on membership and institutions, word processing.

• As a result of the forthcoming Centennial, an enlivened interest in Society history and history of American Physiology in general, *Physiologist* 23(3): 15, 1980.

Soon after joining the Society as Education Officer in 1970, I became aware that its Centennial year was approaching and thought an appropriate time for me to retire would be after the Centennial in 1988. By 1977, with the Centennial only a decade away, I began to experience some nervousness about Society preparations. Fortunately at about this time, in response to a letter by Arthur Otis to Council calling attention to the relatively short time available for planning, a Centennial Celebration Committee and a Centennial Projects Task Force were established. The Committee was to be responsible for the overall planning, with the Task Force composed of individual members or staff for implementation of particular projects. Earl Wood served as the first Chairman of the Committee followed by Peter Chevalier and recently replaced by Alfred Fishman. M. C. (Shelly) Shelesnyak served until recently as Task Force Director on a part-time basis.

In 1981, I began to feel frustrated by the inability to make time to work on Centennial activities. With many immediate pressures filling my days, I realized that some full-time staff would be required to achieve a majority of the goals established by the Committee. We were fortunate to learn of the availability of Toby Appel, a Ph.D. in History of Science, with an already established specialty in the history of biology and medicine, and succeeded in employing her as Historian/Archivist and the first full-time staff member primarily working toward Centennial objectives.

Since there was little chance of finding funds for additional staff, some form of volunteer work appeared to be the Society's best prospect. The thought then occurred to me to retire from the Executive Secretary role myself and ask the Council to select a replacement and to accept my volunteer appointment as Task Force Director. This was accepted by Council, a Search Committee established, and a new Executive Secretary-Treasurer selected.

My immediate plan is to work full time on Centennial projects. Reports of these activities will appear in forthcoming issues of *The Physiologist.*

It should be clear from the above recital of my lifetime connections with APS that working toward a Society Birthday Party will be a labor of love for me. (It was a surprise to find that I have personally known 49 of the 59 Presidents of APS serving through July 1986.) It is to be hoped the Centennial will dispel some of the miasma generated by concern about loss of "image" of physiology as a modern science. The scientific sessions of the thematic program of the 1987 FASEB meeting, "A Century of Progress in Physiology," should display its unique role of fusing advances in specialty fields into new concepts of function in the intact organism.

Orr E. Reynolds
Executive Secretary-Treasurer

Call for Historic Films

It has been suggested by Dr. A. P. Fishman, Chairman of the Centennial Committee, that at the Centennial Meeting of APS in 1987 there be a continuous showing of historic films in physiology. A few such films are already available to APS. For example, a film taken at the International Physiological Congress in Boston, 1929, has recently been donated. A film on Pavlov has been offered, and APS already has a copy of the classic film of August Krogh on microcirculation in the frog. Other films illustrating the history of physiology are desired. If you know of a film of historic interest that can be borrowed for the Centennial—either a film that traces an historical development such as the well-known film on Harvey and the circulation of the blood, or an old film, such as the Krogh film mentioned above, which by its association with a famous physiologist has become historic—please write to Dr. Toby Appel, Historian/Archivist, American Physiological Society.

Historical Section

Departmental History

Physiology Department
Medical University of South Carolina
Charleston, South Carolina

The Medical College of South Carolina was the first medical school south of Baltimore and the fourteenth medical school in the United States at the time of its founding in 1824. Its location in Charleston was natural for the times, for it has been said of those times that "at a period before Dr. Benjamin Rush began his brilliant career as an author, there were more experiments made, more observations recorded, and more medical writings ushered into public view by the physicians of Charleston than of any other part of the American Continent" (6). Such an intellectual atmosphere was thus the seed for efforts to improve medical education and the practice of medicine in the South.

The School founded in 1824 did not include a Chair in Physiology. It was not until the school was reorganized in 1832 as the Medical College of the State of South Carolina that a Chair in Physiology was created.

The subject of Physiology was taken from the Chair of Practice and made an independent professorship to entice **James Moultrie, Jr.,** M.D. onto the faculty.

Dr. Moultrie was a fourth-generation Moultrie physician in Charleston. His great-grandfather, grandfather, and father were all Edinburgh-educated physicians who practiced medicine in Charleston. James Moultrie, Jr., received classical education in England but, unlike his ancestors, had an American medical education, graduating from the University of Pennsylvania at the age of 19. He began practice in his native Charleston and immediately became involved in efforts to improve the education and licensing of physicians. He authored a "memorial" to the South Carolina Legislature in 1823 requesting a charter and funding for a College of Medicine. The request was refused, but a similar request for a charter without funding was granted the following year. Dr. Moultrie was offered the Chair in Anatomy in this new Medical College of South Carolina in 1824 but refused because he believed it would not have been proper to accept a position created by an endeavor in which he was so actively involved and because he feared that success of the endeavor was jeopardized by lack of State funding. However, he did accept the newly established Chair in Physiology in the school's reorganization of 1832.

The course of study in physiology consisted of three hours of lecture and recitation each week from October until March of each year. A student had to attend for two years of didactic courses in addition to an apprenticeship with a practicing physician. The courses were repeated each year so that students had two repetitious years of instruction. It has been written that "Dr. Moultrie's lectures were so labored and elaborately minute analytically, and so metaphysically subtle abstractly that much of the time he talked above the student's heads. His fellow professors have told us that it was 'his avowed purpose in his teachings rather to lecture his hearers up to his level than to lower himself to theirs!" (7). How familiar this rings!

Dr. Moultrie's consuming efforts were directed at improving medical education and the practice of medicine. His ideals for a well-rounded scientific education are contained in a speech delivered at the opening session of the College in 1834. In this speech he stated that medicine may be called a summary of many sciences and then detailed its relation to mathematics, philosophy, physics, zoology, agriculture, music, poetry, painting, fine arts, and the classics. In 1836, in an address before the State Legislature, he called for standardized admission requirements and a lengthening of medical education to three or preferably four nonrepetitious years, each consisting of five to seven months. In this same address he once again emphasized the need of State financial support and the necessity for salaried faculty. He proposed a system of base salaries supplemented by limited practice similar to the system used in France at this time (1). Dr. Moultrie was a man far ahead of his times in South Carolina, for his proposals fell on deaf ears and were not realized entirely for over a century—the first salaried clinical faculty positions were established in 1938, the four year curriculum in 1890, and State financial support in 1912.

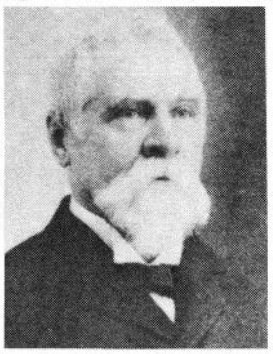
Extensive laboratory investigations in physiological mechanisms were not carried out by Dr. Moultrie. However, he regularly published his observations and some theoretical papers in the *Journal of the South Carolina Medical Society* and the *American Medical Journal.* No funds or laboratory space were available to him except the funds he used from his private medical practice. He utilized his office and hospital rounds to make his keen observations. Time, too, was certainly a limitation, for he had a large practice to look after at all times.

Dr. Moultrie was one of the founders of the American Medical Association, becoming its first Vice-President. He became President of the American Medical Association in 1854 and served the organization admirably. His stature on the faculty of the Medical College is evidenced by his serving as Dean of the Faculty on three occasions—1835-36, 1840-41, and 1847-50. In the years just prior to the Civil War, the faculty enjoyed the distinction of being one of the most successful in the United States from the standpoint of numbers of

students. Only three other schools had larger enrollments.

The faculty disbanded in 1861, and most became involved in the Civil War by serving the Confederacy. The College was reopened in 1865. While the College was always in need of better financial support, the reopening was faced with even greater need and fewer prospects of obtaining the need because Charleston was no longer wealthy. This community and the state as a whole were economically ravaged. Despite the difficult times, the faculty reassembled, and Dr. Moultrie once again assumed the Chair in Physiology. Two years later in 1867 he resigned because of ill health and died in 1869.

Following Dr. Moultrie's resignation of 1867, **Francis Turguard Miles,** a graduate of the College of Charleston and the Medical College of the State of South Carolina (1849), was appointed to the Chair in Physiology (3). Dr. Miles served briefly as an assistant to Dr. Moultrie prior to the Civil War, so that some degree of continuity was maintained. Dr. Miles had studied in France as well as in Charleston, and his credentials were impeccable. He remained only two years and moved to Washington, DC, where he was involved in the founding of Washington University College of Medicine, later to become the University of Maryland College of Medicine. He served as Chairman of Physiology at Maryland and served as President of the American Neurological Association in 1879–80.



Dr. **Middleton Michel,** a Charleston medical practitioner, was elected to succeed Dr. Miles in 1869 and served as Chairman until his death in 1894. Dr. Michel was born in Charleston but was educated extensively in France. He began his medical studies in Paris as a student of Richet, Criuveilhier, Longet, and Coste in the École de France. While attending classes he taught anatomy at the École Practique in the French language to the complete satisfaction of both faculty and students. Thus his teaching abilities were recognized early in his developing career. He received a diploma from the École de Médecine in 1845. The next year after attending lectures at the Medical College of the State of South Carolina he was awarded the M.D. from this institution and began his practice in Charleston. He never really left teaching, for he founded the Summer Medical Institution and gave lectures in anatomy, physiology, and midwifery each summer from 1848 until the Civil War. Thus, when elected to the Chair in Physiology at the Medical College, he was returning to his love of teaching. It has been said of him, "All his life he taught. All else subordinated to that as his life's dominant purpose and main program. His practice was accordingly undertaken primarily to pay expenses and add valuable material to his teaching armamentarium" (8).

The course in Physiology consisted of two twenty-week sessions of three hours of lecture each week. The 1878 course description stated the goal, "To exhibit physiology as the fundamental basis of all medical superstructure without which neither medicine is practiced with propriety, nor surgery with skill" (4). According to some, Dr. Michel's command of language and scientific knowledge made the lectures a memorable experience for students in attendance (8).

Research funding was still absent, and Dr. Michel's researches consisted of observations made in the course of his surgeries and medical practice. His publications of these works were mainly in magazines of the Medical Society and number approximately twenty.

Evidence that Physiology in the Medical College became the responsibility of men other than the holder of the Chair began to appear in 1892. These additional participants in the teaching were, like the Chairman, active medical practitioners in the Charleston community. R. S. Kirk, M.D. was appointed Assistant to the Chair in that year and served in that capacity until 1899, five years after Dr. Michel's death in 1894.

Dr. **Edward F. Parker** was elected to succeed Dr. Michel. Dr. Parker, at the time, had an active medical practice and was a Clinical Professor of Diseases of the Eye, Ear, Nose, and Throat at the College. He was an 1889 graduate of the Medical College of the State of South Carolina, a board-certified eye, ear, nose, and throat specialist and, as such, was the first specialist to practice in Charleston.

Dr. Parker published numerous articles of his clinical observations in the *Transactions of the South Carolina Medical Association.* He served as Dean of the College from 1906 until 1908 and Professor of Physiology until 1911, after which he became Professor of Diseases of Eye, Ear, Nose, and Throat. During Dr. Parker's tenure as Chairman, he had several assistants to help with instruction. Henry Horlbeck, M.D. served as instructor from 1900 to 1901, William Mazyck, M.D. served as instructor as well as Assistant to the Chair in Surgery from 1902–1905, and McMillan King Mazyck, M.D. was Lecturer in Physiology from 1906–1916.

In 1913, following Dr. Parker's resignation to devote his time to the Professorship in Eye, Ear, Nose, and Throat, Paul Marshall Rea, M.A., Director of the Charleston Museum and Professor of Biology at the College of Charleston, was appointed Professor of Physiology and Embryology. Professor Rea was a graduate of Williams College and received his M.A. degree from Williams in 1901. He became Professor of Biology at the College of Charleston in 1903 as well as Director of the Charleston Museum. His interests were in the physiology and anatomy of Abigochaeta and Annelida as well as the fauna of coastal South Carolina.

The Medical College of the State of South Carolina was officially established as a State-supported Institution in 1913. In the takeover arrangement, "full-time" salaried professorships in the basic sciences were authorized, but the funds appropriated were insufficient to

support even these chairs in the College (2). Professor Rea like almost all other faculty was dependent even now on outside sources of income. Professor Rea consequently continued as Director of the Charleston Museum during his entire tenure as Chairman of Physiology. H. R. Simons, M.D., a local medical practitioner, lectured in the physiology courses in 1912 and 1913, and Leon William McGrath, M.A. was an instructor from 1913 to 1915. Malcolm Chester Pfunder, B.S. assisted Professor Rea from 1916 to 1918, when Professor Rea returned to the Charleston Museum on a full-time basis.

In 1919, **John van de Erve,** M.D., became the first salaried "full-time" Department Chairman. Dr. van de Erve received a B.A. degree from Hope College in 1895, a M.A. degree from Princeton University in 1897, a B.D. from Princeton in 1910, a M.S. from Chicago in 1910, and the M.D. from Rush in 1911. He was an active Presbyterian minister from 1897 to 1911, when be became Professor of Physiology and Pharmacology at the University of Alabama. From there he became Professor of Physiology and Pharmacology and Associate Dean at Marquette University in the years 1913–1919.

The fact that six years had elapsed between the acceptance of financial responsibility for the Medical College by the State and the appointment of the first salaried "full-time" chairman in Physiology was symptomatic of the meager support the State provided the College. Such meager support was to continue unfortunately for many years, due in part to the economic conditions of the State which had fallen to 48th among the Forty-Eight. A hoped-for reemergence to the forefront of medical education was thus repeatedly dashed by harsh economic realities and sometimes by political misunderstandings. Nonetheless, evidence of the faculty's aspirations early after State sponsorship was, with public and alumni support, the construction of new facilities including a Physiology-Pharmacology Building by 1920, and later additions during the 1930's and 40's. The 1920 description of the new building describes for the first time a research laboratory available to the Professor of Physiology and teaching laboratories for the two departments. In 1920, the Physiology course consisted of 100 hours of lecture and 188 hours of laboratory in the second year of the medical curriculum. The course description was as follows (5):

> "The course in physiology embraces a systematic and sequential presentation of the subject in lecture, oral and written quizzes, demonstrations and extensive laboratory exercises.
>
> "So far as feasible the practical work runs concomitantly with the didactic assignments.
>
> "Emphasis is placed upon the training afforded the student in the effective use of precision instruments, particularly those valuable for clinical diagnosis.
>
> "The power of observation is cultivated and the correlation and coordination of observed facts together with their most obvious clinical application developed.
>
> "For this reason experiments, illustrating functions, are performed on the living animal, and, wherever possible, on man himself, that the medical student may understand the fundamental principles of physiology and readily apply them in this later surgical and medical practice."

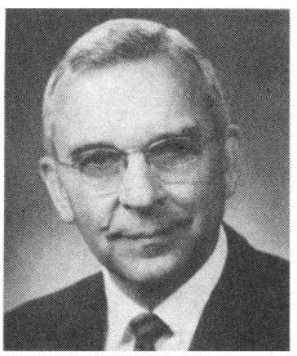
This course description was little changed during the tenure of Dr. van de Erve between 1919 and 1944.

Financial support from the state remained meager and slowed the development of the department. Not until 1927, when C. C. Hood, Ph.D., and T. H. Brynes, M.D. became Instructors of Physiology, is there evidence that faculty other than Prof. van de Erve were hired into the Department. In 1929, these were replaced by W. E. Gower, M.S., M. W. Hemingway, Ph.D., B.S., and John M. van der Erve, M.D. as Instructors. In 1933 **Frederick W. Kinard,** Ph.D. joined the Department as Instructor and remained until 1980 when he retired as Professor of Physiology and Dean of the College of Graduate Studies. In 1936, H. D. Bruner, M. D. joined the faculty as an Instructor and remained until 1939. Bruce Richardson, M.S. became Assistant in Physiology in 1938 and remained until 1940. R. W. Wager, Ph.D. was apointed Instructor in 1942, and in 1943 James A. Richardson, M.S.. received a dual apopintment as Instructor of Physiology and Pharmacology.

Dr. John van de Erve died in 1944 ending a tenure of twenty-five years as Professor of Physiology. Dr. van de Erve with his fellow physiology faculty members regularly published their experimental observations on muscle, gastrointestinal, cardiovascular, and metabolic functions. Research in these years was hampered by the absence of funds. To today's observer it seems incredible that any research was possible or that the school survived with the level of State support made available. Money problems appeared to be continuous since the founding of the Institution but particularly so in the eighty years between the Civil War and World War II.

Dr. F. W. Kinard became interim Chairman in 1944 and served in that capacity until 1947. During this time Ragnar N. Danielson, Ph.D. was appointed Instructor of Physiology, so that the Department consisted of Kinard, Wager, Richardson, and Danielson during the interim period.

With promises of eventual faculty and facility expansion in accordance with the development plan formulated by the Dean and Trustees in 1944 (2), Dr. **Theodore George Bernthal,** M.D. was appointed Chairman in 1947. Dr. Bernthal was a graduate of the University of Michigan and served on the faculty there from 1929 to 1940. At Michigan he was a member of Gesell's group in respiratory physiology and began his works on the carotid body. He left Michigan to join the faculty of Vanderbilt University and remained there from 1940 to 1946.



Dr. Bernthal's presence brought to the Medical College its first member of the American Physiological Society. Dr. Bernthal became a member of the Society in 1932 while he was a member of the faculty of Michigan. Dr. Kinard became a member of the Society in 1947, the year of Dr. Bernthal's arrival. Thus the department began its affiliation with the American Physiological Society and has continued to encourage its faculty to associate professionally with the Society ever since.

Dr. Bernthal, with the now-present broader funding for research from the National Institutes of Health, infused a renewed interest in research, but the teaching responsibilities remained heavy for such a small department and continued to demand extensive time commitments. Nonetheless, the 1948 listing in the Medical College catalogue for the first time described the availability of physiological research and fellowships to the student body of medical, pharmacy, and nursing students. In this same year a Committee on Graduate Studies was formed with representation from each basic science department of the College and chaired by Dr. Kinard of the Physiology Department. Graduate programs leading to both the master of science and doctor of philosphy degrees were formulated and approved for admission of students. The first graduate student in physiology was admitted in 1951 and the first Ph.D. was awarded in 1955. This program has produced fifteen Ph.D. recipients and twelve M.S. recipients since its inception.

Faculty expansion still was limited by restrictive State funding such that the size of the department increased by only one faculty member beside the usual turnover in a period of almost fourteen years. In 1948, Dr. Wager left and was replaced by Wilson Greene, Jr., M.D., who remained one year, to be replaced subsequently by Bernard Metz, Ph.D. Dr. Metz progressed through the academic ranks to Professor and served the department for over 20 years until his death in 1971. Dr. Thomas B. Calhoon joined the department in 1952 as an Assistant Professor and resigned in 1963 to join the faculty at Ohio State and later to become Chairman at Louisville. The years 1949 to 1963 were stable years, with Dr. Bernthal, Kinard, Danielson, Metz, and Calhoon making up the faculty. Excellent teaching was a force of this faculty.

In 1963, John Gill Blackburn, Ph.D. was appointed instructor to succeed Dr. Calhoon. 1964 saw the beginning of a long awaited and anticipated growth of the department. New basic science facilities were in the planning stages as were new colleges of dental medicine and allied health sciences. To accommodate the college growth the department was authorized to begin adding faculty. The year 1964 say the addition of Edward Otey, Ph.D., a respiratory physiologist, and Charles Wells, Ph.D., a renal physiologist. In the following year of 1965, Sidney Katz, Ph.D., a neurophysiologist, and Alan D. Horres, Ph.D., a respiratory physiologist, joined the faculty.

In 1967, Dr. Bernthal became ill but continued to plan vigorously for the future. Final plans for the new departmental facilities were completed, modernization of student laboratory instrumentation was achieved, and the additional courses for the new dental medicine students were begun. Dr. Bernthal died in late 1968 without seeing plans for expansion completed and realized. Dr. Kinard once again became interim chairman and served until July 1, 1971. Several additions to the faculty were made in this period to continue the departmental growth. In 1968, William C. Wise, Ph.D., and Darrell D. Wheeler, Ph.D., both cellular physiologists, were appointed Assistant Professors. In 1969, Margaret C. Conrad, Ph.D., a cardiovascular physiologist, was appointed Associate Professor, and Rupert L. Green, Ph.D., a cardiovascular physiologist, was appointed Assistant Professor. The following year, 1970, Gerald Whitfield, Ph.D., a cardiovascular physiologist, was appointed Assistant Professor. Dr. Conrad resigned in 1977 and was appointed to the Chair in physiology at Eastern Virginia Medical School. Dr. Whitfield resigned to attend dental college.

On July 1, 1971, Harold G. Hempling, Ph.D. began his tenure as Chairman, coming from Cornell Medical School. Dr. Hempling received his A.B. from New York University, his M.A. from Oberlin College, and his Ph.D. from Princeton University. He joined the faculty of the University of Pennsylvania College of Medicine in 1953 and left to join the faculty of Cornell University Medical College in 1957.

The department now was housed principally in newly completed facilities on the fourth floor of the Basic Science-College of Dental Medicine Building. The original departmental facilities continued to be utilized for research space and held for continued expansion. In 1972, Jerome G. Ondo, Ph.D., an endocrinologist, and John Pritchard, Ph.D., a cellular physiologist, joined the department. In 1974, Henry F. Martin, Ph.D., a neurophysiologist, was appointed, along with Richard Suddick, D.M.D., Ph.D. and Saidee Silverthorn, Ph.D., a marine biologist. These faculty additions brought the number of faculty to fourteen, the largest number ever assembled in the department.

Christopher M. Fredericks, Ph.D., a reproductive physiologist, joined the faculty in 1975 to replace Gerald Whitfield. James S. Graves, Ph.D., a cellular physiologist, joined in 1976 to replace John Pritchard, and Ralph Hollingsworth, Ph.D., a bioengineer, replaced Saidee Silverthorn in that same year. In 1978, James A. Cook, Ph.D. and George E. Tempel, Ph.D. joined the faculty after Dr. Kinard retired and Dr. Suddick left to develop an oral biology program at Louisville. Dr. Regina Frayser, who was Professor of Research Medicine and Ophthalmology, was awarded a joint appointment as Professor of Physiology.

Since 1978, the faculty size and makeup has been stable, remaining at thirteen full-time appointments and one split appointment with the Department of Medicine. Although there is a slight concentration of faculty with research interest in cell physiology, there has been no obvious or concerted effort to establish a team approach to the ongoing research activities. Rather, each investigator has been encouraged to pursue independent research projects. Nonetheless there is evidence of movement toward cooperative team effort on the part of some departmental faculty. This is particularly true in the area of neurophysiology and in research on endotoxic shock. Departmental emphasis continues to shift toward research productivity, resulting in 27 publications and 21 abstracts by the faculty during the academic year of 1982–83.

Teaching excellence has continued to be a prime effort of the department, and pride is expressed in the accomplishments and performance of our students. Much

effort is directed to this end in offering separate allied health, nursing, pharmacy, dental, medical, and graduate physiology courses to approximately 450 students annually.

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Alan D. Horres

Announcements

International Symposium on Magnesium and Its Relationship to Cardiovascular, Renal, and Metabolic Disorders

The American Society for Magnesium Research is sponsoring a program on the role of magnesium in the etiology and treatment of cardiovascular, renal, and metabolic disorders for physicians, physiologists, nutritionists, and specialists concerned with recent developments in this rapidly evolving area. The symposium will be held 12-15 February 1985, at the Los Angeles Hilton Hotel, Los Angeles, CA. *Information:* Dr. Nachman Brautbar, Div. of Nephrology, Dept. of Medicine, University of Southern California, Los Angeles, CA 90033 (213/483-4600, 213/226-4768, or 212/270-2616).

International Hypoxia Symposium

The Fourth International Hypoxia Symposium will be held February 12–16, 1985, at Chateau Lake Louise, Alberta. The theme of the symposium is Hypoxia and Cold. Topics will include cold injuries, effects of hypoxia, and exercise and altitude. *Course coordinators:* Drs. John Sutton and Charles Houston. *Cosponsors:* CME Divisions, McMaster University, University of Calgary, and the Arctic Institute of North America.

Tenth International Symposium on Gastrointestinal Motility

The Tenth International Symposium on Gastrointestinal Motility will be held September 8–11, 1985 in Rochester, MN. This meeting will feature presentations in basic and clinical sciences related to gastrointestinal motility. The purpose of this meeting is to bring together investigators and clinical scientists whose research is focused on the pharmacology, physiology, and pathophysiology of gastrointestinal motility at both the organ level and at the level of the single cell. Oral communications, poster sessions and invited state of the art lectures will be featured. *Information:* Joseph H. Szurszewski, Mayo Clinic, Rochester, MN 55905.

International Symposium on Life in the Cold

An international symposium titled Life in the Cold will be held at Stanford University's Conference Center at Fallen Leaf Lake near Lake Tahoe October 6–11, 1985. The symposium will include invited papers, voluntary papers, and poster presentations on topics related to adaptations to cold. Topic areas will include cellular and biochemical aspects of cold adaptation and freezing resistance, mechanisms of thermogenesis, physiology of torpor and hibernation, regulation of body temperature, seasonal responses and endogenous rhythms, and survival of man in the cold. *Information:* H. Craig Heller, Dept. of Biological Sciences, Stanford University, Stanford, CA 94305.

Pilgrimage to Yale

HSIANG-TUNG CHANG
Shanghai Brain Research Institute
The Chinese Academia of Sciences
Shanghai, Peoples Republic of China

Like a falling leaf blown in the autumn wind the course of life is sometimes determined by fortuity not by will. It was purely by chance that I came to the United States.

I was born to a poor family in a desolute village of North China and was unable to go to a regular primary school until the age of 14. Only through struggle and hard work did I manage to receive a higher education in Peking. I had never given a thought to the possibility of studying abroad until an unexpected opportunity arose in 1942 while I was struggling for survival in a small town of the interior in Kweichow Province during the darkest days of the Japanese invasion.

This almost unbelievable story must go back to the 1930s. After graduation from the National University of Peking I became a laboratory assistant to Professor Ging-Hsi Wang, who pointed out to me the path leading to the world of neuroscience. Under his direction and supervision my first scientific paper entitled "An Auditory Reflex of Hedgehog" was written and published in the accredited *Chinese Journal of Physiology.* In 1934 when he became the director of the Institute of Psychology, Academia Sinica, I was offered a job in his Institute. As a good teacher and scientist with a remarkable acumen in research and deep understanding about the nature of science education, he stressed many times to his students the importance of neuroanatomical foundation in the study of neurophysiology. At his suggestion and encouragement I spent almost seven years in the laboratory of neuroanatomy, and this experience proved to be decisive in shaping my way of thinking in my later scientific career.

The Institute of Psychology where I had long worked in my formative years was unfortunately destroyed by the Japanese during World War II. In the summer of 1937 when the Japanese Army had already occupied Shanghai and Süchow and the fall of Nanking was imminent, nearly all of the staff members of the Institute including the administrative personnel had fled to safety, leaving the Institute practically deserted. As a single young man without the burden of a family, I together with another laboratory assistant, Chu Ling-Wei, volunteered to stay and to take the responsibility of evacuating the books and equipment of the Institute to a safe spot in the interior provinces. Chu was a graduate of the Peking Union Medical College, later studied in the University of Michigan, and became a virologist. A deep sense of responsibility and loyal devotion to the Institute prompted us to take on the formidable task of salvaging the books and equipment that we had used every day for several years. We agreed to stay until the last minute in an effort to transport them to safety.

One evening of August 1937, when we had just finished our emergency packing, the city of Nanking was heavily bombed in a surprise attack by Japanese planes. No air-raid alarm had been sounded, and the residents of Nanking were caught completely unprepared. We rushed to the basement for shelter when we heard the roar of the Japanese bombers over our heads. The Institute was badly shattered and a part of the laboratories collapsed. After having recovered from the shock I found myself buried under the rubble and debris surrounded by choking smoke and dust but had miraculously escaped any serious injury; the only thing I lost was a pair of glasses that were sucked away by the shock waves.

A few days later, Chu and I managed to get aboard the last steamer sailing up the Yangtze River for Hankow. The boat was so overloaded and disorderly that some passengers even tied themselves to the rail for safety. There was no food or water on the boat. At the river post of Wuhu, the first stop in our voyage, Chu decided to go ashore to look for something to eat despite the warning that the boat might leave unannounced at any time. Unfortunately he was just minutes too late returning, and he missed the boat as I stood helplessly on the deck watching him struggling in the crowd on the shore.

Three weeks later when I moved further inland from Wuhan to Changsha, I met Chu again quite accidently on a railway train. I was surprised to spot him ragged and tired, squatting among the crowd of refugees. We were of course very excited and happy at this unexpected rendezvous on the train and shared a hearty meal in the dining car to celebrate our reunion. He told me all that had happened to him since our separation in Wuhu. After he missed the boat, he was unable to find a way to follow me to Wuhan. In desperation he decided to go back to the deserted city of Nanking, where he hoped to find a friend supposedly remaining in a government office, the Commission on National Resources, to help him. Fortunately he arrived at Nanking only a few hours before his friend was about to depart by a sampan across the Yangtze River. His friend gave him a pistol for self defense just in case they were harassed by bandits or Japanese soldiers. From Pukou, a railroad terminal on the north bank of Yangtze River, he made a detour to Changsha by train via Hsu-chou, Cheng-chou, and Wuhan.

We finally reached the collecting station of Academia Sinica in Changsha, where I was assigned to the Transportation Corps to take care of the shipment of hundreds of crates of books and equipment belonging to several institutes of the Academia Sinica. Our immediate destination was Kuei-lin, but nobody knew where we would finally end up. We used all possible carriers, railroad cars, trucks, steamers, sampans, and coolies rented

or commandeered. As a wartime service the job assigned to me was a sort of noncommissioned serviceman working in the Transportation Corps of the National Academy of Sciences. I was constantly on the move on roads and waterways along a line ranging from Changsha, Hengyang, Chüan-chou, Kuie-lin, Liu-chou, to Dan-chou. For five years after leaving Nanking, I never had a chance to settle down in any place for longer than three months.

On one mission in 1940 when the Japanese Army had already taken Wuhan and threatened to advance in the direction of Kuei-lin, a young man, Chou Jin-lung, and I were assigned to the job of moving our staff further inland. We hired about forty river boats to sail upstream the Liu River toward Dan-chou, a small town about 140 miles north of Liu-chou. I found myself "commander" of the spectacular fleet of sampans with Chou Jin-lung as my lieutenant. Chou told me jokingly that I would be shot first, if the boatmen revolted. But nothing happened during the voyage, and we arrived at our destination safely and triumphantly.

Chou was then a young man, intelligent, honest, and friendly to everybody, working as a technician in the Institute of Geology, Academia Sinica. Though suffering from a severe peptic ulcer, he always was cheerful and ready to do the heavier work. Because of the inadequate nourishment, hard work, irregular living on the river boat, and lack of proper medication, his health deteriorated so rapidly that he had to be sent back to Kuei-lin for hospitalization as soon as we arrived at Dan-chou. A few weeks later he died of gastric perforation in the hospital.

Chou had read widely and knew many things. Living together with each other on the same boat for several weeks we developed an intimate friendship. I learned a lot from him about philosophy of life and human value. We mutually decided that we should go to Yenan to join the anti-Japanese fighters or do something useful for the country rather than be refugees fleeing endlessly from the invading Japanese. During the years of 1940–41 the Japanese occupied almost all the coastal cities and about half of the territory of China. Hundreds and thousands of the Chinese people were slaughtered by the Japanese invaders or died of starvation while the best-equipped division of the Chinese Army were reserved for waging a civil war. The corruption and ineptitude of the Kuomintang government also infuriated everybody. A deep sense of humiliation, anger, and despair gnawed at my heart. Chou's death prompted me to make the decision to quit the Institute of Psychology and to head northward to Yenan, although I knew nothing about Yenan nor how to get there.

With the fervor of youth I determined to pack up immediately and bought a ticket for Chungking and then Yenan. Looking back, I now realize that I was very naive and emotional in making such an important decision without considering the practical problems involved and the serious consequences. The wartime highway system in China was extremely disorganized so that only the most hardy or desperate souls would dare to make such a long trip. There were usually no stations along the highway where one could get adequate food and accommodation for the night. Passengers had to get out of the bus and run for safety when there was a Japanese air raid. After riding for 12 days on the bus from Kuei-lin I reached Kuei-yang, the capital of Kweichow Province, where I was supposed to make a transfer to Chungking. As soon as I put up at a small inn near the bus stop, I found that my wallet and a piece of luggage had been stolen. I had no money to buy the ticket for the rest of my journey. I could not even pay my hotel bill. I knew no one in the city, so there was nobody to whom I could turn.

While wandering aimlessly on the street, tired, hungry and depressed, I suddenly felt a big hand on my shoulder. I was startled with a strange feeling of being seized by secret agents or gansters of the underworld society. I turned my head to see what was the matter, and to my great surprise I found the smiling face of an old high-school friend who had also been a schoolmate at the University of Peking. What a relief! After we had greeted each other, I briefly told him of what had happened to me since I had last seen him in Peking and of the mischief I had endured in Kuei-yang. He took me to a restaurant, gave me a hearty meal, and then lent me some money. From our conversation I understood that he was then a Commissioner of Education of the Kuei-yang municipal government and was able to offer me a good job. Through him I learned of many old friends working in the area of Kuei-yang; among them were Dr. Chi Deng-ko, Professor of Anatomy, and Dr. Wang Chih-chun, Professor of Physiology, Kuei-yang Medical College. They suggested that I should take a job jointly teaching in neuroanatomy and neurophysiology in their respective departments. I accepted the offer. However, before the appointment was made, there was a teaching vacancy in the Department of Physiology in the Army Medical School in Asshun, located about 40 miles west of Kuei-yang, and I was chosen to fill that better-paid position on strong recommendations of Professors Chi and Wang.

To satisfy my desire for new knowledge in science and medicine I went to Kuei-yang on Sundays to spend hours in the Red Cross Library, which during the war was the only place in China where one could find current journals and books published in the Western world. There I discovered John Fulton's *Physiology of the Nervous System,* the only book of the kind published up to that time. I was so much impressed with the book that I recommended it with great enthusiasm to my colleagues in the Army Medical College and made the statement at a faculty gathering that I would be very happy if I could spend some time in the laboratory of this great master of neurophysiology. I was ridiculed by some sharp-tongued gentlemen, who labeled me as a day-

dreamer. "If a poor man like you could ever go to the United States, the sun would rise in the west," one of them remarked in public. My feelings were very hurt. Believing that nothing is impossible if you dare to do it, I resolutely wrote a letter that evening to Professor John Fulton, inquiring about the possibility of my studying in his laboratory. Since I wrote this letter more to relieve my mental distress than to expect to be accepted in Yale, I naturally forgot all about it afterward.

Three months later, however, an overseas telegram was delivered to me by the mailman. I declined to accept it without even looking at it, thinking that it was a mistake because I knew nobody abroad, and I asked the man to send it to another Chang, a professor of pharmacology, who had wide foreign associations. Half an hour later the mailman returned and asserted that the telegram was indeed for me because the professor said so. I opened it and found to my surprise that the telegram consisted of three words, "Yes letter follows." I was really perplexed, since I had never thought that there would be a reply to my letter.

A month later a letter arrived. It was signed by Dr. Francis Blake, Dean of the Yale Medical School, granting my application as a Visiting Fellow working in the Department of Physiology. I was promised a grant covering my living expenses during my stay at Yale if I could find any way to get to the United States. It looked as if my dream would come true. With great excitement and delight, I immediately went to my intimate friends to ask for advice. They agreed unanimously that I should not miss this opportunity, and so encouraged by their enthusiasm and support, I decided to sell my meager belongings and books to collect money for my passage to the United States.

To prepare for the trip I went to Chungking, the wartime capital, to be interviewed by countless government officials and to fill out a countless number of forms. All the paperwork was complete after about six months, an extraordinarily short period of time, thanks to the letter of Dr. Blake of Yale University.

During World War II all the seaports of China were sealed and the coastlines occupied by the Japanese. There were no commercial airlines operating between China and the outside world, and the only connection was through the military transport planes flying irregularly between Chungking and Calcutta. If an ordinary civilian wanted to get on board those planes, he must first secure a passport and a visa from the United States. If he wanted to have a U.S. visa, he must prove that he had enough U.S. dollars to finance his living in the United States; and if he wanted to buy foreign exchange at official rate from the Central Bank of China, he must present the foreign student certificate granted by the Ministry of Education, which was impossible unless he could prove himself to being admitted by an institution in the United States. So the telegram and the letter from Dean Francis Blake of the Yale Medical School were the crucial documents that made it possible for me to initiate the series of events to come to the United States.

On New Year's day, 1942, I finally boarded a military transport plane flying from Chungking to Calcutta, India. Calcutta was then a frontier city under the British rule, very close to the Japanese-occupied Burma, where air-raid sirens sounded almost every day and regular transportation was largely paralyzed. Most travelers were stranded in the city. Fortunately, at the hotel I met a group of young Chinese students who were being sent by the Chinese Government to the United States for training in navigation and seamanship. Through them I found one of my old schoolmates who was then serving as a liaison officer in the Allied Command Headquarters for the China-India-Burna Theater, and I contacted him for help. He advised me to take the Liberty Ship (wartime U.S. destroyer) that was scheduled to leave shortly for the United States. I was of course very happy that I could leave Calcutta soon. Two days later, without explanation, I was instructed by my friend to immediately take a transcontinental train to Bombay and to wait there for another opportunity instead of taking a Liberty ship in Calcutta.

I learned later that the reason for this sudden change of plan was a sociopolitical one. A young girl, Anna Chen, who had been admitted to an American College for graduate studies, was also waiting in Calcutta for transportation to the United States. Her father, a high government official, had asked my friend in the Allied Command Headquarters in Calcutta to take care of his daughter and was concerned about her safety on a Liberty ship, since they had become favorite targets for the Japanese submarines operating in the Indian Ocean. It was probably for this reason that I was asked to escort her to the United States by some less risky means.

We waited another two weeks in Bombay before we could get on board the 30,000-ton liner *Mariposa,* which was commandeered during the war to transport about 3,000 Australian and New Zealand soldiers returning from the Mediterranean Theater. The ship was so overloaded that the passengers had to have their meals on shifts. Mealtimes were so oddly scheduled that we sometimes had to get up at midnight for breakfast. There were emergency drills almost every day during the first two weeks of our voyage. We experienced mixed feelings when we sighted the two escort destroyers running alongside our ship, because it meant that we must be in danger of being attacked by the enemy but also that we were under the protection of the Allied naval forces.

After a 30-day voyage from Bombay via the Indian Ocean, South Australian waters, Bass Strait, Tasman Sea, New Zealand, South Pacific Ocean, we finally landed at San Pedro, California. On arrival at San Pedro, the passengers were screened by the U.S. Immigration officers and taken to a hotel in Los Angeles. Ten days later I arrived at New York by a transcontinental train.

In a hotel in New York I again saw some of the Chinese naval cadets I had met in Calcutta. They told me the tragic story of the sinking of the Liberty ship which they had been on and which I also had intended to take. The ship had been torpedoed by the Japanese submarines and sank almost immediately at the mouth of the Red Sea. Only five of their party of twelve Chinese Naval cadets survived.

On March 24, 1943, I arrived at New Haven by train and the next morning was received by Professor John F. Fulton in his office of the Department of Physiology, Yale University School of Medicine. In triumph an adventuresome journey had just been concluded and another journey in search of knowledge begun.

The Rabbit as a Research Subject

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Rabbits made the cover and a feature article of *National Geographics World* publication in April, 1982. They made it because children love them as pets and as something to cuddle and because National Geographic Society wanted to tell children many more things about them, how they live, how they vary in size, color, etc. (72). Rabbits, however, have many other uses. They are raised for the broad spectrum of colors and textures available in their fur, both for pets and for fur. They are used extensively in some countries as a source of meat. Seven percent of the meat consumed in France, for example, is rabbit. They have also become pests in some countries such as Australia. However, the rabbit has provided a very valuable subject for biomedical research. A recent report shows that approximately 300,000 rabbits were acquired by nonprofit biomedical research organizations in fiscal year (FY) 1978, a 47% increase over the FY 1968 survey (12). Additional numbers of rabbits are used for research by commercial and various federal organizations. Improvement in the rabbits' health has been brought about by better nutrition, sanitation, husbandry procedures, and technology allowing the raising of animals under barrier-maintained conditions. This has also made the rabbit more useful as a research tool. This improvement in the quality of life for the rabbit would not have happened without biomedical research, which often relied on the rabbit as the research subject. Many animal species have contributed to our store of medical knowledge, and through their use advances in medical technology have been made for the benefit of mankind. It is the intent of this article to attempt to review the role that the rabbit has played in contributing to biomedical research.

History of Rabbits in Research

Because general physiology of cells, sera, tissues, and organs of rabbits exhibit a similarity to that of humans, rabbits have been and will continue to be excellent models for many human diseases or conditions. The probability of finding an animal model truly identical to a specific human pathology is low. However, similar models do exist, and often the use of animal models in more than one species provides greater insight into determining the etiology of the disease entity for humans. The rabbit is large enough to provide adequate quantities of tissue for experimental work without pooling of samples but is small enough to be more economical than dogs or monkeys. Blood samples can be taken from birth onward in sufficient quantity to run a series of biochemical tests to study the effect of age during the development of a particular pathological condition. The rabbit provides an excellent mammalian model system to investigate placental transfer of drugs, metabolites, and steroids because both rabbits and humans have the same type of placentation (hemochorial), allowing the closest contact between maternal and fetal circulation (35, 60). Mutant bearing stocks and inbred strains of rabbits are valuable as animal models for studying vital processes related to disease of human beings. The intermediate body and skeletal size, ear vascularization, immunological response to antigens, timed ovulatory response, nest-building phenomena, response to presumptive teratogenic drugs, and the simplicity of care relative to the larger animals have given the rabbit a unique importance in biomedical research.

Historically, the rabbit was discovered in Spain about 1100 B.C. by the Phoenicians, and although some attempts at domestication were made during the Greek and Roman days, true domestication was not initiated until about the 16th century (26, 70). However, little in the way of breed formation or formal genetics was attempted until the early 20th century. Studies of the inheritance of size by MacDowell, Castle, Wright, Punnett, Bailey, etc. were initiated about 1910. The embryological basis of growth was demonstrated by Castle and Gregory in the 1930's. The rabbit has long been established as the most used subject for experimental ophthalmology, and the literature discloses investigations of various aspects of this animal's ocular anatomy as far back as the 17th century. Anatomically there are both similarities and differences between the eye of the human being and eye of the rabbit. It is perhaps true to say that while the gross anatomy and development, and some features of neurology and biochemistry in the rabbit are different from those of the human, there are valuable similarities in the electron-microscopic appearance of the tissue, some of the physical properties, physiology, and most biochemistry (75). Recent research involving one of the most promising new tools, the surgical laser, has been thoroughly studied using selected animals that simulate closely the human tissue response to this form of radiation. Animal models vary depending on the tissues to be irradiated. For studying the effects of the laser in the eye, the rabbit provides an excellent model system and has been used extensively in this area (21).

A few examples of early research where the rabbit was utilized to advantage are as follows. The first embryo transfer work was performed by Walter Heape in 1891 using rabbits to answer a basic scientific question concerning the influence on the phenotype of the embryo by the uterine environment. Many great discoveries were made during the 19th century that were the result of animal and basic research into diseases that plagued both humans and animals. Louis Pasteur has been credited with much of the early work on attenuated vaccines, probably his most notable work was on rabies, which he was able to attenuate through passage in rabbits. For

nearly a century Pasteur's vaccine was the only post-exposure treatment available for rabies in humans. The rabbit was also used by the physician Jean Villemin and the veterinarian Jean-Baptiste Chauveau to prove that tuberculosis was transmissible both by inoculation and by ingestion (21). The rabbit skeleton has also provided, for Sawin and co-workers use since the 1930's, a grid on which to unravel some of the mysteries of normal and abnormal growth and development. They used partially inbred stains having specific growth patterns and then superimposed a variety of dwarfing genes on this matrix to provide data for a series of articles from the 1940's through the 1970's. Their work has added considerable insight into the complex nature of the etiology of growth (81, 83).

Comprehensive reviews of much of the early literature can be found in the articles by Sawin (82), Nachtsheim (71), and Robinson (79). Two bibliographies, Herman in 1942 (55) and Makepeace in 1956 (67) provided over 8,000 references covering a variety of subjects with the rabbit starting in the late 1800's. The recent volume *The Biology of the Laboratory Rabbit,* published by Academic Press, provides an update to these early reviews and shows how the rabbit is used in many areas of biomedical research.

Medlars II, the National Library of Medicine's Medical Literature Analysis and Retrieval System, has in its data bank for the period since 1966 over 130,000 bibliographic citations linking the rabbit to studies in almost all areas of biomedical research. Major subject areas include genetics, blood, embryology, immunity, parasitology, physiology, neoplasms, anatomy and histology, growth and development, metabolism, and microbiology.

Research Areas/Systems in Which the Rabbit Has Been Used or Has Potential For Use

The rabbit as mentioned earlier has been contributing to new medical knowledge for many years. Probably the first reports were in ophthamological research as indicated in the 17th century. However, the rabbit has played a unique role in reproductive physiology since Heape in 1905 first noted that the rabbit was a reflex ovulator; i.e., ovulation can be induced and precisely timed, thereby increasing its usefulness in this area. Following Heape's observation, Walton and Hammond in 1928 reported direct observations of the rupture of the graafian follicle in the rabbit and set forth some of the earliest hypotheses explaining the mechanisms involved. The balance of this article discuss, by research areas or systems, many of the diseases and conditions, spontaneous, induced, or inherited, for which the rabbit has been used or has potential for use as an animal model and the human counterparts of those diseases and conditions.

Aging

Degenerative diseases occur in man and all other species with increasing age. The National Institute of Aging (NIA), National Institutes of Health, sponsored a task force of 50 scientists to review the use of various vertebrate species as animal models for research on aging. The committee report was published in 1981 entitled, *Mammalian Models for Research on Aging* (11). The section prepared by the Subcommittee on Lagomorphs and Rodents Other Than Mice contains considerable information citing the use and potential for future use of the rabbit as a model for research on aging. Good survival data under well-defined conditions is almost nonexistent. Rabbit breeders usually cull their animals as reproduction declines. Available data suggest a life span of approximately 8 years, although a few scattered reports suggest that under ideal conditions this may be increased to about double that number. One of the most significant pathogens, *Pasteurella multocida,* that is present in most rabbit colonies of the world and reduces life spans should be absent in any long-term study. There are a number of changes that have been observed in rabbits with increasing age. These are reviewed in the NIA report and include changes in blood components, cardiovascular parameters, endocrine levels, rate of cartilage formation, nerve responses to stimuli, and visual parameters.

The aging process in humans effects changes in all of the body systems and may lead to chronic and/or degenerative type illnesses that are not solely diseases of aging. These will be discussed under the heading of the system in which they occur

Alimentary

Cholera and Cystic Fibrosis

Cholera has recently been recognized as an enterotoxin-induced secretory disease of the small intestine. It is characterized by an absence of gross or microscopic destruction of mucosa and by the presence of a biochemical "lesion," namely an alteration in adenosine 3',5'-cyclic monophosphate (cAMP) of villous epithelial cells, induced by an exotoxin of *Vibrio cholerae,* and a consequent increased movement of water and electrolytes from plasma to gut lumen. Cholera enterotoxin induces chloride secretion; decreased sodium absorption; fluid, potassium, and bicarbonate efflux; and discharge and accelerated synthesis of goblet cell mucus. Affected small bowel loops are distended with translucent fluid containing flecks of mucus (rice water stools).

Cystic fibrosis is a secretory disease of a different nature. Originally named for the end-stage fibrosis and cystic dilatation of the pancreas, the disease has more recently been recognized as a generalized derangement in transport of electrolytes and production of mucus. Excessive loss of sodium and chloride occurs in sweat, salivary, and lacrimal glands, and excessive tenacious mucus is produced by intestines, pancreatic ducts, bile ducts, salivary glands, trachea, and bronchi. Recognition of the primary role of the abundant thick mucus has led to the synonym "mucoviscidosis." Clinical signs are a reflection of the organs or systems primarily affected. Hypersection of tenacious mucus in the neonate results in intestinal obstruction, known as "meconium ileus." Obstipation caused by tenacious intestinal mucus in later life is designated the "meconium ileus equivalent." Obstruction of pancreatic ducts leads to infantile loss of pancreatic function, accompanied by maldigestion and steatorrhea and followed by the classic fibrosis and cystic change. Occlusion of bile ducts by mucus results in a characteristic focal biliary cirrhosis, and hypersecretion of mucus in trachea and bronchi leads to classic respiratory "cystic fibrosis," a bronchitis, bron-

chiolitis, bronchiectasis, and emphysema, followed by pneumonia resulting from obstruction by mucus of the flow of air, and deranged ciliary activity.

Mucoid enteritis is a subacute fatal disease in young rabbits and has long been a major source of economic loss to commercial rabbitries. The consistent clinical signs and the characteristic postmortem findings enable accurate diagnosis of mucoid enteritis. One feature that is not to be found in this diesease is "enteritis." Mucoid enteritis is a misnomer, for there is no hyperemia, congestion, local leukocytic response, necrosis, or fever.

Mucoid enteritis of rabbits appears to be a subacute enterotoxin-induced secretory disease. As is the case in cholera, affected rabbits hypersecrete electrolytes, water, and mucus from a histologically healthy epithelium. The effects are of more insidious onset and longer duration than those of cholera. Although most published reports regard mucoid enteritis as a disease of 2–3 days' duration, careful observation will reveal signs as early as 7–8 days prior to death. The fluid-filled small-bowel loops in mucoid enteritis appear morphologically similar to the isolated loops produced by enterotoxin. The sodium levels in the fluid, as well as the serum electrolyte changes, suggest a secretory biochemical alteration of intestinal epithelium (61).

That mucoid enteritis of rabbits may be an animal model of cystic fibrosis is significant. Hypersecretion of mucus, mucous casts in glandular lumina, tenacious mucous plugs in intestinal lumen, inspissation of intestinal contents, secondary ileus, and succession splash are features common to mucoid enteritis of rabbits and the intestinal form of cystic fibrosis. Although other features of cystic fibrosis, such as deranged motility of cilia or excessive sodium and chloride in sweat and saliva, have not been shown to occur in rabbits with mucoid enteritis, the comparable aspects nevertheless deserve in-depth investigation. In vivo and in vitro studies of colonic mucosa of rabbits with mucoid enteritis should allow greater understanding of the biochemical alterations occurring in mucus hypersecretory states. Furthermore, mucoid enteritis may represent a link in pathogenesis, at the cellular level, between two previously unrelated types of human disease: enterotoxin-induced diarrheas and cystic fibrosis. Cholera is characterized by acute derangement of electrolytes, considerable secretion of water, and acute discharge of mucus; mucoid enteritis by subacute derangement of electrolytes, oderate loss of water, and subacute discharge of mucus; and cystic fibrosis by chronic derangement of electrolytes, slight loss of water, and chronic discharge of mucus (61).

Cancer

Herpesvirus-Induced Tumors

The model nonhuman primate systems used to date for investigations of *Herpesvirus saimiri* (HVS) and related oncongenic herpesviruses have limited availability and are expensive. Recent studies have demonstrated clearly the induction of malignant lymphomas in inbred rabbits. Unlike the primate model systems, the rabbits have the advantage not only of low cost and availability but also of the additional advantage of developing both histological types of lymphoma in response to HVS. The rabbits thus represent an excellent system for evaluating immunochemotherapy and antiviral and antitumor drugs, including interferon or cytosine arabinoside, on T-cell lymphomas. Moreover, they also provide an animal system to investigate the role of cofactors such as tumor promoters, chemical carcinogens, and herpesviruses in certain cancers such as Burkitt's lymphoma and nasopharyngeal carcinoma (1, 22).

Adenocarcinoma

The frequency of spontaneous endometrial carcinoma is especially high in older rabbits. Generally, human endometrial carcinoma is associated with glandular hyperplasia; rabbit carcinoma is associated with senile atrophy. Constitutional abnormalities, such as dwarfism and toxemia of pregnancy, are associated with endometrial carcinoma of the rabbit as often as diabetes, obesity, and hypertension are associated with endometrial carcinoma of humans. Although the relationship between hyperestrinism and human endometrial carcinoma remains controversial, senescence of the endometrium seems important in spontaneous adenocarcinoma of the endometrium of rabbits; the administration of estrogens appears to reduce the number of tumors. In humans, cessation of menstruation is related to the frequency of endometrial carcinoma, and hormonal dysfunctions, such as the Stein-Leventhal syndrome, have been associated with endometrial carcinoma in young patients. Further metabolic and endocrinological studies on the carcinogenesis of endometrial carcinoma of rabbits will contribute greatly to the elucidation of the human counterpart (3).

Wilms' Tumor, Nephroblastoma

Nephroblastoma in rabbits transplacentally induced by ethylnitrosourea (35) and spontaneous human Wilms' tumors are similar in many ways. Ultrastructural features of the renal blastema cells compared with the findings in human cases leads one to believe in an almost identical histogenesis of the rabbit and human nephroblastoma. The mesenchymal constituents in rabbits are less developed. Experimentally induced nephroblastomas in rabbits of the III/J inbred strain do metastasize and share many of the important characteristics of the human disease. This offers an opportunity to test chemotherapy or combined surgical and radiation treatment. Investigation with this animal model could be used to study the pathogenesis of Wilms' tumor in human beings (50, 51).

Lymphosarcoma

An inherited lymphosarcoma has been reported with a neoplastic involvement of lymphoreticular organs and other organs, especially kidneys, corresponding to a pattern observed in lymphosarcoma of other domestic animals. Specifically it resembles in many ways the visceral lymphosarcomatosis of cats, which has been proved unequivocally to be caused by feline leukemia virus. Rabbit and cat lymphosarcoma similarities involve both sites of onset and distribution of the neoplastic lesions and the hematologic findings of a predominantly aleukemic picture. This additional model is valuable for oncogenic studies (6, 36).

Cardiovascular

Systemic Hypertension

Here the rabbit has been utilized primarily to show the genetic relationship of blood pressure values. For example, selected strains of rabbits have been shown to

have increased systolic blood pressure of about 30–40 mmHg above normotensive animals. The frequency of hypertension could be increased in succeeding generations by selection and inbreeding (9, 38).

Cardiomyopathy

This is a nonspecific term applied to conditions in which the lesions are located in the myocardium rather than the other anatomic structures of the heart and not secondary to lesions primarily involving other cardiac structures. The term is very broad, encompassing a wide variety of etiologic agents. Although cardiomyopathy in humans is much less common than ischemic myocardial disease associated with coronary athrosclerosis, the condition is an important cause of myocardial failure often leading to severe functional decompensation and death. Cardiomyopathy has been reported in rabbits due to stress associated with severe crowding. Animals exhibited aggressive behavior during their confinement. At necropsy heart weight was normal, but there was dilation of the ventricles in most animals. Histologically there was myocardial edema with both myocytolysis and coagulative necrosis of myofibers. The multifocal areas of necrosis were replaced with fibrous connective tissue, and basophilic muscinous degeneration was a common finding in long-term survivors. The endocardium was thickened with collagen and elastic fibers in animals surviving over one month. Thickening tended to be focally concentrated at the apex of the ventricles. Although this model is not strictly a spontaneously occurring condition, it is useful for structural and functional studies of the diseased myocardium. There are similarities with etiopathic endomyocardiopathy seen in southern Africa. But the model differs in the extent of myocardial degeneration and fibrosis from either myocardial degeneration or myocardiopathy as usually encountered in western countries (10).

Hemorrhagic Shock

The rabbit is one of the few species that exhibits the myocardial zonal lesions following hemorrhagic shock as exhibited in humans. These lesions are not present in either squirrel monkeys or rhesus monkeys. Therefore, the rabbit provides an excellent model system in which to study such pathology (49).

Action Potential and Cardiac Excitability

The rabbit is one of the few species that shows the same high and more horizontal plateau of its electrocardiogram (ECG) present in humans and carnivora. The myocardial electrolyte composition is also quite similar. The T wave of the rabbit is quite similar in its polarity to that of the human, usually opposite to QRS in direction, and also shows the same changes as the result of drugs in electrocardiology, particularly in those experiments where there may be a risk of cardiac damage. Such experiments, investigating basic properties of cardiac muscle, can be done with a minimum of cost and equipment. ECGs of rabbit and guinea pigs, in fact, show the greatest similarity to human ECGs and provide excellent models for investigations concerning excitability, activation, and repolarization of the heart (65).

Atherosclerosis

Due to the limitations of studying atherosclerosis in humans, animals have become particularly important in atherosclerotic research. A large number of animal models have been developed. Rabbits were the first to be used as models of atherosclerosis. In 1908 Ignatowsky produced intimal lesions resembling human atherosclerosis by feeding diets of milk, meat, and eggs to rabbits. He believed that a high level of animal protein was the etiologic agent, whereas it was subsequently shown that cholesterol was the atherogenic component of the diet. Young rabbits undergo two different types of arterial changes. Schenk and co-workers have described spontaneously occurring mediomineralization in rabbits. These lesions occur primarily in the aortic arch and thoracic aorta, consist of mineralization of the media, and resemble Mönckeberg's medial sclerosis of humans. Zeek was able to breed rabbits selectively for the presence or absence of this type of arterial lesion. Rabbits fed a high-cholesterol diet develop an extreme hypercholesterolemia very rapidly. In addition to the arterial lesions induced, rabbits also deposit fat and cholesterol in most organs, resulting in a syndrome resembling more nearly a lipid storage disorder than atherosclerosis. Even though it is true that the condition in the subhuman primates probably more closely resembles the pathology in humans, the rabbit is still utilized by some as in important model particularly as a lipid storage disorder (8, 40, 53, 86).

Experimental Endocarditis

Polyethylene catheters with their tips at the entrance to or within the right side of the heart produce sterile marantic endocarditis and tricuspid valvulitis. Introducing as few as 10^2 microorganisms within the catheter predictably produces staphylococcal endocarditis. The course of the disease is variable, some animals surviving for six weeks. The technique is simple and does not require hemodynamic, immunologic, or endocrine manipulations of the animals. Splenomegaly was frequently found in association with endocarditis, but positive blood cultures were inconstant. Kidney infections were observed, but there were no examples of proliferative glomerulonephritis. This model is suitable for the study of the bacteriological, pathological, and immunologic aspects of bacterial endocarditis and reproduces some of the complications of indwelling venous catherization that have been observed in humans (41).

Drug Metabolism

Marijuana Psychoactivity

An inherited susceptibility in the rabbit to Δ^9-tetrahydrocannabinol (THC), the major psychoactive cannabinoid of marijuana (24), provides a new and exciting model for studying the psychoactivity of marijuana and related compounds. The major characteristics of cannabinoid-produced psychoactivity in humans, i.e., dose-effect relationships, minimally effective (intravenous) doses, specificity of response to only psychoactive cannabinoids, reversible tolerance development, EEG correlates, and cannabidiol-Δ^9-THC interactive effects are also characteristics of this new rabbit model of Paul Consroe at the University of Arizona, Tucson.

Amphetamine

The rabbit and other species were utilized to determine the pharmacokinetic constants describing the distribution and elimination of amphetamine in different species of domestic animals. An understanding of the metabolic pathways by which amphetamine is metabo-

lized in the rabbit, for example, and other species, gives us extremely useful information in understanding how these drugs may be metabolized in the human. For example, it was shown that oxidative deamination was the major metabolic pathway for amphetamine in the rabbit. A very small fraction of the dosage was excreted unchanged in the urine. This is in contrast to the carnivores, in which approximately one-third is excreted unchanged in this method (4).

Other genetic differences in drug metabolism are known and available in the rabbit including rapid and slow acetylators (54, 89) and the ability to hydrolyze atropinesterase and a number of related compounds (90).

Ear

Otitis Media

This denotes inflammation of the middle ear cleft and associated cavities, the eustachian tube, and mastoid air cells. It is an important and common cause of morbidity in children. In a retrospective study of children in South Carolina, 84% were found to have had at least one episode of otitis media, while 40% had four or more attacks. In certain population groups, for example, the North American Indians, the Alaskan Eskimos, and Australian Aboriginals, otitis media constitutes an even greater morbidity problem. Otitis media in the rabbit has been reported to be associated with *Pasteurella multocida* infection. Since a high proportion of the rabbit colonies throughout the world have *P. multocida* present in them, models for studying this condition are easily obtainable. In the rabbit the susceptibility to this infection is also under genetic control, and therefore by selection a high percentage of animals can be obtained having the right disease conditions (37, 68).

Eye

Entropion

In entropion the lid margin is inverted so that the lashes irritate the eye causing keratoconjunctivitis. Primary congenital entropion occurs with a reasonable frequency in rabbits and is probably under genetic control, thereby providing a good animal model for surgical or other treatments (42).

Glaucoma

The elevation of the intraocular pressure beyond the physiological norm often results in irreversible blindness through retinal and optic nerve degeneration. Glaucoma affects more than one million people and is one of the three major causes of blindness in the United States. The overall frequency in the human population above 40 years of age is approximately 2%. This frequency increases with advancing age. In infants and children, congenital and pediatric glaucoma is a significant cause of blindness. Glaucoma is a condition, however, with multiple etiologies. Many forms are asymptomatic until they produce extensive irreversible damage. The rabbit and the dog provide the two most commonly utilized models for study of glaucoma, and in fact the inherited glaucoma in the rabbit has probably been studied more extensively than in any other species. Associated with the glaucomatis condition in the rabbit, however, is a reduction in fertility that has made it difficult at times to provide sufficient numbers of young animals for experimental work (43).

Albinism

This is an inherited disorder of melanin metabolism in humans in which the melanocytes of the eye, skin, or both fail to produce the normal amount of melanin. There are a variety of metabolic conditions that result in albinism: from a defective tyrosinase, which reduces the transformation of tyrosine to melanin; to another inherited condition where the tyrosinase is present and partial pigmentation may result, particularly common in blacks; to a third condition or sex-linked disorder for which the metabolic defect is unknown. The rabbit along with many other species provides a model of albinism. In fact with the rabbit there is a graded series of alleles at the C locus providing a stepwise reduction in color, thus giving a gradual system to help unravel the etiology (44).

Optic Nerve Hypoplasia

Hypoplasia of the optic disk and nerve may be unilateral or bilateral, vary in the extensiveness, and be associated with good or reduced vision. It may produce amblyopia, nystagmus, strabismus, and inability of visual fixation. The condition may occur by itself or associated with other ocular and forebrain malformations. Uni- or bilateral optic nerve hypoplasia has been reported in rabbits and other species (45).

β-Adrenergic Response

Research utilizing the rabbit has enabled investigators to conclude that decreased β-adrenergic responsiveness, the common pharmacological effect of the iris-ciliary body following either topical timolol or epinephrine, may be responsible for the decrease in aqueous humor formation observed in human glaucoma patients using these medications. The investigation with the rabbit shows that the timolol, which has a high receptor affinity for β-adrenergic receptors, binds reversibly to ocular pigment, thus prolonging its bioavailability as a β-adrenergic antagonist. In addition, the topical epinephrine has two time-related effects, an initial β-adrenergic-adenylate cyclase stimulation followed by β-adrenergic-adenylate cyclase desensitization. Use of the rabbit in ocular research here has added one more dimension to our knowledge regarding the control of elevated intraocular pressure associated with human glaucoma (5).

Outflow Facility

Glucocorticoids have been shown to increase intraocular pressure in sensitive humans and in young rabbits. The mechanism of this effect appears to be related to a decrease in the facility of outflow of aqueous humor. It has been postulated that this decreased facility is due to an alteration in extracellular matrix components, such as glycosaminoglycans, in the outflow pathway and collagens. Results using the rabbit as a model system suggest that dexamethasone causes an increase in collagen synthesis in the target cells most closely related to the outflow pathway. Further it suggests decreased synthesis of glycosaminoglycans, glycoproteins, or possibly glycolipids in these same cells (56).

Genetics/Heredity

Prior to 1900, only minimal work had been done on the genetics of the rabbit. Even though the dominance of wild type over nonagouti and other genes was known as early as 1683, it was not until the need for developing

various breeds of rabbits that the early genetic studies of coat color and hair morphology by pioneers such as Castle and others were initiated (26). Recent genetically determined animal models not discussed in detail elsewhere include diaphragmatic hernia (30), vestigial pulmonary arterial trunk (14), retroesophageal right subclavian artery (15), adrenal hyperplasia (31), macrostomas, a model for Treacher Collins syndrome (33), left ostium straight (16), and narrow axis, an anomaly of the second cervical vertebrae (17). These models, if exploited, can add additional breadth to our store of knowledge.

Genital Tract

Gonadal Dysgenesis

Dysgenesis of the gonad occurs in many species including humans and in a variety of forms. They may be associated with such cytogenetic disorders as the classic Turner's syndrome, Klinefelter's syndrome, or with a variety of less well-defined conditions with or without chromosomal involvement. The disease in humans may be spontaneous or have a familial basis. Hypogonadia in rabbits causes partial or complete sterility in both sexes. Gonad size is markedly reduced and associated changes in secondary sex characteristics and histological changes in the gonad are evident, thus providing a model for some forms of gonadal dysgenesis (34).

Hematopoietic

Coagulation

The use of isolated rabbit livers and spleens in a profusion apparatus has enabled the investigation of coagulation factors VIII and IX for some important human pathologies, von Willebrand's disease and hemophilias A and B. The similarity of the perfusion in the rabbit and human systems enabled researchers to utilize the rabbit for investigations of this human problem (19).

During the isolation of dicumarol and its related compounds rabbits were used as test animals, in part because some of them were found to be resistant to the drug on a genetic basis. Dicumarol, which is used extensively in dealing with thrombosis problems, acts by reducing the concentration of the plasma prothrombin complex. It antagonizes the function of vitamin K. Because of the availability of the rabbit, scientists were able to isolate dicumarol, which then enabled them to expand their knowledge about the blood coagulation abilities of vitamin K. The various experiments that ensued alerted investigators to the possibility that vitamin K might be useful for human beings afflicted with obstructive jaundice (84).

Pelger-Huët

This inherited anomaly of human leukocytes is characterized by distinctive shapes of the nucleus of leukocytes, by a reduced number of nuclear segments best seen in neutrophils, and by coarseness of the nuclear chromatin of neutrophils, eosinophils, basophils, lymphocytes, and monocytes. Rodlike, dumbbell-shaped, and peanut-shaped nuclei with smooth, round, or oval individual lobes contrast with the irregular lobes seen in normal neutrophils. As a result, the granulocytic nucleus appears young in shape but old in structure. The Pelger-Huët anomaly may be a feature of preleukemia. This anomaly has been discovered in rabbits and due to the inherited condition has been maintained in Germany and is available to the scientific community for studying this particular condition. In the rabbit skeletal malformations are often associated with the blood disorder (23).

Complement

There are at least 18 distinct serum proteins compromising the unactivated complement system in humans. There are also numerous deficiencies of the complement system's proteins, more so, in fact in humans than in the various animal models. The rabbit provides a model system for deficiency of C6. It is inherited as an autosomal recessive trait in both species. In the rabbit there are prolonged clotting times and retarded prothrombin consumption. This can be corrected in the rabbit by the addition of purified C6. To date similar studies of C6-deficient humans have not provided evidence of this coagulation abnormality (2).

Immune System

Tumor Immunity

Neoplastic transformation of rabbit cells by Kirsten murine sarcoma virus (Ki-MSV), the Ki-MSV pseudotype of baboon endogenous virus [Ki-MSV(BaEV)], and the Moloney-MSV pseudotype of feline leukemia virus [M-MSV(FelV)] provides both virus producers transformed by Ki-MSV and Ki-MSV(BaEV) and nonproducers transformed by M-MSV(FelV). The ability to produce sarcoma in rabbits should provide a useful additional model for studying chemo/immunotherapy as well as immunoprevention of rabbit cancers (76).

Immune Damage

An animal model of hypersensitivity pneumonitis is reported. Rabbits were sensitized with ovalbumin in complete Freund adjuvant. Three weeks after immunization, the animals were placed in an aerosol chamber and challenged with ovalbumin in 0.15 M sodium chloride aerosolized by ultrasonic nebulization. The amount of antigen retained after challenge was studied using ^{125}I-labeled ovalbumin and was found to be approximately 0.2% of the total aerosolized antigen. Histologically, lesions in the lungs were seen by 24 hours and had essentially cleared at 6 days. Abnormalities included thickening of alveolar septa and increases in mononuclear cells, lymphocytes, phagocytic macrophages, and eosinophilic granulocytes within alveolar walls and spaces. Distribution of these lesions was patchy, involving most conspicuously the alveolar ducts distal to the termination of respiratory mucosa, thus illustrating an allergic alveolitis. Other histological abnormalities included peribronchiolitis and vasculitis. No similar lesions were seen in unsensitized challenged animals or in sensitized unchallenged control animals. This model allows study of the pathogenesis of hypersensitivity pneumonitis and elaboration of the role played by the lung in various types of immune damage (77).

Integument

Contact Dermatitis

Dermatitis caused by exposure of the human skin to various chemical compounds is well known. Substances with which people come into contact in their work, such as synthetic resins, turpentine, acids, and alkalis, are

possible contact irritants. A variety of other substances are either common allergens or substances or plants producing irritation and/or allergenic compounds. Two clinical entities are included in the syndrome of contact dermatitis. These are allergic contact dermatitis and irritant contact dermatitis. The rabbit is one of the few species commonly used to illustrate and study these two conditions (39).

Hyperpigmentation

Hyperpigmentation of exposed skin areas, comparable to that seen in less than 1% of patients chronically dosed with chlorpromazine after intensive long-term therapy, has been produced in 16 out of 16 chronically dosed pigmented rabbits, receiving between 20 and 30 mg/kg per day. Thirty minutes ultraviolet irradiation of a clipped or shaved area produced clear-cut hyperpigmentation of naturally pigmented skin areas in about 4 weeks. The characteristic occurrence of granular pigment in the dermis, which is normally free of pigment, was also observed. Hyperpigmented rabbits did not develop any concomitant ocular pathology, as seen in some patients on long-term high-dosage chlorpromazine therapy (25).

Nervous System

Hydrocephalus

In this disorder there is an increased quantity of cerebral spinal fluid in the ventricular subarachnoid system. Hydrocephalus can be induced easily in rabbits; feeding the pregnant doe a vitamin A-deficient diet results in a high frequency of hydrocephalic young. The critical maternal blood level of vitamin A, below which a significant frequency of hydrocephalus was seen, was about 30 mg/100 ml of serum. Both the frequency and the degree of hydrocephalus vary in part by the level of vitamin A provided the pregnant doe (52, 59).

Spina Bifida

This is frequently a devastating condition in humans that varies greatly in the expression of the condition from a small blip often in the lumbar area to rather extensive involvement of the spinal column. Both conditions have been reported in the rabbit: the small localized condition reported by Nachtsheim (71); and an extensive bifid spine being reported by Crary et al. (18) and Kitchen (58).

Syringomyelia

In humans the basic lesion in syringomyelia is a fluid-filled tubular cavitation or syrinx that extends through many spinal cord segments. The rabbit model has an average age of onset for this inherited condition (*sy/sy*) between 4 and 6 months of age. Both sexes are affected (66).

Respiratory

Emphysema

"Emphysema is a condition of the lung characterized by an increase beyond the normal size of air spaces distal to the terminal bronchiole with destructive changes in their wall." Emphysema can be subdivided into panlobular, centrilobular, paraseptal and irregular emphysema, depending on which part of the respiratory acinus is predominantly affected. The different forms may occur together and the actual lesions observed do not always fall into clear-cut categories. Emphysema is found to be fairly common in older rabbits, particularly those that are 2.5 years or more of age. The emphysema was irregularly distributed and largely of the panlobular type (87).

Skeletal

Achondroplasia

Achondroplasia is a skeletal dysplasia with predominantly metaphyseal involvement. It is defined as a disproportionate-limbed dwarfism with rhizomelic accentuation. Achondroplasia and related syndromes have been described in many species. There are four genetic conditions in the rabbit that have resulted in a form of achondroplasia; these are associated with the *ac, Da, cd,* and *Pg* genes. The analogy of the twentieth century animal models to human achondroplasia has been based primarily on gross morphology of the skeleton. Some more recent histological and clinical chemistry data are being reported allowing a better comparison with specific human disorders. References to the rabbit and a variety of species are given in the review by Fox and Crary (32).

Cleft Palate

This is characterized by a cleft of variable size extending through the hard palate or soft palate or both. Cleft lip or harelip may be a unilateral, bilateral, or median cleft of the upper lip, which may extend superiorily to involve the nose. Both conditions have been observed to occur in rabbits and are thought to be due to an interaction of genetic and environmental influences. These have been observed to be present with a variety of associated defects including hydrocephalus, spina bifida, kyphosis, and chondrodystrophic and achondroplastic dwarfism (46).

Arthrogryposis

Arthrogryposis multiplex congenita is a syndrome characterized by congenital immobility of the limbs with fixation of multiple joints in either flexion or extension and with muscle wasting. It occurs in two forms, one of myogenic origin and one of neurogenic origin. Data from the Jackson Laboratory (Webber, Fox, and Crary, unpublished observations) show that lethal muscle contracture, an inherited condition in the rabbit, exists and is being used by three investigators now to develop a model system for studying this condition (47).

Kyphosis

The curvature is rarely encountered as a single entity but is often associated with syndromes. In the rabbit, kyphosis occurs in most rabbits with the recessive trait for spina bifida. This conditions mimics some human conditions associated with spina bifida (48).

Syndactyly

This abnormal union of the digits is generally restricted, in humans, to a soft tissue union or webbing between the fingers and toes. It occurs in association with other malformations in a variety of species including the rabbit where it is frequently associated with ectrodactyly (hypoplasia of the extremities, total or partial absence of the fingers or toes) (64).

Ectrodactyly

Human ectrodactyly has many forms and the etiology is unclear, although both genetic and environmental factors are undoubtedly operative. The brachydactyly

mutation in the rabbit available in France provides a model in which prevention of the limb amputation is possible by hyperbaric conditions, thus allowing investigation of the etiology of this pathology (20, 69, 74).

Mandibular Prognathism

This is a condition where the lower jaw is either larger than normal or occludes in a position forward to that which is normal. The etiology may lie in genetic patterns noted historically in the royal families of the Hapsburgs or it may be the result of an oversecretion of the pituitary gland as in acromegaly. The human literature on this subject is quite variable and confusing. Mandibular prognathism in the rabbit appears to be due to a decreased length of the maxillary diastema. A similar cause has been reported for humans. A hereditary basis for the occurrence of this prognathism in the rabbit is very strongly suggested, making it a readily available model (29, 57).

Osteopetrosis

Human osteopetrosis is an inherited disorder characterized by severe generalized osteosclerosis. Other radiographic abnormalities include increased bone density, lack of corticomedullary differentiation, metaphyseal splaying, "bone in bone" effect, and transverse rarefaction lines in metaphyses and vertebrae. The radiographic abnormalities may be discovered as an incidental finding in asymptomatic adults. A hereditary condition in the rabbit associated with the autosomal recessive gene *os* and phenotypically resembling Albers-Schönberg's disease is being used by Dr. Sandy Marks to investigate this condition (88).

Musculoskeletal System

Osteoarthritis

Degenerative arthritis has been produced consistently in adult rabbits by the injection of the proteolytic plant enzyme papain into the hip joint. Arthritic changes were recognizable radiographically after 6 weeks. A progression of changes occurred, from loss of acid mucopolysaccharide staining in the matrix, fibrillation, fissuring, and erosion of articular cartilage with death of chondrocytes in the weight-bearing areas to secondary bony changes of subchondral sclerosis, occasional cysts, and osteoformation. Synovial inflammation occurred with accumulation of cartilage and bone debris in the inferior capsule and later capsular thickening. This arthritis is sufficiently similar to human osteoarthritis to be useful as a model for further studies of the pathogenesis of the disease and the effects of different methods of treatment (7).

Osteomyelitis

Since the advent of antibiotics, acute osteomyelitis has become a less frequent cause of admission to the hospital and mortality from the disease has declined. Chemotherapy is not, however, a panacea, and chronic osteomyelitis still develops with disturbing frequency. The injection of *Staphylococcus aureus* recovered from a child with osteomyelitis into rabbits produces a model whose pathological and radiological appearances are similar to the human disease. Exploitation of this model may aid in answering questions about the pathogenesis and therapy of osteomyelitis (73).

Urinary System

Cystic Disorders of the Kidney

These vary greatly in their age of occurrence, whether they are unilateral or bilateral and whether they involve the cortex, medulla, or both. They range from large polycystic kidneys that usually result in morphological changes and reduced renal function to small cortical benign "simple" cysts. An autosomal recessive model for the "simple" cysts has been reported in the rabbit. Both sexes are affected. The cysts are not usually observed until the animals are about one month of age or older. They appear to be of tubular origin and found in the cortex (27).

Vesicoureteral Reflux

Normally when the bladder is emptied, a valvular mechanism prevents the urine from reentering the ureter. When this mechanism is abnormal in humans, a reflux of urine back up the ureter occurs during voiding. This can occur in children with urinary tract infections. Reflux occurs in 40–80% of rabbits depending on the particular report. Specific strains and sex differences may be a factor here. Under properly controlled conditions the rabbit provides a fertile field for studying the relations among bacteria, reflux, and pyelonephritis (78).

Diabetes Insipidus

The syndrome of diabetes insipidus characterized by excessive water drinking and voiding copius amounts of dilute urine has been reported in humans and several animal species including the rabbit. In the rabbit this has only been reported as a case report to date. However, if additional cases are found and particularly if an hereditary basis for this is observed, the rabbit would provide a good model system for studying primary polydipsia or the abnormal urge to drink water. Diabetes insipidus can actually be traced to one of three basic defects: *1*) the ability to synthesize and/or release vasopressin, i.e., the hypothalmic diabetes insipidus; *2*) the inability of the kidney to respond to antidiuretic hormone; and *3*) the abnormal urge to drink water (85).

Diabetes Mellitus

Human diabetes mellitus is not a single disease but rather a group of disorders having in common hyperglycemia. The two major categories include type I or insulin dependent, which is characterized by an absolute deficiency of insulin, and type II or noninsulin dependent, where insulin is present but still not able to maintain glucose hemeostasis (62). Rabbit models for investigating this important disease include both L-asparaginase-induced (63) and inherited (13, 80) models.

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Health Benefits of Animal Research

The preceding article is the fourth in a series dealing with different species of animals in research. It is planned to subsequently reprint these articles as chapters in a book, *Health Benefits of Animal Research,* with introductory material and an index edited by Dr. William I. Gay.

Reporters and Researchers Both to Blame in Telling the Real Story

The following was presented by Dr. **Walter C. Randall** at the Society's Public Affairs Committee Workshop in Lexington, KY. Dr. Randall was on a panel with representatives from the press and media to discuss the roles and responsibilities of reporters and researchers in newsworthy events.

"It is difficult for experimental physiologists to understand what the flack is all about in reading newspaper editorials and watching television accounts of alleged cruelty or mistreatment of animals in a modern research laboratory. In our (physiolgists') real world we know such cruelty or mistreatment to be very rare. As a result, you and I, together with a vast majority of our scientific colleagues, have simply ignored the charges; we have done nothing to refute the nonsense; and we have made almost no remonstrance to the completely irresponsible reporting of the news.

"We know with certainty that animals are used as substitutes for human beings in research. We understand that virtually every advance in medical science has been predicated upon knowledge gained through experiments involving animals. The benefits to mankind from these achievements are staggering, yet sometimes difficult to measure. Each of us has specific examples which document our case (control of diabetes, poliomyelitis, infectious diseases, heart disease, endocrine disorders, you can name it within your own research field); and we know that virtually every human alive has profited from such contributions.

"We have lived through 80% of the research upon which modern medicine's spectacular ability to handle disease is now based. We can reflect upon situations in our own lifetime when nothing could be done to relieve pain or to avoid deterioration and death. But, because of our research, those situations have dramatically abated. Still, we recognize that much remains to be done and animal models continue to be critically essential to further advances in medical knowledge and treatment.

"Where is all the mystery about the necessity of further animal research? From whence comes all the rhetoric? Who thinks up these horror stories that generate thousands of letters to Congressmen who, in turn, draft bills which would legislatively terminate much biomedical research? The termination of the very research which has resulted in such dramatic decline in the death and suffering of their constituents, their colleagues, and their own families.

"I have indicated the complacency of you, my scientific colleagues, in the face of a critically threatening situation. I have called a large portion of the reporting by the press and the media as 'irresponsible journalism.' Both indictments are intended to bring out a smoldering flame which burns beneath it all. We need to learn what fuels the flame and how to extinguish it.

"Animal rights activists object to all sacrifice of animals for the benefit of humans. A few even refuse to eat meat. However, most of their rhetoric is based upon poorly informed, superficial, and emotional arguments. Animal welfare advocates see the question as a moral issue and insist that animals be used only when absolutely necessary. They want animals to be cared for properly and to suffer as little as possible. They want experiments to be carried out in a truly scientific manner, and they want the results to be disseminated so that duplication of experiments may be eliminated.

"Physiologists are interested in the animal's welfare too. Many are totally dependent upon whole animal models, while others require living cell preparations or fractions. But we are also aware that most of the dogs and cats employed in research are doomed to die prematurely because they have been abandoned by their owners. When caught they will be impounded and killed, generally not too humanely. Some 12–15 million cats and dogs are killed every year by the pounds, simply because there is no other way to handle them. We use only 1 or 2% of this number in research and very rarely is such an animal subjected to physically painful manipulations. True, there have been a few dramatic illustrations of potentially painful experiences, but what can be more terrifying than the picture of an infant pulling a scalding kettle from the stove, a fiery crash on our expressways, or a flaming torch that was once a military vehicle in Lebanon?

"You and I remember when people who suffered burns over 50% of their bodies had no chance of survival. Today they can expect to live, thanks entirely to anesthetized animals employed in burn research. Dr. Howard Green, Chairman of Physiology at Harvard University, recently explained how research on cultured human skin saved the lives of two boys who sustained severe burns over 97% of the body surface. He states, 'I fully appreciate the desire of animal lovers to see as much research as possible carried out in cultures rather than on animals. But if no animal research were permitted, even the materials for cell cultivation would be lacking. Extension of basic discoveries to human treatment would become quite impossible. . . . Those who advocate prohibition of animal research may love animals, but they do not understand what the effects of such a prohibition would have on all those children and adults who benefit from medical research.'

"All of these arguments and illustrations are totally (and probably nauseatingly) familiar to you. But I remind you that we will soon be out of business because of your complacency—your almost total lack of expressed concern for the problem. Like me, you have never 'had time' to talk about your research before your local Kiwanis or Lions Club, or the JayCees. Therefore your neighbors know little or nothing about the problem. They (neighbors) elect what seem to be reasonable business men, politicians, or lawyers to represent them in the Congress. They (neighbors) assume these representatives know what they are doing when they vote to elimi-

nate use of pound animals or to assure that 25% of the research funds appropriated for the National Institutes of Health be directed toward the development of substitutes for animals in research. The legislator knows full well what computers have done for business, so it's reasonable to him or her that the computers can be programmed to substitute comparable miracles in medical research. You haven't told him or her that you must learn facts through experimentation before they can be fed into a computer. You haven't told him or her that you can't learn to control his or her hypertension by working solely with cell cultures.

"Recently I was approached by the program chairman of my local Kiwanis Club and asked to speak about my experiences last fall in Mainland China. I agreed to do so, provided he give me equal time to talk about the role of animals in cardiovascular research. He looked surprised and said his program was already filled except for the hour for the China talk. I told him that this hour remained open because without the one topic, I wouldn't give the other. He found the time for both and the Kiwanis members were profoundly interested in how animal research had made possible their own bypass operations, how insulin had kept a wife alive and comfortable, and how measles and polio were brought under control.

"I called the newspaper and television handling of the problem irresponsible. I realize their daily papers must attract attention in order to sell and that the broadcasters must attract an audience. It is an old story that good deeds do not make good news. But why do such stories almost invariably exaggerate our mistakes, falsify facts, or actually manufacture fake illustrations of our cold and calloused handling of animals? Virtually all laboratories utilizing mammals in research have submitted their protocols for critical evaluation by peers in the field of research involved. The most authoritative opinions available have been directed to the evaluation of these protocols. Why does the reporter or editorialist accept exclusively the view of the radical activist who may or may not be a novice scientist? Why does the reporter allow his emotional love for a pet to denigrate all medical research utilizing humanely treated, anesthetized animals and animals otherwise destined to die in the pound? Why doesn't he check out his story before it is published? Why does the editor print the story which damns all of medical research without so much as questioning its source or the validity of its premise? If the editor did so, I can't believe that he would permit his paper to tell such one-sided stories or that he would totally omit the overwhelmingly constructive side of the story describing the marvelous contributions of animals in medical research.

"I spent the last three weeks in the distribution area of *The Buffalo Evening News.* It featured stories nearly every day on the marvelous advances in treating heart disease, including heart transplantation. Not a single mention of the crucially important contributinos of animals to that spectacular success story in medicine. Why? It is a marvelous opportunity to explain why cardiac transplantations virtually stopped a few years ago, due to inadequate fundamental understanding of immunochemical rejection reactions and that only through animal-based research were those problems solved so that transplantation can now be resumed. And note the headlines of Saturday's (8/25/84) *Lexington Herald-Leader,* 'Heart Patient in Louisville Has Transplant.' The article demonstrates beautifully the imminent availability of this modern medical miracle to Kentuckians, but not a word about the intervening years of careful research upon experimental animals which made it possible.

"The nation's outstanding newspapers have featured stories originating in supposed violations of animal welfare codes, often without probing to learn the truth about their so-called exposes. They write screaming headlines without printing the other side of the story. Television shows have featured film directly from the animal rights antiresearch files without questioning their validity or general applicability. *USA Today* (8/5/83) attempted to present both sides of the question but commissioned their cartoonist to feature a caricature of a terrorized cat, which revealed their 'front-and-center' position.

"How can the American public hope to achieve a real understanding of the proper role of animals in biomedical research today? How can the American Physiological Society correct the misrepresentations which are being foisted upon the Congress and the public? We need help from the experts in this form of communication; from a responsible news media, which can teach us how to go about it and who will tell both sides of one of the most dramatic and important stories of the entire century. What could be more exciting to readers than to hear about a battle in which 300,000 Americans are saved annually rather than killed by cardiovascular diseases? This is the stuff good stories are made of and research involving vitally important animal models is at its very core."

Past President's Address

It Was A Good Year

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In one of his better-known aphorisms, Hippocrates acknowledged somewhat wistfully that life was far too short for all that had to be learned and done. This sentiment applies equally to the presidency of the American Physiological Society. The presidency affords little opportunity for deep reflection and far-sighted contemplation (Figure 1). Instead of gazing reflectively from afar, the President is immediately directed into an unfamiliar forest (Figure 2) of policies, rules, strategies, uncertainties, and decisions that can be appreciated but not extensively explored within the short span of one year.

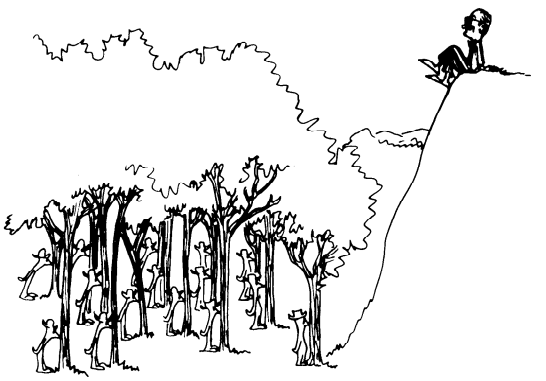


Figure 1
Before assuming office. The *President-elect* anticipating the opportunity to contemplate the forest and the trees before assuming office. This is a mirage.

A summary of all that the President encountered can be found in the archives of the Society. In this report, I confine myself to a few areas that I probed in depth. And I leave to my successors the responsibility for depicting current initiatives and ongoing activities with which they will be preoccupied. Among those on the horizon are the outcome of the search for a successor to Dr. Orr Reynolds as Executive Secretary-Treasurer, the prevalent restlessness about the future of physiology, the need for defining the territorial imperatives of physiology within the broad sweep of the life sciences, future prospects for scholarly activities and livelihood of Ph.D.'s in physiology, enhancing the roles played by women and minorities in physiology, the vitality of future meetings and publications of the Society, future relations of the Society to the Federation (FASEB), academic-industrial relations as they apply to physiological research, and the position of the Society as a pacesetter among the life sciences. Each of these topics has become an important consideration of the Council and each warrants more time than I am allotted for the presentation.

I will deal briefly with the following: the continued progress of the American Physiological Society toward sectionalization; animal welfare and experimentation; the American Physiological Society in international physiology; the continued need for long range planning. Although each is presented separately, all should be considered within the framework of the future of physiology.

Presented at the Fall Meeting of the American Physiological Society, Lexington, KY, August 1984.

The Continuing Move Toward Sectionalization

Looking back, during the 14 years that I served on the Publications Committee and the 7 years or so that I attended meetings of Council as Chairman of the Publications Committee, the Society has moved slowly but inexorably to accommodate the trend to specialization in physiology. This progression is readily traceable on three fronts: the internal structure of the Society, the programs of the Society, and the publications of the Society (Figure 3).

Internal Structure of the Society

Until 1954, special interests in physiology were satisfied by unofficial gatherings at the time of the American Physiological Society's annual rites of spring. These groups conducted their affairs in personal encounters and gatherings as only remote concerns of the President and Council (Figure 4). Occasionally, the unmet needs of these groups for meetings, programs, and publications led to annoyance and frustration followed by mounting pressures for independence. The first instance of this kind occurred a few years after the founding of the American Physiological Society in 1887 when psychologists formed their own society. Again, in 1906, another group of rebellious physiologists founded the American Society of Biological Chemistry. Further outcroppings did not occur for the next 40 years. But

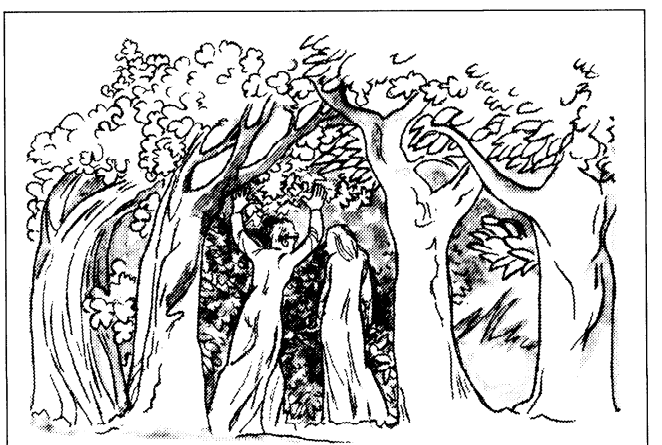
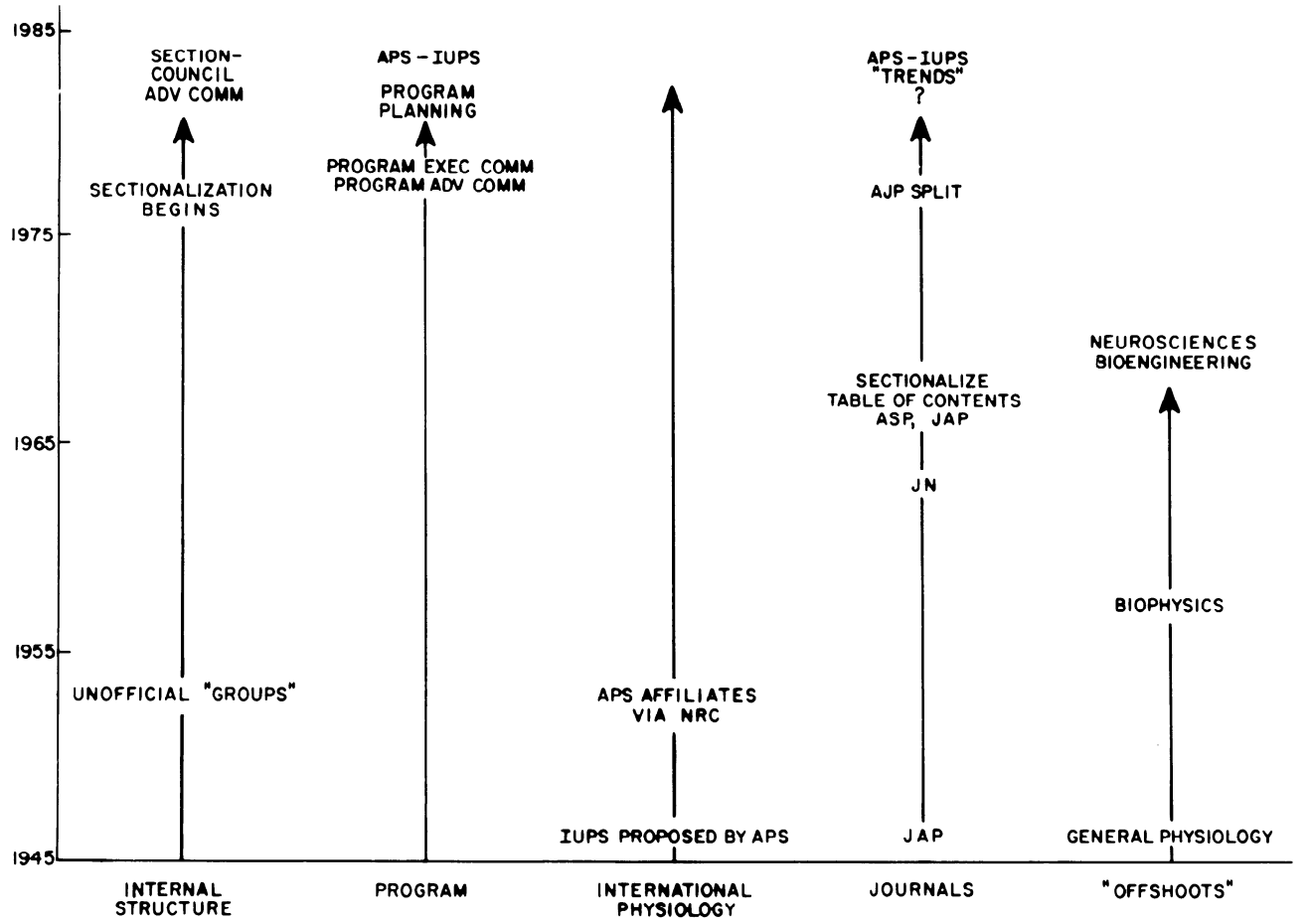


Figure 2
Once in office. The President and the Executive Secretary-Treasurer of the American Physiological Society. Entering the forest of policies, rule, strategies, uncertainties, and decisions.

Figure 3

Highlights in the moves to sectionalization with respect to the internal structure of the Society, the programs of the Society, and the publications of the Society. For reference, also shown is the role of the American Physiological Society in international physiology and the emergence of new scientific societies as offshoots of the American Physiological Society.



then general physiologists budded off to form a new society in 1946, biophysicists in 1956, and neuroscientists in 1968. Each time that one of these groups went its own way, the American Physiological Society took stock of its goals and flexibility with respect to emerging frontiers in the physiological sciences.

Each separation to form a new society was a disappointment to the American Physiological Society. Of all the fundamental sciences, physiology has traditionally stood for integration and coordination. The *American Journal of Physiology* exemplified the global aspirations of physiology as a science. Fractionation of the Society not only amputated a portion of its corpus but also strained the remaining fabric and threatened future disruption.

One clear alternative was reorganization of the Society and journals to anticipate and accommodate new areas and directions in physiology. One solution was sectionalization according to specialties in physiology. Over the years, this prospect was repeatedly discussed, usually with animation and occasionally with great heat. But not until 8 years ago was a consensus reached that the Society would survive sectionalization. Since then implementation has moved ahead at full speed (Figure 3). In 1984, a high point in the move toward sectionalization occurred with the establishment of the Section Advisory Committee, a body comprised of section leaders who can communicate directly with the Council and the Long Range Planning Committee (Figure 5). The first meeting between Council and the Section Advisory Committee this year was reminiscent of the first meeting between friends acting as negotiators for different constituencies, willing and even anxious to cooperate but not knowing what to do or how to do it. But one outcome of the meeting was the awareness that the Section Advisory Committee needs to develop a workable organization that can relate to Council. And, as soon as that is done, the Committee has to tackle the formidable problem of standardizing the composition, organization, and operating procedures for each section. All involved in the first meeting recognized that sectionalization and the creation of the Section Advisory Committee provide a new mechanism by which special interests of physiology can be cultivated within the framework of the Society and by which members of Sections—future as well as present (Table 1)—can have ready access to the planners and policy forming components of the Society.

Table 1

APS Sections—1984

Cardiovascular	History of Physiology
Cell and General Physiology	Nervous System
Comparative Physiology	Neural Control and Autonomic Regulation
Endocrinology and Metabolism	Renal
Environmental, Thermal and Exercise	Respiration
Epithelial Transport	Water and Electrolyte Homeostasis
Gastrointestinal	

Sectionalization and the Scientific Programs

One major reason for the existence of the American Physiological Society is its scientific meetings, particularly the spring meeting. Until 1976, the program for the spring and fall meetings was pieced together by the administrative staff in Bethesda with the help and advice of ad hoc committees. In 1976, a task force appointed by Council (that I chaired) recommended a new system consisting of two tiers: a Program Executive Committee charged with making final decisions and a Program Advisory Committee that would develop the components of the program with the advice of the individual sections of the Society (Figure 3). This plan was adopted and seems to be operating well. Not only have the programs of the Society benefitted from the new arrangement, but the Program Executive Committee is becoming increasingly involved in the shaping of international programs, especially those under the aegis of the International Union of Physiological Sciences. It is also destined to play a key role in organizing the schedule of topics and speakers for the centennial celebration of the Society in 1987.

Figure 4
Until 1954, special interests in physiology were encouraged by the American Physiological Society in the form of personal encounters and small meetings that occurred beyond the direct line of vision of the President and Council.

Sectionalization and Publications

There seems to be little question that the split of the *American Journal of Physiology* into five independent journals has been both a scientific and financial success.

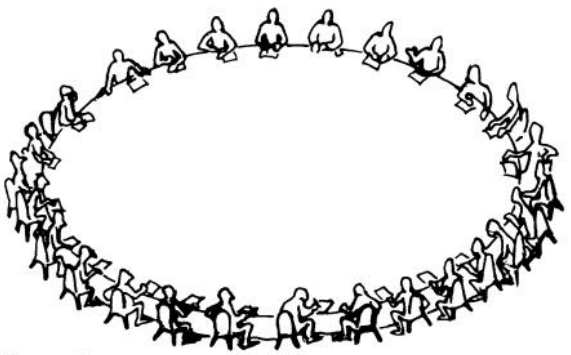


Figure 5
Joint meeting of the Section Advisory Committee and the Council. By this arrangement, section leaders and their constituencies are ensured direct access to the Council (and to the Long Range Planning Committee).

Figure 6
Creation of an international journal jointly with the International Union of Physiological Sciences has been a long hard climb.

This success story has been amply documented elsewhere (1). However, in addition to providing for the immediate needs of the specialties in physiology, this move also anticipates the likely need for new specialty journals as emerging fields in physiology find that opportunity for publication and access to the proper audiences are not adequately provided for by existing journals.

A new initiative with respect to publications is an ongoing effort with the International Union of Physiological Sciences (IUPS) to create an international journal of physiology (Figure 6). Deeply engaged in orchestrating and implementing this venture are Drs. Schmidt-Nielsen and Valtin for the IUPS and Drs. Morgan and Fishman for the APS. Dr. Reynolds and Mr. Geiger have been invaluable allies. It is anticipated that the new international journal will feature science news, reviews, and perspectives rather than the traditional scientific papers now published in the journals of the Society. The major goals of the journal will be the timely depiction of news of interest to physiologists, the identification and description of new frontiers in physiology, the instruction of specialists in one field about other areas of physiology and of other sciences related to physiology, and provision of a broader perspective to physiologists and biologists everywhere. One corollary of this plan will be the demise of *The Physiologist*: within the new journal will be continued a separate section of news of interest to members of the American Physiological Society. This section will not appear in the copies of the journal distributed abroad.

Animal Welfare

Physiology is rooted in animal experimentation. Until the middle of the 19th century, physiology in Great Britain consisted largely of inferences about function based on anatomy. But once British physiology became an experimental science, it ran into difficulty. In 1876, increasing agitation by antivivisectionists and the threat

of an unfriendly report by a Royal Commission charged with assessing the need for legislative steps to monitor operations on living animals, led to the formation of the Physiological Society in Great Britain (Figure 7).

"With the growth of Experimental Physiology, and the sister science Experimental Pathology, operations upon living animals necessarily began to multiply, and before long a vigorous anti-vivisection agitation sprang up. As the result of the agitation the Government of the day appointed in 1875 a Royal Commission . . . to investigate the subject and to report and advise as to whether it was necessary to take legislative steps in the matter. . . . After hearing an interminable amount of evidence on both sides, the Commissioners eventually produced a Report, which, like all such Reports, was a compromise. Although they had not been presented with any irrefutable evidence that acts of cruelty had been perpetrated upon animals in this country in the pursuit of physiological or pathological investigations, they nevertheless agreed to recommend that the practice of vivisection should be regulated by Act of Parliament and that it should only be permitted to persons to whom a license had been granted by the Home Secretary on the advice of certain responsible authorities. . .

"In consequence of the Report of the Royal Commission and the knowledge that it was the intention of the Government to bring in a Bill dealing with the subject, it was evidently desirable for physiologists to form an association which might come into communication with the minister in whose hands the conduct of the Bill would be placed, with the view of modifying proposals which seemed to hamper unduly the progress of experimental medicine. Thus the anti-vivisection agitation was the cause of the formation of the Physiological Society." (1)

From then on, periodic outbursts against vivisection for research were to hamper the progress of physiology (Figure 8). As is usually the case in this type of protest, most of those concerned about the use of animals for research purposes are well motivated and reasonable; not infrequently, their perceptions, suspicions, misconceptions, and remonstrances are helpful by promoting reappraisals of current practices. But every now and then

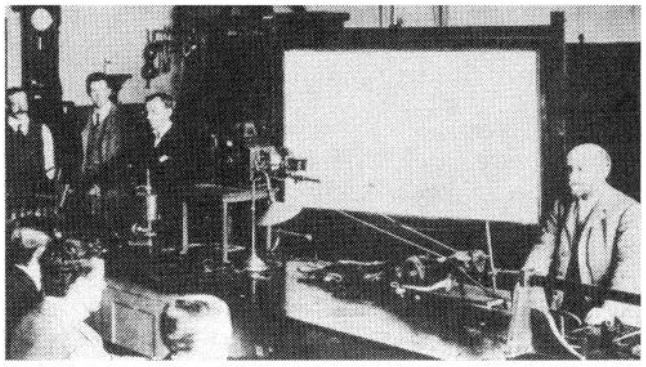
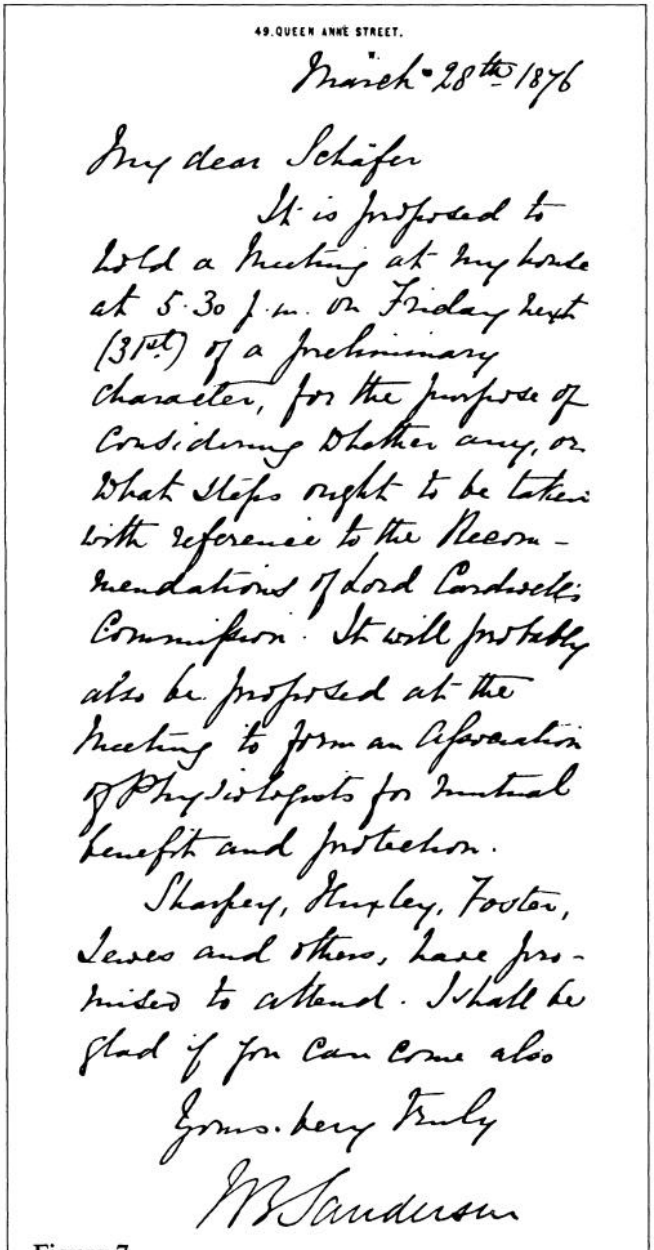


Figure 8
The "Brown Dog Case." Accused by an ardent antivivisectionist of cruelty in their handling of dogs in their experiments, Bayliss (*far right*) and Starling (*left, near screen*) staged a demonstration of their experiment, and Bayliss used the above photo in his suit for defamation of character. H. H. Dale is next to Starling. Bayliss won the suit (1).



49. QUEEN ANNE STREET.
W.

March 28th 1876

My dear Schäfer

It is proposed to hold a meeting at my house at 5.30 p.m. on Friday next (31st) of a preliminary character, for the purpose of considering whether any, or what steps ought to be taken with reference to the Recommendations of Lord Cardwell's Commission. It will probably also be proposed at the meeting to form an Association of Physiologists for mutual benefit and protection.

Sharpey, Huxley, Foster, Lewes and others, have promised to attend. I shall be glad if you can come also

Yours very truly

J. B. Sanderson

Figure 7
Letter from Professor J. Burdon-Sanderson convening a group to deal with increasing agitation by antivivisectionists and to deal with the impending report of the Royal Commission of 1875. [Reprinted with permission (2).]

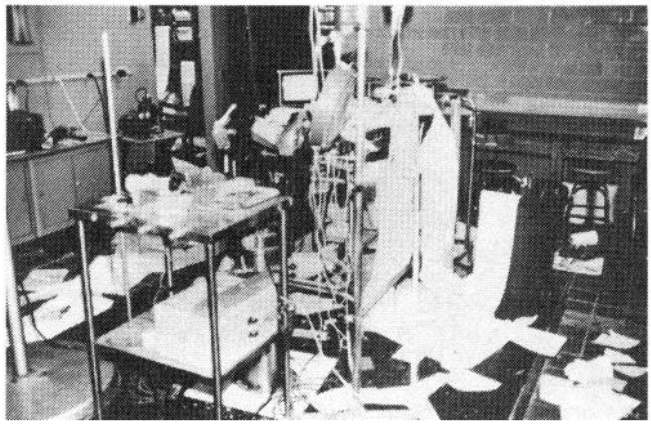


Figure 9
The scene after a raid by terrorists on a research laboratory at the University of Pennsylvania.

Table 2
Recent Raids by Antivivisectionists
Using Terrorist Tactics

1981	September	IBR (Taub)	17 monkeys seized	PETA
1982	June	University of Maryland	48 rabbits stolen	Band of Mercy
	December	Howard University	35 cats stolen	ALF
	December	Naval Medical Center (Bethesda)	1 dog stolen	ALF
1983	January	University of California (Berkeley)	3 cats stolen	ALF
	January	Naval Medical Ctr	1 dog stolen	ALF
	December	UCLA (Harbor)	12 dogs stolen	ALF
	December	Johns Hopkins	6 rats stolen	ALF
1984	May	Cal State Sacramento	22 rats stolen	ALF
	May	University of Pennsylvania	video records stolen	ALF
	July	University of Pennsylvania	8 pigeons stolen 3 rats stolen 2 dogs stolen	ALF

(Not included are unsuccessful break-in attempts, bombing of faculty member home, demonstrations, harrassments, and other incidents here and abroad.) (Courtesy of W. M. Samuels)

things get out of hand. Occasionally, as is happening at the present time (Table 2), individuals and groups adopt the mindless tactics of terrorists, raiding laboratories, destroying records, and interrupting research important not only for science but also for the health and welfare of animals and humans (Figure 9).

These are criminal offenses. They take place primarily on holiday weekends. One organization (Animal Liberation Front) has claimed responsibility for all break-ins since mid-1982. The stolen animals have not been recovered. The timing of the break-ins seems to be synchronized with the prospect of a favorable press and of legislative activity on the state or federal levels. Experimental scientists are poorly organized and ill-equipped to deal directly with either the onslaughts or the offenders. Security measures are examined and reinforced; the police are sought as allies; counsel is sought from the law. But probably the most useful tool available to scientists is education (Figure 8) to dispel misconceptions among those rational antivivisectionists who will listen about the practice of animal experimentation.

During the past year, the American Physiological Society has assumed a leadership role among the societies representing the life sciences in focusing attention of health agencies and scientific bodies on animal welfare. As part of this effort, it has sounded the alarm to other concerned societies and has arranged for strong representations to be made conjointly by leaders in biomedical science to the National Institutes of Health and the National Academy of Sciences. These strenuous efforts have influenced federal and state legislation, promoted reviews of and improvements in animal experimentation, alerted individual laboratories to the need for protective measures against criminal incursions, encouraged scientific bodies to educate the public, and prompted reexamination of the ethical guidelines for the protection of both animals and scientists. The American Physiological Society is traditionally committed to necessary animal experimentation, to enlighten the public about the nature of this need, and to ensure that animal experimentation is conducted under proper experimental conditions.

International Physiology

During the past year, members of Council expressed interest in having the American Physiological Society

Figure 10
Contemplating the role of the American Physiological Society in international physiology

increase its role in international physiology. As a first step, inventory was taken of the history of the International Union of Physiological Sciences and its relation to the American Physiological Society (Table 3). Next, the current state of international physiology was assessed along with the extent to which the American Physiological Society was involved (Figure 10).

The conclusion was reached that the American Physiological Society is poorly represented in international physiology, particularly with respect to the International Union of Physiological Sciences, which it was instrumental in founding. Organization of physiology on an international scale can be dated to 1888, when the first International Congress was held. In 1919, the International Council of Scientific Unions (ICSU) was established (Table 4), relating to the United States by way of the National Research Council. The Physiological Congress remained independent of it. Organization of international physiology took a promising turn in

Table 3
Evolution of the International Union of Physiological Sciences (IUPS)

1888	First International Congress of Physiology
1919	International Council of Scientific Unions (ICSU) established (initially named International Research Council) • Relates to U.S. via National Research Council • International Physiological Congresses independent of ICSU
1946	UNESCO cultivates international culture and science (via ICSU)
1948	APS Council votes to form IUPS
1949	ICSU rejects APS-initiated proposal to form IUPS because of proposed permanent leadership
1953	IUPS formed with APS as a founding member of IUPS • Concept of "adhering bodies" • General Assembly elects Council
1954	NRC replaces APS as affiliating body to IUPS • U.S. National Committee to include pharmacology, general physiology—appointed by NRC • U.S. National Committee nominates members of general assemblies of IUPS • NRC pays IUPS dues
1955	ICSU accepts IUPS as a member

1946 with UNESCO, relying heavily on the International Council of Scientific Unions (ICSU) as its implementing arm, undertook to promote international science as well as culture. At approximately the same time, the American Physiological Society became sensitive to the minor role that it was playing in the content and programs of the international congresses. As a result, and after much deliberation, the Council of the American Physiological Society recommended in 1948 that an International Union of Physiological Sciences (IUPS) be formed. The first proposal to establish IUPS, initiated by APS, was rejected by ICSU primarily because the proposal stipulated that the leadership of the proposed IUPS be self-perpetuating. IUPS was formally established without the prior approval of ICSU at the International Physiological Congress in 1953. The American Physiological Society became a founding member.

Included in the statutes of IUPS was the concept of "adhering bodies" that would represent individual countries. At the time of the founding, the American Physiological Society was the adhering body for the

Table 4
American National Committee of IUPS as Constituted in 1954

Society	Members
APS	3
ASPET	2
SGP	2
At large	1

APS, American Physiological Society; ASPET, American Society of Pharmacology and Experimental Therapeutics; SGP, Society of General Physiologists

The members of the U.S. National Committee have been repeatedly changed over the years, but the APS continues to play a prominent role.

United States. However, for political and financial reasons, the National Research Council replaced the American Physiological Society in 1954 as the adhering body. The National Research Council, in turn, appointed a U.S. National Committee, which included not only the American Physiological Society but also representatives from pharmacology and general physiology. Only then did ICSU accept IUPS as a member. Although the U.S. National Committee was to nominate individuals for membership in the general assembly of the IUPS, no direct line of communication or responsibility was established between the U.S. National Committee and the Council of the IUPS. One benefit to the American Physiological Society for relinquishing its original role as the "adhering body" was that the National Research Council was to pay the IUPS dues. Since 1954, the end result of these arrangements has been a complicated ramifying system that operates ineffectively in promoting American physiology and physiology elsewhere.

Table 5
Some Weaknesses in IUPS-APS Relations

U.S. Members of Council of IUPS are self-perpetuating and virtually independent of APS
IUPS not a predominant concern of NRC
Inconsistent role in programs of international congresses
Commissions often inconsequential

Certain weaknesses in this relationship are currently being reviewed by the U.S. National Committee (Table 5). One troublesome issue is that Americans on the Council and committees of the IUPS seem inclined to operate independently of the U.S. Committee and to have reverted to the self-perpetuating status that was resisted at the outset by ICSU. Also, even though it was a founding member of IUPS, the American Physiological Society has played little role in shaping the programs of inter-

Table 6
APS Directions in International Physiology

- Support IUPS, e.g. as in creating new journals
- Strengthen APS presence on U.S. National Committee of IUPS
- Encourage corresponding membership in APS
- Initiatives in promoting international meetings of IUPS and other (Cambridge 1985)
* Closer ties with foreign physiological societies (reciprocal memberships for visiting scientists)
- Creating of APS International Physiology Committee

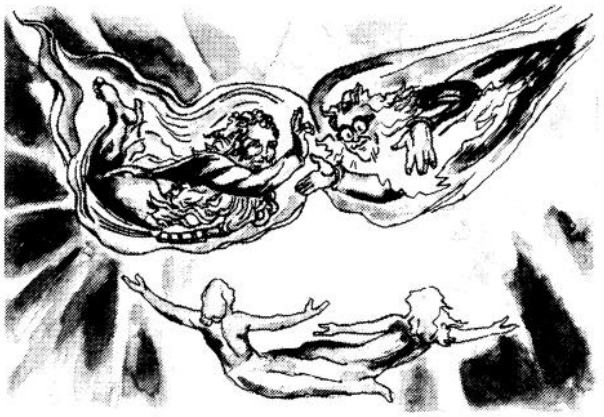


Figure 11
The American Physiological Society (APS) and the International Union of Physiological Sciences (IUPS) should continue to relate closely, and the APS will continue to promote the interests of the IUPS for the sake of international physiology.

national congresses, consistently offering suggestions about topics and speakers to which little heed has been paid. Finally, commissions appointed by the Council of IUPS seem to assume a life of their own, issuing statements and documents that occasionally conflict with the needs and practices of the American Physiological Society.

Because of these inadequacies, the Council of the American Physiological Society has recommended that several steps be taken to promote the interests of the Society in international physiology (Table 6). From the outset, it agreed that its membership in the IUPS should not be jeopardized and that as a large constituent of the international organization, it should further the interests and development of the IUPS (Figure 11). For example, the Council has encouraged the discussions between the American Physiological Society and the IUPS about the creation of an international journal. However, certain directions are to be pursued independently by the American Physiological Society. Notable among these will be an increased effort to recruit distinguished foreign scientists as corresponding members of the American Physiological Society. Closer ties are also to be sought with foreign physiological societies. Arrangements are being made for reciprocal memberships for visiting scientists. A joint meeting with the British Physiological Society has been planned for Cambridge, England, in 1985. Finally, within the framework of the American Physiological Society, a Committee on International Physiology was created to further the interests of the Society in international physiology. The U.S. National Committee of the IUPS has been alerted to the renewed interest of the American Physiological Society in international physiology as has the Foreign Secretary of the National Academy of Sciences. The outcome of these initiatives remains to be seen.

Long Range Planning

During the course of this year, the Council received the report of the Long Range Planning Committee, chaired by Dr. Robert Berne. This thoughtful document made important suggestions concerning the structure and function of the society and its programs. One of its recommendations that the Council acted upon immediately was the creation of the Section Advisory Committee discussed above. Other suggestions, such as revamping the program of the annual spring meeting, are under consideration. Most important, the Council accepted the recommendation that an ongoing Long Range Planning Committee be created and that the future of physiology be a major and immediate concern of this new advisory body.

1948 Was a Good Year

As may be seen in Table 1, the events on each pinpoint the years of 1947 and 1948 as a turning point in the evolution of the Society (Figure 12). Why was this so? A little reflection and research has suggested several contributing factors. The time was shortly after World War II, when scientists were once again in their laboratories, a little older, much wiser, and dedicated to making up for lost time. Physiology was in a heyday, intellectual ferment was high, and some could not even be contained within the framework of the Society, e.g., "general physiologists" formed a society of their own. Seasoned leaders in physiology, experienced in the affairs of the Society were at the helm for several years in a row so that continuity in planning and implementation could be sustained. In 1947, the Society had moved into new quarters and acquired its first Executive Secretary, Dr. Milton Lee; under his leadership meetings and publications were restructured. In 1948, the Society also held its first fall meeting, and the *Journal of Applied Physiology* was founded.

An important question is whether recent years will also prove to have been "good years." Clearly the Society will never be the same after sectionalization of its internal structure, its publications, and its mentality. It will be a rewarding experience 20 years from now to look back at the circumstances and events that are prompting new directions for the Society and to assess if 1983-1984 was also a good year.

Concluding Remarks

As indicated at the outset of this presentation, I anticipated a contemplative year. But instead of looking from on high during my presidency (Figure 1), I found myself winding my way through a thick forest of thought and activity, occasionally tripping, often climbing, and sometimes falling. En route I had opportunity to pause for a close look at four topics.

Figure 12
The years 1947 and 1948 were landmark years in the history of the American Physiological Society.

Figure 13
The Past President, a little older, much wiser, and infinitely more understanding, pauses to reflect about the past year.

Now that I am once again in the clear, let me pause briefly to reflect on the implications of what I have seen and learned (Figure 13).

The years ahead also promise to be rocky ones for physiology. Nonetheless, as it approaches its centennial in the company of its offspring societies, the American Physiological Society is strong, vibrant, excited, and eager to continue its leadership role i nthe biological sciences. The Society is changing form and function; undoubtedly, in the years ahead, it will continue to evolve in keeping with the changing times and challenges. But, during the past year, the opportunity to appreciate its vital essence as well as its form and substance has convinced me that the American Physiological Society is fully prepared to move with pride and great anticipation into the bright future.

The time of departure also provides a chance to express my appreciation. That it was an uplifting experience can be inferred from the cartoons above based on William Blake's illustrations to the Divine Comedy. Nothing could have been accomplished during my term of office without the help, advice, and occasional solace of the members of Council and the gentle steering of Orr Reynolds and his staff at the offices of the Society. I also am indebted to Mr. Stephen Geiger, who has been steadfast in his devotion to the Society and who has always indulged my personal interest in publications. Walter Sonnenberg always provided a financial ruler at the right time to straighten out the budget. Finally, I am indebted to Toby Appel, who came aboard only recently but has already contributed importantly to the scholarly interests of the Society.

References

1. Fishman, A. P., and D. W. Richards. *Circulation of the Blood. Men and Ideas* (Reprint). Bethesda, MD: Am. Physiol. Soc., 1982, p 419.

2. Sharpey-Schafer, E. A. History of the Physiological Society during its first fifty years, 1876-1926. *J. Physiol. London Suppl.* Dec.: 6, 7, 1927.

132nd APS Business Meeting

Time: 9:30 A.M., Wednesday, August 29, 1984
Place: Hyatt Regency Hotel, Lexington, KY

I. Call to Order

The President, J. B. West, called the meeting to order and welcomed the members to the Society's 132nd Business Meeting. The ballot for election of new members, the proposed Bylaw amendment to enlarge the Publications Committee, and a list of future meetings were distributed with the agenda.

II. Report on Membership

A report on the current status of the membership and deaths since the last meeting were reported by the President-Elect, H. E. Morgan.

A. Summary of Membership Status. The APS membership reached 6,195 of which 4,515 are Regular, 11 Honorary, 117 Corresponding, 593 Emeritus, 750 Associate, and 209 Student members (p. 000). This is an increase of approximately 40 members since the Spring meeting.

B. Deaths Reported Since the Last Meeting. The names of those members whose deaths have been reported since the previous meeting were read by Dr. Morgan, who asked the members to stand for a moment of silence in tribute to them (p. 000).

III. Election of Members

A. Appointment of Tellers. Dr. West appointed G. A. Hedge, L. L. Langley, and C. V. Paganelli as tellers and asked them to collect the ballots for the election of new members.

B. Election of Members. The Executive Secretary-Treasurer, O. E. Reynolds, informed the group that all candidates were unanimously elected with 80 members casting votes.

IV. Amendment to the Bylaws

In compliance with the Bylaws, the proposed amendment to increase the number of Publications Committee members from three to five was published in the June issue of *The Physiologist*. The origin of a three-member Publications Committee dates back to when the Society had a Publications Board of Trustees. However, the Society publications have become a major enterprise with a large budget. The Council, believing it is prudent to enlarge the Publications Committee, offers the proposed amendment for vote.

A motion was seconded and passed unanimously that Article V, Section 1, of the Bylaws be amended to increase the Publications Committee from three to five members.

V. State of the Society and Actions of Council

Dr. West stated that it seems desirable from time to time to step back and ponder on the state of the Society. It is particularly appropriate at this time because of the number of doomsayers around, who are of the opinion that physiology is a discipline that is fragmenting in various directions. Others feel the Society is rather old fashioned and on the decline. Dr. West wishes to share a few statistics about the state of the Society because some members, like himself before serving on Council, may not be aware of what is happening in the Society.

One of the most important functions of an organization like the American Physiological Society is to look after the concerns of its members. The Society does this in the area of animal welfare. There is a very active animal rights movement threatening our use of animals for research, and we should be very vigilant. Bill Samuels in the Public Affairs Office is active in following the various changes in this area and apprising the membership of these issues. This activity is relatively expensive, costing each of us about $10 per year. However, Dr. West believes that it is a small price to pay to prevent changes in the animal welfare laws threatening the work of physiologists.

The two most important activities of the Society are meetings and publications. Over the past 10 years, there has been an upward trend in registration and the number of papers presented at the Spring meeting held in conjunction with the FASEB meeting (Figure 1). The Spring meeting is fulfilling the aim of the Society, enabling members to get together and discuss scholarly aspects of physiology. On the other hand, the Fall meeting picture is not quite as rosy (Figure 2). Since the Albany meeting in 1974, the number of papers and posters started increasing and peaked with the Toronto meeting in 1980. There has been a substantial decline at this meeting for several reasons. It appears that August meetings are poorly attended and, unfortunately, they conflict with several other meetings. The Society is returning to an October meeting for the next 3–4 years, which we hope will improve the attendance. The number of papers in the various areas of physiology at the Fall meeting is uneven (Figure 3). There are no papers in cell and general physiology. Gastrointestinal and liver physiology are poorly represented. These groups have elected the Spring meeting for the presentation of their work. At the Fall meeting, the papers are predominantly from environmental, thermal and exercise; heart and circulation; and respiratory physiology. Beginning in 1986, there is going to be more of a thematic emphasis on the Fall meeting in an attempt to formalize or structure it. On the other hand, there are obviously a large number of the members who feel the Fall meetings are worthwhile, and there is no great threat to their continuance.

In some respects, Society publications are flourishing. The number of new manuscripts received by the various journals continues to increase (Figure 4). Over the last six years, the consolidated *American Journal of Physiology* and the *Journal of Applied Physiology* have increased steadily with the *Journal of Neurophysiology* climbing at a slower rate. Also, there is a steady upward rise in the number of manuscripts that have been pub-

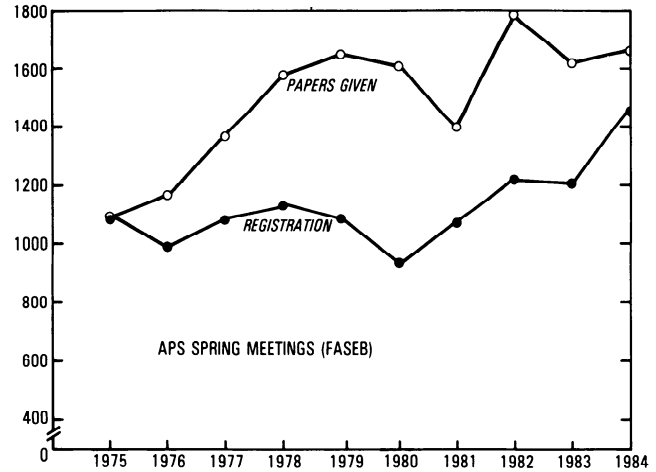


Figure 1
Number of papers given and registration at APS Spring meetings in the last 10 years.

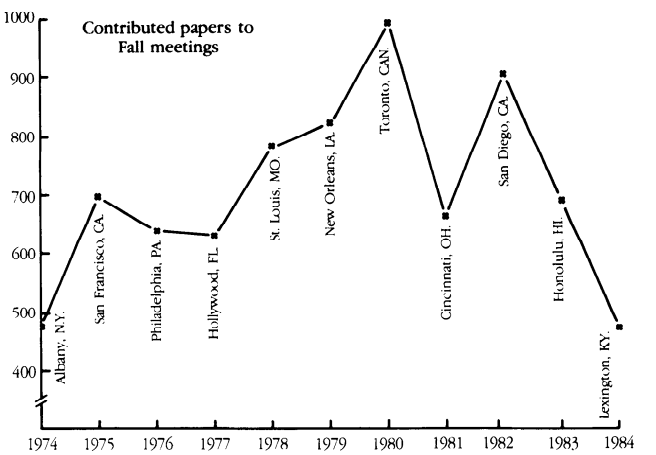


Figure 2
Number of contributed papers to APS Fall meetings for the last 10 years. In this and Figure 1, "papers" includes oral communications and posters.

Contributed Papers by Physiologic Category

APS Fall Meeting 1984

Category	Number of papers	Percentage of total
Cell and general	0	0
Comparative	19	4.0
Endocrine, reproductive	33	7.0
Environmental, thermal, exercise	53	11.2
G.I., liver	10	2.1
Heart, circulation	98	20.5
Muscle	30	6.3
Neurophysiology	16	3.4
Regulatory, integrative	25	5.3
Renal, electrolyte	23	4.9
Respiratory	121	25.6
Other	47	9.9
total	475	100

Figure 3
Breakdown of papers at the APS fall meeting 1984 by category.

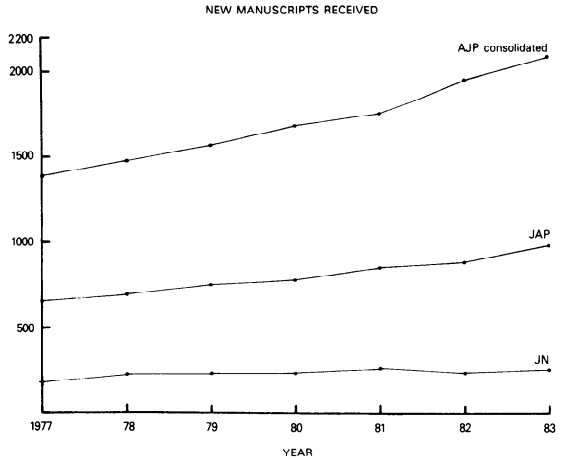


Figure 4
New manuscripts received by the consolidated *American Journal of Physiology, Journal of Applied Physiology,* and *Journal of Neurophysiology.*

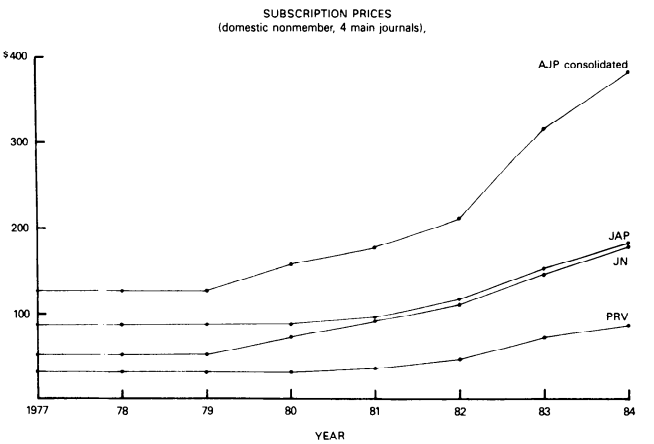


Figure 5
Increase in subscription prices of APS journals over the last 8 years.

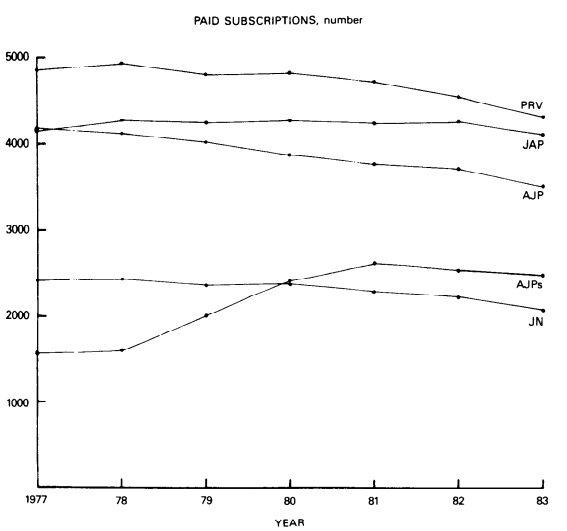


Figure 6
Changes in number of subscriptions to APS journals over the last 7 years. Note the gradual decline in most cases.

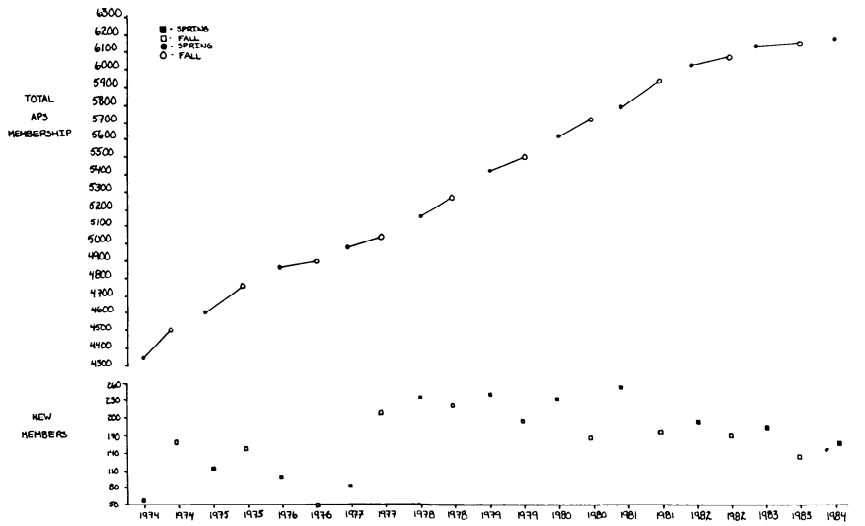


Figure 7
Total membership of the American Physiological Society (top) and number of new members added at the spring and fall meetings (bottom).

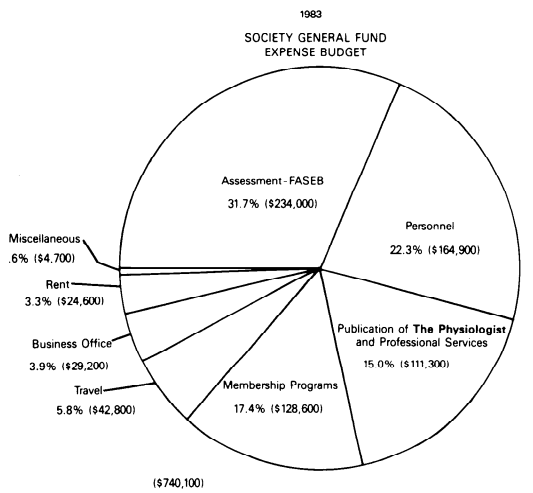


Figure 8
Total Society expenditures in 1983. 77% is accounted for by publications.

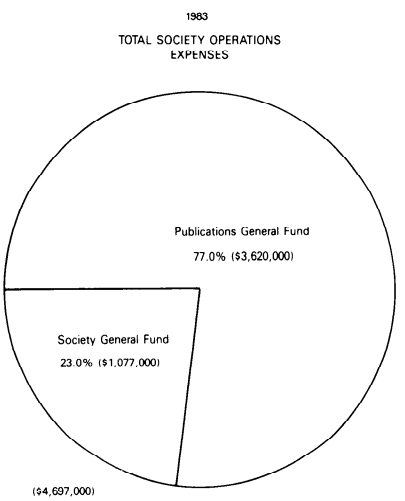


Figure 9
Expenditures of the Society Operating Fund, 1983. This includes all expenditures except publications.

lished. Some disquieting news is that the cost of publications is rising rapidly. This is a nonlinear rise. Subscription prices are set in order to pay for the journals, which are published at essentially no profit. There is a fairly sharp upward trend in subscription prices (Figure 5), but the number of subscribers is falling (Figure 6). This is also happening with other scientific journals, and it will be difficult to determine what will happen over the next 10 years.

The membership of the Society, which approaches 6,500, continues to grow (Figure 7). However, the total number of members is not increasing very rapidly. The number of new members being added each year is essentially constant or slightly declining. This causes Council concern.

Before joining Council, Dr. West said he was extremely ignorant about the Society budget. However, he learned that publications is by far the largest portion of the budget (Figure 8). In 1983, it was 78%. The Society budget, less than one-fourth of the total budget, is relatively small. It includes the overall general operations with the exception of publications. Related to expenses, a large FASEB assessment is balanced by the income from the Spring meeting. There are 55 people in the headquarters office, and the personnel salaries and benefits are the major category of expense (Figure 9).

A substantial portion of the Society budget goes toward publication of *The Physiologist*. Over the next three years, *The Physiologist* will be replaced by the new "Trends" journal, which will be published jointly with the International Union of Physiological Sciences. Society news, the house-organ function of the Society, will be a 16-page insert in the Trends journal.

Dues account for a large part of the Society income. A fairly substantial amount of the income is from voluntary contributions, and the investment income is derived from dues deposited for later use. Over the past 10 years, Society expenses and dues have increased more or less together. Regular membership dues are $80. Dr. West feels that everything possible should be done to prevent further increases. The Finance Committee, which watches this aspect of the budget very closely, requires an annual balanced budget to avoid further dues increases.

Turning to current activities, Dr. West said that Council is concerned about the general problem of the future of physiology. At this meeting, we have renewed our links with the Association of Chairmen of Physiology Departments. In conjunction with the President, Dr. George Hedge, a joint program has been initiated to improve the image of physiology. The new Trends journal will be one way of accomplishing this. This journal will contain summaries of recent important

advances in physiology. The Bowditch Lecture is a remarkable example of the type article that will be summarized in the Trends journal.

The Centennial will be celebrated with a "big party" at the Spring FASEB Meeting in Washington, DC, March 29–April 3, 1987. The theme will be "A Century of Progress in Physiology." The first combined meeting of APS and The (British) Physiological Society will take place September 12–14, 1985. Information and announcements of this meeting will appear in future issues of *The Physiologist.*

In the area of animal welfare, the Society has joined the Association of American Medical Colleges (AAMC) and the American Medical Association (AMA) in organizing a coalition of scientific, medical, industrial, and voluntary health organizations in a concerted effort to support the continued availability of animals for research, education, and product testing.

In closing, Dr. West reported that Council is actively searching for a replacement for Dr. Orr Reynolds, who will be stepping down as Executive Secretary-Treasurer of the Society to devote more time to the Centennial Celebration.

Commenting on the Centennial Celebration, Dr. Aubrey Taylor emphasized the need for all of us to recognize that we are "physiologists celebrating our 100th anniversary" and everyone in the Society should be involved in the celebration.

VI. New Business

In response to a question from the floor concerning publication of a cumulative index of the various journals, Dr. Morgan stated that the indexes for the years 1976–1982 of the consolidated *American Journal of Physiology* and the *Journal of Applied Physiology* were published in November and July 1983, respectively. It is planned to have future cumulative indexes of these journals published every five years.

Another suggestion from the floor was a request to look into the possibility of electronic mail so that communications among physiologists can be accomplished more quickly. Dr. Reynolds announced that this is currently under investigation.

With no other business, the 132nd Business Meeting of the Society was adjourned at 10:10 A.M., August 29, 1984.

Howard E. Morgan, President-Elect

APS Endorsement of AAAS Resolutions

At its August 1984 meeting, the APS Council endorsed the following four resolutions passed by the Council of the American Association for the Advancement of Science in May 1984.

1) Protection of Fundamental Rights of Scientists, submitted by Elliott Schiffmann on behalf of the Medical Scientists Committee, NIH:

Whereas scientists and scientific associations have recognized the United Nations 1948 Universal Declaration of Human Rights, which include "freedom of opinion and expression," "freedom of movement and residence within the borders of each state," "the right to leave any country . . . and to return," and "freedom of peaceful assembly and association"; and

Whereas governments have often infringed upon these freedoms and rights; and

Whereas the Declaration on the Protection of All Persons from Torture and Other Cruel, Inhuman or Degrading Treatment or Punishment, adopted by the UN General Assembly on 9 December 1975, is applicable to scientists who are imprisoned; and

Whereas scientists are frequently singled out for repression or harassment, and reports of physical and psychological abuse of some imprisoned scientists are convincing, therefore

Be it resolved that the American Association for the Advancement of Science reaffirm its commitment to protect the fundamental rights of scientists and to foster scientific and academic freedom, and

Be it further resolved that the AAAS continue its efforts to document and disseminate information on cases of persecuted scientists throughout the world, and to protest their physical or psychological abuse.

The Council voted unanimously to adopt the resolution without change.

2) Openness and Science and Technology, submitted by the AAAS Committee on Scientific Freedom and Responsibility:

Whereas freedom of inquiry and communication contribute to the advancement of science and technology; and

Whereas the American Association for the Advancement of Science is committed to openness as an essential element for the advancement of science,

Be it resolved that the AAAS urge its affiliates and academic institutions to examine their policies, reaffirm their commitment to freedom of inquiry and expression, and make these policies publicly known.

The Council voted unanimously to adopt the resolution without change.

3) Openness and National Security, submitted by the AAAS Committee on Scientific Freedom and Responsibility:

Whereas progress in science and technology is greatly enhanced by open communication; and

Whereas such progress promotes both the national security, however defined, and the general welfare; and

Whereas public availability of unclassified scientific and technical information is a necessity for democratic decision-making in a wide range of important public policy issues,

Be it resolved that the American Association for the Advancement of Science strongly reaffirm its opposition to continuing governmental efforts to restrict the communication or publication of unclassified research, and

Be it further resolved that the AAAS expressly oppose agreements which require prepublication approval of unclassified research.

A motion to amend the resolution by deleting the final paragraph carried. The Council voted to adopt the resolution as thus amended.

4) Appeal on Behalf of Academician Sakharov and Dr. Bonner, submitted by the Workshop on Scientists and Human Rights—Present and Future Directions of the AAAS Committee on Scientific Freedom and Responsibility:

Whereas Andrei Sakharov and Yelena Bonner have demonstrated a deep personal commitment to the advancement of science and human progress as well as a forceful and compassionate defense of human rights standards worldwide; and

Whereas the present isolation of Academician Sakharov and Dr. Bonner by the Soviet Government prevents them from the exercise of their professional work as well as the exercise of their basic human rights, which include the right to leave one's country and the right to obtain medical care of one's choice,

Be it resolved that the American Association for the Advancement of Science:

- In a collegial defense of the scientific and human rights of Academician Sakharov and Dr. Bonner, urge the Soviet Government to end the present isolation of these scientists and to allow them to seek medical care of their own choice;
- Urge the appropriate Soviet authorities to allow travel abroad of Academician Sakharov and Dr. Bonner; and
- Urge its affiliates and individual members to expedite sending messages of concern to the Soviet authorities.

The Council voted unanimously to adopt the resolution without change.

Joint Meeting
The Physiological Society and American Physiological Society
September 12–14, 1985
Physiological Laboratory
University of Cambridge, UK

As announced previously (*Physiologist* 27: 74, 1984), a joint meeting is planned between the (British) Physiological Society and the APS next September. The February 1985 issue of *The Physiologist* will carry an article describing procedures for attendance and contributing to the meeting as well as a return card for requesting a package containing the abstract, housing, and registration forms and appropriately addressed envelopes. *Deadline for receipt of abstracts will be June 1, 1985.*

An important feature of the meeting will be a symposium, "Transduction at the receptor level in the visual and auditory systems," in honor of Sir Alan Hodgkin.

Program Advisory Committee Report

The Program Advisory Committee (PAC) met on Monday, August 27, 1984, in Lexington for the purpose of planning the 1985 fall meeting.

The following sections of APS were represented at the meeting: Neurophysiology (J. Trubatch), Endocrinology and Metabolism (G. Hedge), Environmental, Thermal and Exercise Physiology (C. Gisolfi), Renal Physiology (G. Navar), Respiration (M. Hlastala), History of Physiology (N. Staub), and Comparative Physiology (D. Jackson). The Buffalo Local Committee, which will host the 1985 Fall Meeting, was represented by Dr. Charles Paganelli, and Dr. Vivian C. Abrahams represented the Canadian Physiology Society, which will be a cosponsor of the meeting. The IUPS Commission on Gravitational Physiology, which will meet jointly with APS in Niagara, was represented by Dr. Orr E. Reynolds. The meeting was also attended by Dr. Walter C. Randall, Chairman of the Long Range Planning Committee, and Dr. Pat Harris of the Program Executive Committee (PEC).

The 1984 fall meeting continued the declining trend of recent years with both number of papers submitted and registration at their lowest levels in ten years. Council expressed great concern on this issue, and have asked the Program Executive Committee to develop recommendations for improving the fall meeting. The issue was discussed at the meetings of the PAC and PEC. It was agreed that the PEC would develop a proposal to improve the attraction of the fall meeting for discussion with the Long Range Planning Committee and presentation to Council at their meeting in Anaheim. APS members wishing to submit suggestions on this matter should forward them as soon as possible to Dr. Michael J. Jackson, Department of Physiology, George Washington University Medical Center, 2300 Eye St., NW, Washington, DC 20037.

The local committee and the sections represented at the meeting proposed an excellent slate of symposia for the 1985 fall meeting. The following list includes those approved by the PEC for presentation: *1*) Membrane proteins and the cytoskeleton, organized by F. Sachs, proposed by Local Committee; *2*) Oxygen damage and repair (2 sessions), organized by S. Matalon and A. Taylor, proposed by Local Committee; *3*) Receptors: their role in health and disease, organized by D. Triggle, proposed by Local Committee; *4*) Physiologic functions in concious behaving animal models, organized by D. Faber, proposed by Local Committee; *5*) Cellular and membrane function at high pressure, organized by S. K. Hong and P. Hogan, proposed by Local Committee; *6*) Functional activity and the plasticity of neurons, organized by G. R. Pilar, proposed by Neurophysiology Section; *7*) Hormonal, physiological and clinical studies of factors affecting heat production during malignant hyperthermia (2 sessions), organized by C. H. Williams, proposed by Environmental, Thermal and Exercise Physiology; *8*) Pleural space functions, organized by N. Staub, proposed by Respiration Section; *9*) Integrative and cellular aspects of aldosterone action, organized by E. Schneider, proposed by Renal Physiology Section; and *10*) Renal functional derangements in hypertension, organized by B. Zimmerman, proposed by Renal Physiology Section.

In addition, two proposed symposia were referred to the program committee of the IUPS Commission on

Gravitational Physiology for inclusion in their component of the program. These are Gravitational Physiology, organized by X. J. Musacchia, proposed by Environmental, Thermal and Exercise Physiology Section; and Space Physiology—A New Frontier, organized and proposed by J. West. Also, Dr. Abrahams indicated that the Canadian Physiology Section would program three symposium sessions drawing on the strengths of Canadian physiologists.

Dr. Paganelli indicated that the local committee had not decided on a theme for the refresher course, and that this information would be forwarded to the PAC when a topic had been identified.

M. J. Jackson, Chairman

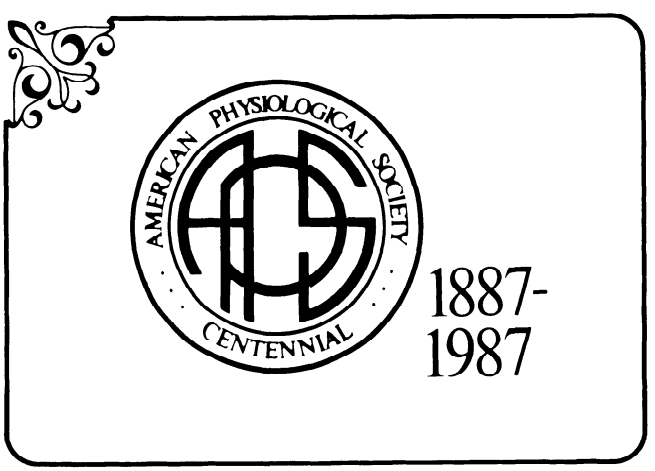
New APS Publication Cell Membrane Technique Book

Voltage and Patch Clamping With Microelectrodes, edited by Thomas G. Smith, Jr., Harold Lecar, Steven J. Redman, and Peter W. Gage, brings under one cover a comprehensive treatment of the various methods of voltage and patch clamping with microelectrodes. These clamping techniques are among the most powerful methods available for studying the fundamental events of cell membrane excitation. The recent explosion in the use of microelectrode voltage- and patch-clamp techniques and the absence of a ready source of information about these methodologies generated the need for a book such as this.

One purpose of the book is to help experimenters select the best technique for their particular application because there is no universally "best" voltage- or patch-clamp system. Pursuant to this goal is some consideration of the theory and practice and the advantages and drawbacks of each type of clamp. Another purpose is to provide some "how-to" information, as well as considerations of limitations and artifacts, about each system.

It should be noted that this book has itself been something of an experiment: it represents the first venture by the editors and the American Physiological Society of accepting manuscripts on computer tapes and disks.

Voltage and Patch Clamping With Microelectrodes contains 268 pages and 99 figures. The U.S. list price is $39.50. APS members may purchase a copy at $31.50 each when ordering from the American Physiological Society Subscription Department, 9650 Rockville Pike, Bethesda, MD 20814.



APS Sections

Cell and General Physiology

The Cell and General Physiology Section of the American Physiological Society will award $100 to each of three young investigators whose research as represented by an abstract submitted to the Spring FASEB meetings in the field of cell physiology is judged to be an outstanding contribution. Recipients will be selected from those scientists who submit abstracts by February 15, 1985 to the Program Chairman of APS-Cell: Dr. Paul J. DeWeer, Dept. of Physiology and Biophysics, Washington Univ. School of Medicine, 660 S. Euclid Ave., St. Louis, MO 63110.

Qualifications of Recipients: 1) A recipient must be first author on an abstract submitted for the FASEB meeting. *2)* A recipient must be performing research in the field of cell physiology. *3)* A recipient must be within five years after receiving his/her degree (Ph.D. or M.D.). *4)* A recipient must submit with their abstract a letter from the Department Chairman confirming their eligibility.

The recipients will be notified before the FASEB meeting and will be invited to be guests of APS-Cell at the annual Banquet-Lecture at which time each will receive the award.

R. Fedda, Secretary

Comparative Physiology

The Comparative Physiology Section of the American Physiological Society held a business meeting August 30, 1984, in Room F, Lexington Center, Lexington, KY. A quorum of the offices was present consisting of H. T. Hammel, Chairman, S. C. Wood and D. C. Jackson.

It was announced that *1)* Dr. Donald C. Jackson, Div. of Biomedical Sciences, Brown University, Providence, RI, was elected as the new councilor for our section; *2)* Dr. William K. Milsom, Dept. of Zoology, University of British Columbia, Vancouver, BC, Canada was elected Secretary; and *3)* Dr. Larry I Crawshaw, Dept. of Biology, Portland State University, Portland, OR, was elected to the APS Program Advisory Committee to represent our section. These three new officers will serve until 1987. The officers for the coming year are Dr. Steven C. Wood, Chairman (term expires 1985); Dr. Robert Blake Reeves, Councilor and APS Section Advisory Committee (term expires 1986); Dr. D. C. Jackson, Councilor (until 1987); Dr. W. K. Milsom, Secretary (until 1987); and Dr. L. I. Crawshaw, Program Advisory Committee (until 1987).

Dr. Jackson announced that a symposium on "Concepts of Efficiency in Biology Systems," proposed by Dr. R. W. Blake, received a high priority. It was decided, however, to have one or two tutorial lectures at Fall '85 meeting of APS before the actual symposium that will occur at the Spring '86 APS/FASEB meeting. Dr. Crawshaw forwarded an urgent request for suggestions or proposals for symposia for future meetings.

It was decided to create a young investigator award to be given annually for the best abstract and presentation in Comparative Physiology. The award will be titled the Scholander Award and will be accompanied by a cash award of $500.00 along with a certificate from the American Physiological Society. Applicants for the

Scholander Award must be first author on the abstract, must present the study in the Comparative Physiology Slide or Poster session of the Fall APS meeting and must be not more than five years past their highest degree. Applicants will be judged by a five-member panel composed of at least two members of the Comparative Physiology Council, the chairman of the slide or poster session, and two senior comparative physiologists selected by council. The presentation will be judged without prior judgement of the abstract. Members of the APS and friends of Professor P. F. Scholander are encouraged to contribute to the Scholander Award Fund. Contributions are tax deductible, and checks should be made payable to the American Physiological Society with a notation "Scholander Award Fund."

M. E. Heath, Acting Secretary

History of Physiology

The History of Physiology Section held its first luncheon meeting on August 19 at the APS Fall Meeting in Lexington, KY. Twenty-two members of the Section and friends attended. They were greeted on this historic occasion by Dr. John B. West who presided over the meeting. The results of the election of officers, held by mail vote this summer, were announced. Dr. West was elected Chairman, Dr. Norman Staub is Program Advisory Committee representative, Dr. Ralph Kellogg is member-at-large of the Steering Committee, and Dr. Toby Appel is Secretary-Treasurer. Dr. Staub announced that history will soon be included as an option for the programming of 10-minute contributed papers. He encourages members of the Section and others to write to him with suggestions for papers and symposia for future meetings.

Dr. A. Clifford Barger gave a talk accompanied by slides at the luncheon on "The Life and Times of Walter Bradford Cannon: A Progress Report." for several years, Dr. Barger and his co-authors, Dr. Saul Benison, and Mrs. Elin Wolfe, have been collecting and organizing material for a massive biography of one of the most important and fascinating figures in the history of American physiology, Walter B. Cannon. The first of two volumes is scheduled to appear in time for the APS Centennial.

Another luncheon meeting is planned for the FASEB Spring Meeting in Anaheim on Wednesday, April 24, 1985. Robert G. Frank, Ph.D., Medical History Division, UCLA, will speak on " 'Innocents Abroad'?: American Physiologists in European Laboratories." Any member of APS who would like to be a member of the Section should write to Dr. Orr Reynolds. There are no dues.

T. Appel, Secretary-Treasurer

Nervous System

The participation of the Section on the Nervous System in APS activities has been increasing dramatically over the past few years. The section sponsored four symposia at the FASEB meeting in Chicago (including one that was adopted into the FASEB theme), all of which were well attended.

As a result of the last election, Lorne Mendell, Charles Edwards, and Janett Trubatch will serve as members of the steering committee through 1987. The other members of the steering committee are Don Humphrey, Jim Blankenship, Ian Phillips, Evelyn Satinoff, James Lipton, and James Houk. Please feel free to contact any member of the steering committee with your ideas and suggestions for symposia, summer workshops, state of the art, and other invited lectureships and activities.

This spring at the FASEB meetings, the section, in conjunction with the Cardiovascular and Autonomic Controls sections, is sponsoring a four-part symposium, "Update in Cardiovascular Neurobiology." In addition to the clinical symposia dedicated to the Neurobiology of Neurological Disorders to complement the scientific sessions, we have planned to have the second annual Neuro mixer and post-doc exchange the Tuesday of the Meeting. James Lipton is in charge of the program.

J. Trubatch, Chair

Member Contributions

Contributions to the Society may be made to the General Operating Fund or other designated purpose. The donor may commemorate an event or memorialize an individual.

Contributions from the following members are gratefully acknowledged.

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NEVILLE, MARGARET C
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Emeritus	593
Honorary	11
Corresponding	117
Associate	750
Student	209
Total	6,195

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News From Senior Physiologists

Richard Eckstein to Roy Greep:

Thank you for the birthday greeting. My wife and I just returned from a two week Alpine Tour which was most enjoyable.

I retired from my research in cardiovascular work in 1979. Since then I have gone into the hospital three part days each week to see my psychiatric patients and to attend meetings to keep my Medical Education Credits up to date to meet the requirements for renewing my Medical License. In addition, I serve on the committee to read and approve all the human research protocols submitted to the Department of Medicine of Case Western Reserve.

Since my retirement from research I receive a flood of journals of all sorts, but chiefly cardiovascular. I try to sort out the articles that are of interest to me, and I continue to be amazed at the growing amount and complexity of the information in all fields.

My wife and I remain in reasonably good health, but I have a cataract in one eye which interferes with my reading. I plan to have it operated in the near future. We live in Orange Village, which is 11 miles from the university. The lots are 1½ acres each. When people ask what I do, I usually say read journals, mow grass, rake leaves, and shovel snow. We attend lots of plays and concerts.

4360 S. Hilltop Rd.
Chagrin Falls, OH 44022

Charles (Chuck) Lloyd to Roy:

This will thank you for the birthday greeting and its notification that I have become recognized as a genuine old fogie. It has been quite some time since we last talked. In 1976 my wife Katharine died. I have since married Dr. Sallie Schumacher, a clinical psychologist specializing in marital and family therapy. We have demonstrated that the classical concept that 80–90% of sexual dysfunction is psychogenic is very wrong. About 80% of our patients have organic diseases.

Among other projects, I have also been collaborating with the Department of Behavioral Sciences at the University of Connecticut, where I am Visiting Professor of Anthropology. I have been examining by ultrasonic imaging the carotid arteries of Alaskan natives (Aleuts, Eskimos, and Indians), who are believed to have low incidence of coronary occlusion and strokes. It is evident that diets high in marine fats (fish and marine mammals) with low levels of arachidonic and eicosapentanoic acid are less atherogenic than diets rich in beef and pork fat. Getting these loose ends of a varied career in science written up for publication withou secretarial assistance or the stimulus of graduate students and ready access to library facilities is keeping me occupied for the time being.

Bowman Gray School of Medicine
Wake Forest University
Winston-Salem, NC 27103

Steven M. Horvath to Bob Alexander:

I was supposed to retire some six years ago but have been recalled each year and also this year. I have retired as Director of the Institute but continue to teach half time. This has given me the opportunity to devote more of my time to research, and this has been exciting. I am in closer contact with my graduate students and postdoctoral fellows now that I don't have to shuffle paper. It has also resulted in improvement in my research support, and consequently I have had more stimulus and have rediscovered some of my earlier interests. I also have more time for clinical research. All in all, retirement has not been a problem; in fact, I have been able to do more than before nationally, internationally, and more importantly in the laboratory.

Institute of Environmental Stress
University of California
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Future Meetings

1985	
FASEB Annual Meeting	April 21-26, Anaheim
Joint APS/The (British) Physiological Soc Mtg	Sept. 12-14, Cambridge (UK)
APS Fall Meeting	October 13-18 Niagara Falls/SUNY, Buffalo
1986	
FASEB Annual Meeting	April 13-18, St. Louis
IUPS Congress	July 12-20, Vancouver, Canada
APS Fall Meeting	Oct. 5-10, New Orleans
1987	
*FASEB Annual Meeting	March 29-April 3 Washington, DC
APS Fall Meeting	October 11-16, San Diego
*APS Centennial Celebration	

Space Sickness

JOHN M. TALBOT AND KENNETH D. FISHER
Life Sciences Research Office
Federation of American Societies
for Experimental Biology
Bethesda, Maryland 20814

Space sickness, also known as space motion sickness or the space adaptation syndrome, affects about one-half of all astronauts. It is a self-limiting disorder with manifestations similar to those of ordinary motion sickness. However, its precise cause has not been well defined, nor are adequate methods available for its prevention or control. The most frequently cited hypothesis about its etiology is based on the concept of sensory conflict involving mainly the vestibular, visual, and kinesthetic sensory systems. This paper is a synopsis of a report[1] prepared for the National Aeronautics and Space Administration (NASA) by the Life Sciences Research Office (LSRO) of the Federation of American Societies for Experimental Biology (FASEB). The report reflects the views of an ad hoc working group[2] of expert investigators who met at FASEB Headquarters in September 1982 to review space sickness and suggest additional research for consideration by NASA.

The objectives of the LSRO study were to review extant knowledge of the subject, identify significant gaps in knowledge, examine NASA's current and projected research program, and formulate suggestions for research.

Background Information

Because it incapacitates some space flyers and impairs the physical and mental well-being of others, space sickness is, during the first few days of flight, an operationally important problem. Its occurrence (Table 1) and main features (Tables 2 and 3) have been documented. Any impairment of physical or mental capacities during spaceflight is important to crew safety and mission accomplishment. This is particularly significant in short-term space missions such as the Shuttle flights in which an illness lasting 2–4 days could interfere with planned mission activities.

A majority of experts regard space sickness as a variant of ordinary terrestrial motion sickness. Inasmuch as the role of motion in its etiology remains undefined, the term space sickness was preferred by the LSRO Ad Hoc Working Group. Space sickness typically occurs during the initial 1–5 days in orbit and is aggravated by head movement, as well as moving about and performing various tasks in the spacecraft. Data from the Apollo and Skylab programs indicate that the onset of symptoms occasionally occurred as early as 2 h after launch; the manifestations disappeared within 2–5 days after launch (20). The signs and symptoms have ranged from mild gastric awareness and malaise to moderately severe nausea, vomiting, discomfort, and weakness (18, 21, 29, 32, 46). Associated phenomena have sometimes included spatial illusions and the "sopite syndrome," which is characterized by yawning, somnolence, indifference toward mental and physical work, and withdrawal from group activities (19).

Etiology

Two environmental factors are thought to play key roles in the genesis of space sickness: weightlessness and motion. While the passive accelerations resulting from motion of a spacecraft in stable flight may be minor (17), accelerations from movements of head and body during flight can be large, and appear to contribute to the induction of the syndrome (20, 25). However, such head and body motions would not ordinarily induce symptoms on Earth.

In contrast, the motion component in the etiology of terrestrial types of motion sickness is relatively well defined (5, 16, 17, 26, 34, 39). Nevertheless, knowledge of the mechanisms involved in induction of the emetic syndrome of ordinary motion sickness and space sickness is inadequate to explain the phenomena and to offer practical means of prevention and optimal methods of control. Current investigations of the mechanisms of motion and space sickness are based mainly on theories of neural mismatch or sensory conflict, overstimulation with spillover of impulses, or certain postulated effects of the cephalad shift of blood and tissue fluids that occurs in weightlessness.

Reason (33) suggested that a mismatch between information received from the spatial sensors and that in the

[1]Copies of the report, entitled "Research Opportunities in Space Motion Sickness" are available in limited quantities from the Manager, Biomedical Research Program/EBT-3, Life Sciences Division, NASA Headquarters, Washington, DC 20546; from the National Technical Information Service, U.S. Department of Commerce, P.O. Box 1553, Springfield, VA 22161, PB N83-21756; or from the Special Publication Branch, FASEB, 9650 Rockville Pike, Bethesda, MD 20814 at $8.00 each (prepaid).

[2]Participants were: H. L. Borison, Ph.D., Professor of Pharmacology, Dartmouth Medical School; K. R. Brizzee, M.D., Ph.D., Head, Department of Neurobiology, Delta Regional Primate Center, Covington, LA; B. Cohen, M.D., Morris B. Bender Professor of Neurology, Mt. Sinai School of Medicine, NY; M. J. Correia, Ph.D., Professor of Otolaryngology, Physiology, and Biophysics, University of Texas Medical Branch, Galveston; L. Gardner, Ph.D., Chief, Clinical Neuropsychology Branch, USAF School of Aerospace Medicine, Brooks AFB, TX (current address: Johnson Space Center, Houston, TX); J. M. Goldberg, Ph.D., Professor of Physiology and Theoretical Biology, University of Chicago; R. I. Kohut, M.D., Professor of Otolaryngology, Bowman Gray School of Medicine, Winston-Salem, NC; M. J. Kuhar, Ph.D., Professor of Neuroscience, Pharmacology, and Psychiatry, Johns Hopkins University; R. S. Naunton, M.D., Director of Communicative Disorders Program, National Institute of Neurological and Communicative Disorders and Stroke. Special scientific reviewers were: A. J. Benson, M.D., Ch.B., RAF Institute of Aviation Medicine, Farnborough, U.K.; D. J. Lim, M.D., Director, Otological Research Laboratories, Ohio State University.

Table 1
Space Sickness During U.S. Manned Spaceflight Programs

Program	No. of Crewmen	Incidence of Reported Symptoms
Mercury	6	0
Gemini	20*	0
Apollo	33*	11†
Skylab	9	5
ASTP‡	3	0
STS§	6	3

* Includes 4 crewmen who flew twice during program.
† Includes 1 crewman who experienced symptoms on both of two flights.
‡ Joint U.S.-U.S.S.R. Apollo-Soyuz mission.
§ Space Transportation System/Shuttle Orbiter. (See also Editor's Note at end of text.)

neural store from past experience led to motion sickness. An essential component of the theory is a normal vestibular system, and it is noteworthy that persons who lack a functional vestibular apparatus are not susceptible to motion sickness. Certain features of the theory were summarized by Homick (21):

> "The majority of research in progress to define the etiology of space motion sickness is generally based on the premise that the syndrome is the overt manifestation of unresolved sensory conflict. In all likelihood, modifications in otolith behavior which occur during the first few hours in weightlessness are a primary factor in creating sensory conflict. The conflict may be in part intralabyrinthine in origin. That is, the normal synergy that is thought to exist between the semicircular canals and otoliths may be disrupted, thus resulting in modified neural outflow. Also, it is probable that intermodality conflict involving the visual, vestibular and the touch, pressure and kinesthetic senses occurs. The net result may be an inability of the central nervous system to properly integrate the mismatched sensory influx. Adaptive processes in the central nervous system presumably occur as evidenced by the gradual and complete recovery from symptoms of motion sickness."

Overstimulation of the vestibular nuclei with "spillover" or "radiation" into adjacent neural centers has been suggested as a pathogenetic mechanism for motion sickness (2, 8, 13, 35). However, this hypothesis does not account for the absence of sickness during lively horseback riding, for example. Another hypothesis suggests that labyrinthine fluid imbalances may result from the well-documented cephalad shifts of blood and body fluids in zero G and may cause abnormal vestibular function leading to symptoms typical of motion sickness (37, 44). Some additional support for the concept is based on the knowledge that acute changes of air pressure in the middle ear can induce vertigo (1). (See also, Editor's Note below.)

The LSRO Ad Hoc Working Group on Space Motion Sickness considered that the sensory conflict theory is useful in planning research and designing experiments but that it is insufficient, at its present state of development, to explain any underlying mechanisms of space sickness. Indeed, it is possible that there are multiple etiologies for the symptoms experienced by spacecrew members and that not all the observed manifestations result solely from the effects of motion on the vestibular system. An example of a possible alternate etiologic factor might be trace amounts of a toxic compound, such as trichloroacetylene, in the spacecraft breathing atmosphere. However, no evidence of the presence of significant amounts of such toxic contaminants in U.S. manned spacecraft came to the attention of the Ad Hoc Working Group.

Prevention and Control

Because the biological mechanisms of space sickness are not understood, NASA has relied mainly on anti-motion sickness drugs for prevention and treatment of space sickness. These agents have apparently aided in preventing or controlling the syndrome in some, but not all, astronauts. Anti-motion sickness drug evaluations in ground-based studies and in aircraft have shown that agents which possess central anticholinergic actions and drugs which augment central sympathetic activity are effective against acute motion sickness (5). Currently, NASA uses the orally administered combination of scopolamine (0.35 mg) and dextroamphetamine (5.0 mg) for premedication or treatment. During sleep periods, promethazine (45) or diazepam (30) has been suggested. The NASA strategy for anti-motion sickness medication includes individual preflight evaluation of drug effectiveness against the effects of provocative vestibular stimulation and observations of side effects. Astronauts scheduled for space missions are treated according to the

Table 2
Space Motion Sickness*

Probable variant of terrestrial motion sickness
Characterized by:

Inflight
- Onset shortly after beginning to move about in weightlessness
- Symptoms aggravated by movement and persist 2–5 days
- Illusions may be encountered with these movements; spatial disorientation and illusions minimal and of no operational significance
- Nausea, cold sweating, pallor, vomiting
- Crew performance and mission timelines occasionally disrupted
- After adaptation, inflight resistance to motion stimuli is high
- Anti-motion sickness drugs are the only therapy used to date; efficacy has been limited

Postflight
- Isolated symptoms of motion sickness apparently induced by recovery ship motion
- Temporary ataxia and postural dysequilibrium
- No significant illusions or disorientation

Based on Skylab:
- About 50% of crew members will be symptomatic
- Perhaps 15% will be frankly ill
- Incidence appears related to movement within spacecraft
- Medications are useful but not completely effective
- Ground-based tests cannot yet meaningfully predict who will become sick

Experience on STS† 1-3 is consistent with the above data

* Source: Unpublished material from Johnson Space Center Workshop on Space Motion Sickness, June 1982. (See also Editor's Note at end of text.)
† Space Transportation System, Shuttle Flights 1, 2, and 3.

Table 3
Significant Observations from U.S.S.R. Program*

Preflight
- "Active" and "passive" vestibular training techniques used with all cosmonauts
- 6° Head-down tilt during sleep used as fluid shift conditioning technique
- Ground-based tests do not correlate well with inflight symptoms
- Parabolic flight reasonably good predictor of inflight symptoms

Inflight
- Space sickness experienced by 40–45% of cosmonauts
- Main symptoms are sweating, salivation, dizziness, nausea and vomiting
- In all cases symptoms aggravated by head movements
- Periods of adaptation vary from one to several days
- Many crewmen experienced various illusions of body tilt and visual displacement
- No quantitative vestibular response measurements
- Countermeasures included:
  - Antihistamine anti-motion sickness drug
  - Voluntary restriction of head movements
  - Mechanical devices (elastic cap† and pneumatic waist cuff)

Postflight
- Motion sickness symptoms (exacerbated by head movements) seen in some crewmen
- Ataxia experienced by most crewmen
- Hypo- and hyperreflexia of otolith function (ocular counterrolling)
- Increased canal reactivity (cupulogram)
- Tendon hyperreflexia

* Source: Unpublished material from Johnson Space Center Workshop on Space Motion Sickness, June 1982.
† Imparts mechanical load to cervical muscles and restricts head movement.

following plan: *1*) premedication if there has been no previous spaceflight experience or if there is a positive history of space sickness; *2*) no premedication if there is no history of space sickness during previous flights; *3*) inflight treatment if symptoms occur.

A nonpharmacological countermeasure that holds promise is autogenic feedback training (7, 38). This type of method has demonstrated effectiveness in salvaging for flying duties a substantial number of U.S. Air Force aircrew personnel who suffered incapacitating airsickness (12). Whether it may prove to be effective and practical for spacecrew members remains to be demonstrated. NASA's research plans include consideration of this question.

Attempts were made to preadapt some members of the Skylab crew to provocative vestibular stimulation by a regimen of repeated series of head movements with subjects seated in a rotating chair and by weekly sessions of aerobatics in high-performance aircraft (Skylab 4 crew members) (21). Although these procedures appeared to reduce susceptibility to motion sickness induced by ground-based Coriolis accelerations, there was no evidence of their possible benefit during the Skylab 4 mission. Nevertheless, the concept of pre-spaceflight vestibular habituation using ground-based or airborne methods has not been abandoned.

NASA's Research Program

Table 4 lists short titles of examples of the intramural and extramural research and development in space sickness that is a part of NASA's Biomedical Research Program. Responsibility for the administration and scientific management of the research program is shared among NASA Headquarters and the scientific staffs at the Ames Research Center, Moffett Field, California, and the Johnson Space Center at Houston. The research center scientists monitor the extramural university-based investigations and, in addition, conduct intramural investigations. Most of the investigations in the Space Motion Sickness Program are ground based; however, through these investigations, hypotheses are developed that must ultimately be tested in space. Thus the program is logically related to the planned series of inflight experiments in the Shuttle and Shuttle/Spacelab missions. In addition to the research and development tasks listed in Table 4, other activities pertaining to space sickness are conducted as parts of other NASA programs. These include identification of resistant individuals, preflight vestibular habituation, transferability and enhancement of habituation, autogenic feedback training, devices to restrict head movement and load the cervical muscles, and alternate types of preventive drug treatment. Anticipated results of the planned inflight experiments on the Shuttle and Spacelab should answer key questions on the functional status of the vestibular apparatus during weightless flight.

Heightened concern in NASA about the problems of space sickness has resulted in increased effort toward their solution. For instance, a major workshop confer-

Table 4
Short Titles of NASA Research and Development Tasks in Space Motion Sickness

Projects administered by the NASA Ames Research Center
- Anatomy and physiology of vestibular system
- Physiology of vestibular system
- Significance of sensory interactions
- Visual-vestibular habituation spaceflight
- Histochemical aspects CNS emetic centers
- Vestibulocollic reflexes of otolith origin
- Central otolith mechanisms
- Vestibular afferents to area postrema
- Vestibular Research Facility studies
- Biochemical factors in motion sickness
- Semicircular canal/otolith interactions
- Spontaneous vestibular afferents
- Vestibular nuclei neurotransmitters
- Brain-gut interactions in motion sickness
- Vestibular efferent neurons

Projects administered by the NASA Johnson Space Center
- Institutional support, space adaptation research
- Vestibular Laboratory Facility modification
- KC-135 vestibular research/development
- Autogenic/biofeedback laboratory
- Enhanced vestibular test battery
- Toxicology Laboratory prophylactic drug analysis
- Selection criteria and drugs
- Drug effects on vestibular ocular reflex
- Bioinstrumentation and devices for head motion restriction
- Space flight rotator
- Pharmacological countermeasures
- Human performance testing
- Slow rotating test device
- Motion sickness mechanisms
- Intralabyrinthine fluid dynamics
- Postural mechanisms, dynamic conditions
- Vestibular Laboratory operations
- Motion sickness longitudinal study
- Side-effects, antimotion sickness drugs
- Etiology of motion sickness
- Biofeedback flight experiment

ence was held at the Johnson Space Center in June 1982 to facilitate planning for future research; *Proceedings* have been published (22). A majority of the studies and their recommended priorities are consistent with the opinions of the LSRO Working Group. The biological systems approach identified in the *Proceedings* (22) would offer a particularly promising methodology for research planning and experimental design. Similarly, the broadening of the disciplinary approach, the emphasis on chemical-mediating mechanisms in the stimulus-to-vomiting sequence, and the use of interdisciplinary teams to define the physiological correlates of the conflict and mismatch theories and the specific linkages to the effector mechanisms of space sickness are examples of research strategies supported by the LSRO Ad Hoc Working Group on Space Motion Sickness. Finally, another important step was the recent establishment at the Johnson Space Center of a Space Biomedical Research Institute for research on space sickness and the space adaptation syndrome.

Observations of Ad Hoc Working Group

Cause and Mechanisms

Although experience in spaceflight strongly suggests that movements of the head are necessary to induce the syndrome of space sickness, this has not been documented adequately, and a fundamental question persists: "What is the stimulus for space sickness?" Among the questions whose answers are essential for a practical understanding of the problem are *1*) whether the vestibular organs remain physiologically normal in weightlessness; *2*) identification of the neural pathways involved in motion and space sickness including vestibular, visual, proprioceptive, and central; *3*) the associated biochemistry and neuropharmacology; *4*) whether the "final" stimuli in the reflex arcs of nausea and vomiting are neurogenic or chemogenic; *5*) where and by what means adaptation and habituation to ordinary and extraordinary motion stimuli occur; and *6*) the roles of the diencephalon and cerebral cortex.

Peripheral Sensory Organs

Among the sensory systems that may be involved in space sickness, the vestibular system appears to be primarily involved. Many scientists believe the vestibular end organ remains normal during spaceflight; however, there is some conflicting evidence (42). The Working Group identified pertinent topics for which data are either unavailable or seriously incomplete, for example, *1*) the structural and ultrastructural relationships and interactions among the otoconia, cupulae, and hair cells (9, 24); *2*) identification and characterization of the neurotransmitters and chemoreceptors in the peripheral neuroepithelium of the vestibular apparatus (11); *3*) the question whether the semicircular canals are sensitive to gravity (10, 14); *4*) whether information processing occurs between various components of the semicircular canals and the otolith organs (3, 4); *5*) the conflicting data on the origins and effects of efferent stimuli on the vestibular end organs (15); *6*) development and maintenance of accessory structures such as otoconia, otoconial membrane, and cupulae; and *7*) the effects of possible alterations of labyrinthine hemodynamics induced by zero G on vestibular function and composition of the perilymph and endolymph.

Central Nervous System

Pathways in the central nervous system (CNS) involved in transmitting and processing neuronal impulses resulting from motion stimuli have been only partially delineated. A fundamental question concerns where and how the CNS processes motion-induced signals from the vestibular, visual, proprioceptive, and somatosensory sensors. The vestibular nuclei and parts of the vestibular cerebellum probably have key roles in such information processing, but detailed data are unavailable. Examples of other brain stem structures that may participate in the signal processing include the nucleus prepositus, nucleus intercalatus, and nucleus of Roller, all of which seem to connect directly or indirectly with the vestibular nuclei, nucleus tractus solitarii, and area postrema. Neurons have been identified whose cell bodies are in the area subpostrema inside the blood-brain barrier, whose dendrites extend through the blood-brain barrier into the area postrema, and whose axons connect with the nucleus tractus solitarii. Whether they may have a role in the nauseogenic response to motion is unknown. In summary, numerous connections have been found that are of interest in relation to motion and space sickness, although very little is known about their functions (6, 23, 27, 28, 40, 41). Critically important aspects of information processing are adaptation and habituation to the inducing stimuli. Here again, the mechanisms involved are essentially unknown. Moreover, there are no currently available adequate models or methods of analysis for resolution of questions on central processing.

A search is in progress for a possible biochemical link in the chain of events between peripheral sensory stimulation and generation of nausea and vomiting. Demonstration of the existence of such a substance and its localization and characterization could lead to a major advance in pharmacological intervention. Recent studies have demonstrated the presence of antimuscarinic and antihistaminic types of receptors in the vestibular nuclei of rats (31, 43). Such findings represent progress in functional neuronal mapping as well as opportunities for improving pharmacological intervention.

Other CNS areas of interest for which basic data are insufficient include *1*) possible effects of the brain stem reticular formation on responses to motion stimuli at the level of the vestibular nuclei; *2*) roles of the diencephalon and cerebral cortex in motion sickness and habituation to the provocative stimuli; and *3*) the role of the cerebellum in generation of space sickness and the associated processes of habituation.

Methodology and Models

The Working Group noted that few research reports of interest to space sickness have resulted from use of some of the newer techniques of neuroscience such as the 2-deoxyglucose technique, immunocytochemical methods, horseradish peroxidase double labeling, and electron-microscopic autoradiography. These and other techniques are described in the 1978–82 short-course syllabi of the Society for Neuroscience (11 Dupont Circle, NW, Suite 130, Washington, DC 20036). With regard to animal models, dogs, cats, and squirrel monkeys appear to be the most appropriate identified to date; however, search for other suitable animal models should continue. Moreover, new ideas are needed on how best to simulate the dynamic environments of spaceflight, including weightlessness, for use in ground-

based investigations. Finally, available functional tests of the vestibular apparatus are generally inadequate for investigation of space sickness, emphasizing a need for further work in this area.

Countermeasures

Efforts are continuing in NASA on such logical approaches as developing means of preflight identification of susceptible versus tolerant individuals, preflight habituation and its inflight enhancement, self-control of symptoms, and improved drug intervention. However, major progress in countermeasures probably will be slow until the basic mechanisms of motion and space sickness have been elaborated.

Research Suggestions

As a general approach, a program should be planned to map areas of the brain thought to be involved in space and motion sickness and to identify and characterize the associated chemoreceptors, neurotransmitters, and neuromodulators. Related studies should probe the roles of the identified pathways and regulatory substances in the mediation of, and habituation to, space and motion sickness and as leads for discovering new drugs.

Table 5 is a partial list of research suggested by the LSRO Ad Hoc Working Group on Space Motion Sickness. A complete treatment of the research suggestions is contained in the LSRO report to NASA (36).

Table 5
Research Suggested by LSRO Ad Hoc Working Group on Space Motion Sickness

Stimulus-response relationships

- Delineate quantitatively the essential characteristics of the disorder with respect to environmental circumstances, symptomatology, and time course
- Determine with certainty the indispensability of the vestibular apparatus as the key sensory element in space sickness

Reflex pathways

- Evaluate neuronal circuits in the vestibular nuclei and the vestibular centers of the cerebellum in mediating space and motion sickness and as a confirmation of the early experiments described by Tyler and Bard (39)
- Confirm the role of the chemoreceptor trigger zone in the central emetic circuit
- Explore neuronal elements of the vestibulocerebellar circuits for changes in electrophysiologic activity relating to habituation
- Study the participation and functional specificity of chemical mediators at transmission points in the vestibulocerebellar emetic circuit and possible modifying factors such as efferent input
- Examine the interactions among vestibular, proprioceptive, visual, and somatosensory inputs recruited in the genesis of space sickness

Related vestibular neurophysiology

- Study the sensitivity of the semicircular canals to linear acceleration in the alert, chronic normal preparation, and relate this to space and motion sickness
- Investigate in the alert preparation the relationship between afferent vestibular neuronal activity and efferent activity in situations in which the efferent system may participate
- Explore circulatory factors regulating endolymph composition and function as these may affect vestibular function
- Identify and characterize at the single unit level, the afferent input from the vestibular organs resulting from complex motion stimuli such as cross-coupled accelerations

Concluding Remarks

An important part of NASA's Biomedical Research Program focuses on space sickness, a disorder whose adverse effects on the well-being, effectiveness, and safety of spacecrew members, justify extraordinary efforts to resolve the problem.

Space sickness is likely to occur and impair crew well-being and performance in the initial 2–5 days of a mission, during which habituation takes place, resulting in tolerance for the causative stimuli. Thus it is highly significant during the first few days of spaceflight, a factor of some concern in all manned spaceflights, but especially in missions of relatively short duration such as those in the Space Shuttle program.

Space sickness is generally regarded as a variant of the more common type of motion sickness. However, the provocative stimuli are probably somewhat modified from those that cause ordinary motion sickness because the spacecraft and astronauts in orbital flight are in continuous free fall and are therefore in a state of weightlessness. Head and body movements in combination with the influence of weightlessness are thought to be the main sources of the stimuli that induce space sickness.

Development of a widely accepted scientific definition of space sickness is hampered by a lack of data on the precise causal stimulus or stimuli and on the basic biological mechanisms involved in the genesis of, and habituation to, the disorder. The same may be said for ordinary motion sickness except that, for it, the initiating stimuli have been reasonably well documented. As a result of critical gaps in knowledge, research continues to be formulated on the basis of theory and hypothesis. The most popular theories include sensory mismatch, or conflict, and sensory overstimulation and overflow. While these theories appear basically logical, they do not identify the precise adequate stimulus for space sickness, nor do they explain fundamental mechanisms involved in translating the cause into such responses as nausea, vomiting, and habituation.

With the exception of drugs, various approaches toward prevention and control of space sickness have not led to practical countermeasures, for example, means of identifying resistant individuals and vestibular adaptation training. Autogenic feedback (biofeedback) training of aircrew members appears to be a practical method of dealing with airsickness, but whether it may be practical for astronauts remains to be demonstrated. Thus, at present, NASA uses anti-motion sickness drugs, which have proved useful for some, but not all, affected crew members.

Aside from a possible fortuitous breakthrough in countermeasures, satisfactory solution to the problem of space sickness will depend on identification of its cause or causes as well as discovery and elaboration of the basic mechanisms that mediate the syndrome and the associated processes of habituation. Key questions include whether the vestibular apparatus is indispensable to the space sickness response and which factors determine individual susceptibility or tolerance.

Major essential data are unavailable for explaining the train of events that starts with exposure to the causal stimulus, moves into the stage of acute symptomatic response, initiates concomitant processes of adaptation and habituation, and, postflight, may reverse itself

during reaccommodation to the terrestrial environment. Much greater emphasis should be placed on generating research in those disciplines, in addition to vestibular physiology, that offer promising approaches such as the anatomy, biochemistry, pharmacology, and endocrinology of the reflex circuits involved and the use of some of the more recent investigative methods of neuroscience. Such emphasis should aid in broadening the research program and expediting discovery of such essentials as the key neuronal circuits involved, their associated receptors, transmitters, and modulators and the determination of the indispensible anatomic and humoral elements in the reflex pathways of space and motion sickness and their biological mechanisms.

Editor's Note

Since the completion of the LSRO study on space sickness in February 1983, new data and observations of considerable interest for achieving a better understanding of the syndrome have been published or otherwise made public. Examples include experimental evidence for a humoral agent of motion sickness in cerebrospinal fluid (G. H. Crampton, and N. G. Daunton. Evidence for a motion sickness agent in cerebrospinal fluid. *Brain Behav. Evol.* 23: 36–41, 1983); however, new data showing that ablation of the area postrema in cats does not abolish the motion sickness response do not appear to support the concept of a humoral nauseogenic substance [H. L. Borison, L. E. McCarthy, R. Borison, A. K. Mandal, and T. J. Fisk. Motion sickness is not prevented by chronic ablation of area postrema in cats (Abstract). *Federation Proc.* 43: 504, 1984].

From inflight experiments and tests during Space Shuttle missions STS-7 (June 8–24, 1983), STS-8 (Aug. 30–Sept. 5, 1983), and STS-9 (Spacelab-1, Nov. 28–Dec. 8, 1983), information and data were derived that improve the characterization of space sickness. For example, Physician-Astronaut William Thornton, who conducted inflight tests and experiments during STS-8, noted *1*) the importance of head movements in inducing and aggravating symptoms of space sickness; *2*) an absence of sounds of upper gastrointestinal peristalsis in afflicted crew members and the possibility of relieving the attendant discomfort by pharmacological means; *3*) the frequent absence of facial pallor, sweating, and prodromal nausea; *4*) headaches; and *5*) an absence of noteworthy changes in threshold audiometry, audiometric evoked potentials, and electrooculograms [A. Chaikin. Sick in space. *Science 84* 5(5): 50–55, 1984; W. E. Thornton. Unpublished information presented at *Annu. Sci. Meet. Aerosp. Med. Assoc., San Diego, CA, May 9, 1984*].

In Spacelab-1, three of four crewmen suffered space sickness and vomited repeatedly. Their signs and symptoms disappeared after 2 days in orbit. Symptoms included marked epigastric discomfort and malaise; the intensity of symptoms was modulated by head movements. Tactile and proprioceptive cues were palliative, as was closing the eyes. Prodromal nausea was absent or brief before vomiting, and not all the affected crew members exhibited facial pallor and sweating (C. M. Oman. Unpublished information presented at *Annu. Sci. Meet. Aerosp. Med. Assoc., San Diego, CA, May 7, 1984*).

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Announcements

Availability of Iron Report

An ad hoc Expert Scientific Working Group of the Life Sciences Research Office has completed a study of data on iron nutritional status collected during the second National Health and Nutrition Examination Survey (NHANES II). Data analyses and interpretation of the results by the Expert Scientific Working Group form the basis for the report entitled "Assessment of the Iron Nutritional Status of the U.S. Population Based on Data Collected in the Second National Health and Nutrition Examination Survey, 1976-1980." The report, sponsored by the Center for Food Safety and Applied Nutrition, Food and Drug Administration, provides a description of the methodology used to collect data on iron status indicators, and reference data for the U.S. population for hemoglobin level, mean corpuscular volume, erythrocyte protoporphyrin level, transferrin saturation, and serum ferritin level. Three different models incorporating these indicators are described and are used in estimating the prevalence of impaired iron status due to iron deficiency or inflammation. The three models are assessed, and the contribution of inflammatory disease to the prevalence estimates and the influence of factors such as race, poverty, level of education, and parity are examined. Recommendations for additional analyses of NHANES II data on iron and for the conduct of future surveys of iron nutritional status are included in the report. *For copies of report:* FASEB Special Publications Office, 9650 Rockville Pike, Bethesda, Maryland 20814, at $12.00 postpaid.

NRC Postdoctoral Fellowships for Minorities

The National Research Council plans to award approximately 35 Postdoctoral Fellowships for Minorities in a program designed to provide opportunities for continued education and experience in research for American Indians and Alaskan Natives (Eskimo or Aleut), Black Americans, Mexican Americans/Chicanos, and Puerto Ricans. Fellows will be selected from among scientists, engineers, and scholars in the humanities who show greatest promise of future achievement in academic research and scholarship in higher education. Awards in the Postdoctoral Fellowships for Minorities Program will be made in the behavioral and social sciences, humanities, engineering, mathematics, physical sciences, and biological sciences, and for interdisciplinary programs comprised of two or more eligible disciplines. *Application deadline:* 16 January 1985. *Information:* Fellowship Office, National Research Council, 2101 Constitution Ave., NW, Washington, DC 20418.

NRC Research Associateships

The National Research Council announces the 1985 Postdoctoral, Resident, and Cooperative Research Associateship Programs for research in the sciences and engineering to be conducted in behalf of 21 federal agencies or research institutions, whose laboratories are located throughout the U.S. Approximately 250 new full-time associateships will be awarded on a competitive basis in 1985 for research in chemistry, engineering, and mathematics, and the earth, environmental, physical, space, and life sciences. *Application deadline:* January 15, 1985. *Information:* Associateship Programs, Office of Scientific and Engineering Personnel, JH 608-D3, National Research Council, 2101 Constitution Ave., NW, Washington, DC 20418 (202/334-2760).

ALS Research Award

An annual award of $25,000 is being offered for the first time to a scientist or group of scientists who make the most significant contribution to furthering an understanding of amyotrophic lateral sclerosis (ALS). Sole criteria for the award is the achievement of significant progress in ALS research and applies to both advances in therapy and scientific research. *Deadline:* Feb. 15, 1985. *Information:* Awards Committee, ALSSOA, 15300 Ventura Blvd., Suite 325, Sherman Oaks, CA 91403.

A Hydrodynamic Model of The Human Leg Circulation

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The subject of hemodynamics is a normal component of most medical physiology courses. However, practical application of this topic is often lacking. To emphasize the importance of hemodynamic concepts in the clinical realm, we have developed a life-size hydrodynamic model of the human leg circulation to demonstrate the principles that govern the distribution of blood flow under normal and pathological conditions. This model is primarily used with third-year medical students who are taking a required clinical rotation in vascular surgery. The instructor demonstrates and discusses to groups of two or three students each of the four experimental procedures described in this paper. The model is also used with small groups of first-year medical students as a supplementary lecture demonstration.

Model Description

The vascular anatomy of the leg (Figure 1) is comprised of three major vascular beds supplied by the internal iliac artery (buttucks, bladder, etc.), deep femoral artery (upper limb), and tibial arteries (lower limb). These vascular beds are arranged in parallel to each other and with the rest of the systemic circulation. The total resistance (R_T) of all four parallel elements can be described as follows[1]

$$R_T = \frac{1}{1/R_s + 1/R_{ii} + 1/R_{df} + 1/R_t}$$

As discussed in most physiology textbooks, this relationship shows that R_T is less than the smallest individual resistance. Furthermore, if one of the smaller resistances is changed (e.g., $R_{df} \rightarrow \infty$), then only a small effect would be noted on R_T. This in turn, at constant cardiac output, would lead to only a small change in arterial pressure.

[1] Abbreviations: A, aorta; s, systemic circulation; ci, common iliac; ii, internal iliac; ei, external iliac; df, deep femoral; sf, superficial femoral; p, popliteal; tl, large tibial; ts, small tibial; Q, flow; P, pressure; R, resistance.

In the normal limb, the in-series resistance vessels (common iliac, external iliac, and superficial femoral arteries) constitute an almost negligible resistance to flow. However, in certain disease states (e.g., atherosclerosis, vascular compression, or thrombosis) where the diameter of the vessel lumen is reduced or occluded, these in-series vessels may contribute significantly to the total limb resistance.

The model (Figure 2) is comprised of a variable-speed roller pump (Masterflex, Cole-Palmer model 7520-00 with 7015-21 pump head), Gilmont flowmeters (Cole-Palmer, five K-3203-00 and one K-3203-00), pressure gauges (Marshall Town Instruments, FS-11281B), and micrometer resistance valves (Cole-Palmer K-3235-00). The approximate cost of these components is $1,500. The components are arranged as shown in Figure 2 and connected together under the Lucite surface of the model with silicone rubber tubing (0.192 inch ID) and plastic T connectors. Flows are measured in each of the three parallel vascular beds of the leg (internal iliac, deep femoral, and tibial arteries), in the series vessels, and in the remainder of the systemic circulation. Pressures are measured at the common iliac artery (just proximal to internal iliac branch), the external iliac artery (just proximal to deep femoral branch), the superficial femoral artery (just proximal to tibial branches), and the distal ends of the large tibial arteries. In addition, systemic arterial pressure is recorded at the aorta. Resistance valves are used to alter flow in the vascular beds supplied by the tibial, deep femoral, and internal iliac arteries. To simulate arterial stenosis, resistance valves are located on the common iliac, external iliac, superficial femoral, and large tibial arteries. The venous return is directed into a bottle that is open to the atmosphere. The inlet tube for the pump receives its supply from this bottle. The main function of the venous bottle is to trap air bubbles.

Initial hydrodynamic conditions are established by adjusting the pump speed, R_{ii}, R_{df}, and R_t so that systemic pressure (P_s) is 100 mmHg and 10% of the pump output goes through the leg. Of this 10%, the internal iliac artery, superficial femoral artery, and tibial arteries receive 40%, 40%, and 20%, respectively. Setting these control conditions is aided by using a screw clamp (R_s, Figure 2) to adjust systemic resistance. Once set, this clamp seldom needs adjusting. The resistance valves on the common iliac, external iliac, superficial femoral, and large tibial arteries are set at minimal resistance. These control parameters simulate the distribution of flow in a resting nondiseased limb.

Experimental Procedures

The procedures described below are typical of the kinds of hemodynamic problems that this model demonstrates. The purpose of these procedures is to show how altering flow in one vascular bed affects the distribution of pressure and flow throughout the limb. Redistribution of pressure and flow are passive responses in this model. Secondary responses such as flow autoregulation and long-term collateralization can also be demonstrated by changing appropriate resistances following the initial passive response. The flow values given in the data figures are uncalibrated. Therefore,

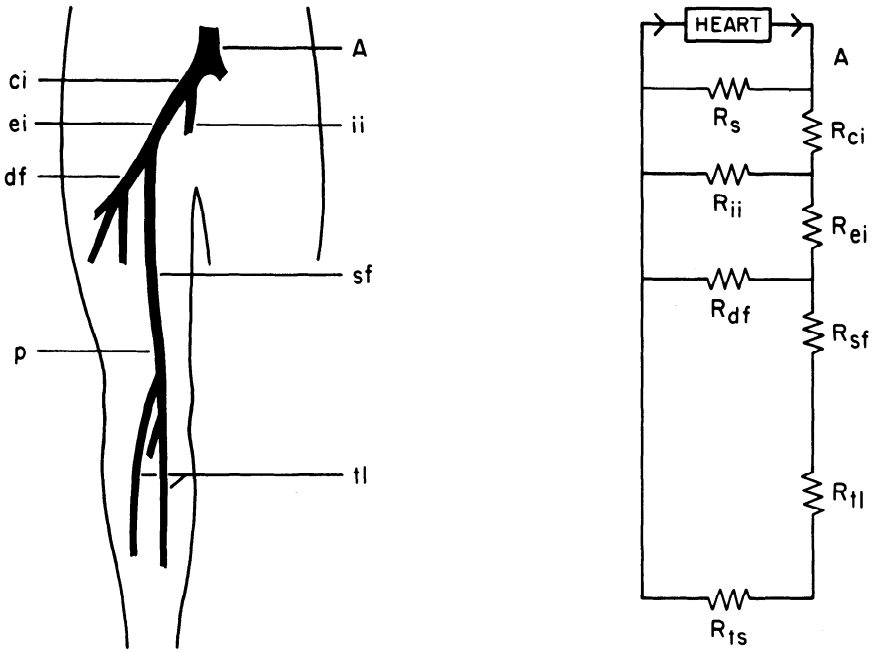


Figure 1
Parallel and series arrangement of leg vasculature. See footnote 1 for abbreviations.

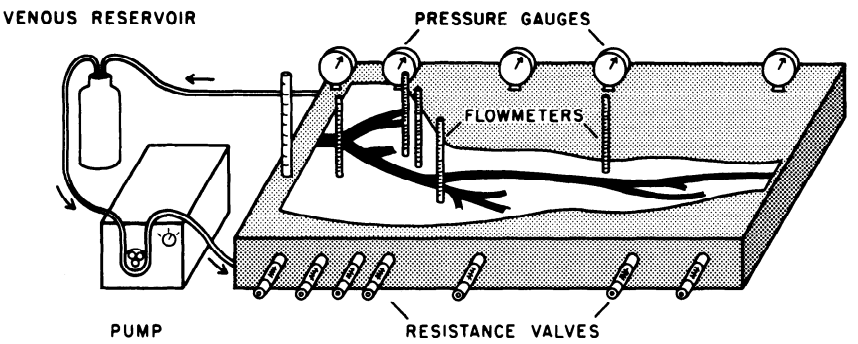
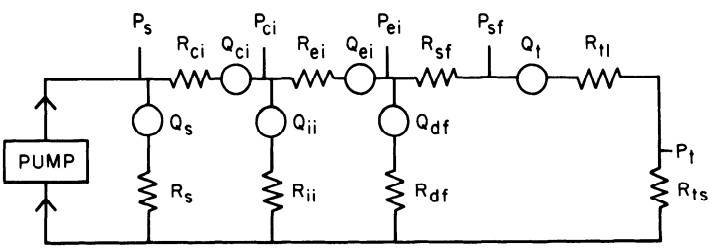


Figure 2
Leg model and diagram showing location of flowmeters, pressure gauges, and resistance valves. See footnote 1 for abbreviations.



when the model is manipulated, the student is looking for qualitative rather than quantitative changes in flow. The flowmeters could be calibrated and scaled to human flow values should quantitative data be desired. However, this is not necessary for teaching the basic concepts which we are describing.

1. Single Vessel Occlusion

The superficial femoral is completely occluded by increasing R_{sf} until distal flow stops. This simulates what occurs in a patient as a result of thrombi, emboli, severe atherosclerosis, vasospasm, or external compression. A common misconception is that this will cause a large increase in deep femoral artery flow. As shown by the model (Figure 3), Q_{df} increases only slightly, and this is due to the small increase in P_s. If pump speed were reduced to simulate baroreceptor reflex effects on cardiac output (i.e., if P_s were kept constant), then Q_{df} would not change in response to occlusion of the superficial femoral artery. This procedure emphasizes that changing flow in one parallel vascular bed does not alter flow in another parallel vascular bed as long as perfusion pressure is not changed to the other bed. In this example, deep femoral flow only depends on its perfusion pressure ($P_{ei} - P_v$) and the resistance of its vascular network [i.e., $Q_{df} = (P_{ei} - P_v)/R_{df}$]. This procedure also demonstrates that increasing the resistance in one parallel vascular bed (e.g., $R_{df} \rightarrow \infty$) has only a small effect on total resistance (R_T) and therefore on systemic arterial pressure.

2. Dilation of Distal Vascular Bed

If the calf muscle were contracted so that its blood flow increased severalfold, what would happen to blood flow in the resting thigh (deep femoral artery)? The most common response to this question is that Q_{df} would decrease. However, when this is done in the model by decreasing R_{ts}, blood flow in the deep femoral shows little if any decline (Figure 4). The reason for this is that unless decreasing R_{ts} also decreases P_{ei}, flow in the deep femoral will not change. Virtually all the increased flow to the tibial vessels can be accounted for by the increased flow in the external iliac. Therefore, the same conclusion is reached as in the previous procedure, namely, that altering resistance and flow in one vascular bed has virtually no effect on flow in other parallel vascular beds. However, this is true only when the distributing arteries (common iliac, external iliac, and deep femoral) are normal (i.e., without significance resistance).

3. Single Artery Stenosis

The presence of a stenosis in the external iliac artery (Figure 5) causes distal pressures and flows to fall (compare resting control flows in Figures 4 and 5). Proximal pressures will increase slightly as a result of increased R_T and P_s. If P_s is held constant by decreasing pump output, proximal pressures will not be different from control and flow to proximal parallel vascular beds will therefore be unchanged. If the calf muscle were contracted so that its resistance decreased, what would happen to flow in the deep femoral artery? This question is similar to the one asked in *procedure 2* except that this time there is a stenotic lesion proximal to both parallel vascular beds. In this case, Q_{df} decreases dramatically as R_{ts} decreases (Figure 5). The reason Q_{df} falls is that P_{ei} (distal to lesion) falls as tibial resistance is decreased. This fall in P_{ei} did not occur in the absence of the lesion because adequate flow could be supplied across the normal external iliac artery. The stenotic artery restricts flow and results in a large pressure drop across the lesion. This pressure drop increases as R_{ts} falls and Q_{ei} increases. Turbulence, kinetic energy losses, as well as viscous energy losses all contribute to the total energy losses and therefore to the net pressure drop across the stenotic lesion. The decrease in Q_{df} as Q_t increases if often referred to as "vascular steal." Although this term is commonly used in the clinical literature, we do not feel that the term accurately reflects the hemodynamic cause for flow redistribution. Flow to the deep femoral is not "stolen" by the tibial vascular bed. Rather, deep femoral flow passively changes in response to an alteration in P_{ei}.

4. Multiple Artery Stenoses

In this last procedure, R_{ei} and R_{sf} are increased to simulate multiple stenotic lesions. The presence of these lesions causes significant pressure drops to occur across these arterial segments (Figure 6). Distal flows will fall because of decreases in perfusion pressure. In response to stenotic lesions, distal vascular beds will undergo short-term and long-term reductions in resistance (autoregulation and collateralization, respectively) to help maintain adequate tissue perfusion. This is simulated in the model by decreasing R_{df} and R_{ts}. Therefore, the flow values indicated in Figure 6 represent this partially compensated state. When similar lesions are found in patients, flows may be near normal at rest. However,

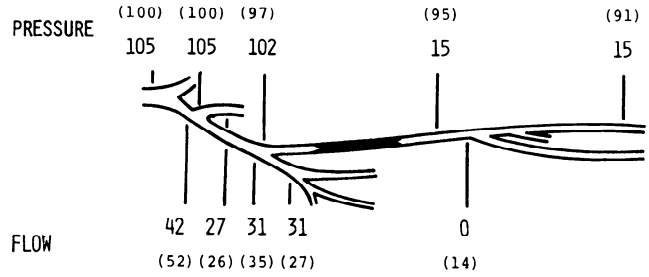


Figure 3
Effects of superficial femoral artery occlusion on distribution of pressures and flows. Smaller size numbers in parentheses are values before occlusion; larger size numbers are values after occlusion.

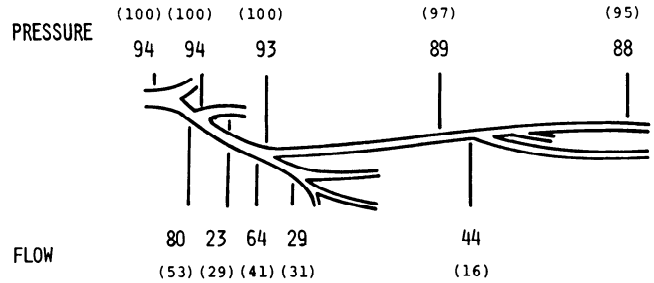


Figure 4
Effects of decreased tibial vascular resistance (e.g., calf exercise) on distribution of pressures and flows. Smaller size numbers in parentheses are resting values; larger size numbers are values during decreased R_{ts}.

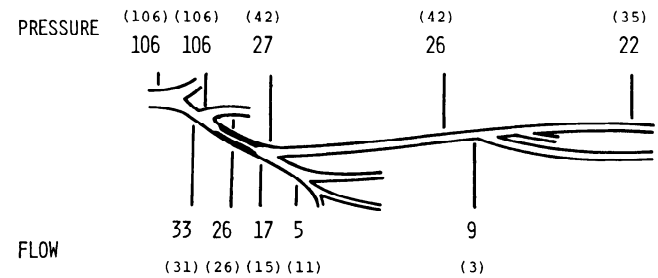


Figure 5
Effects of external iliac stenosis on distribution of pressures and flows during decreased tibial vascular resistance. Smaller size numbers in parentheses are values in resting leg with ei stenosis; larger size numbers are values during decreased R_{ts}.

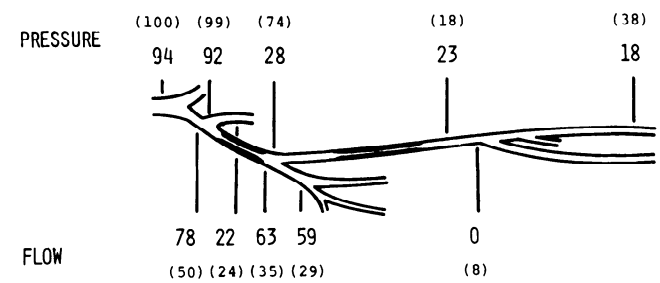


Figure 6
Effects of multiple stenotic arteries (external iliac and superficial femoral) on pressures and flows during whole limb exercise. Smaller size numbers in parentheses are values in resting leg with ei and sf stenotic lesions; larger size numbers are values during whole leg exercise (decreased R_{df}).

upon walking, the patient may complain of severe pain in the calf (i.e., intermittent claudication), which disappears within several minutes of ceasing activity. The hemodynamic basis for the intermittent claudication is shown in Figure 6. When walking begins, the resistance in the deep femoral vascular bed decreases and Q_{df} increases (active hyperemia). As this occurs, Q_t falls precipitously. Although the calf muscle is also contracting, it is unable to significantly decrease its resistance because it is already nearly maximally dilated at rest because of the very low resting perfusion pressure. The reason for the fall in calf blood flow is that the pressure distal to the external iliac lesion decreases as R_{df} decreases and Q_{df} increases. The resulting loss of perfusion pressure to the tibial vascular bed causes a passive reduction in flow to the calf. This is another example of the "vascular steal" phenomenon. The reduction in calf blood flow at a time of high oxygen demand results in ischemic pain.

Summary

This model is a useful tool for helping students to understand the hemodynamic principles that govern blood flow within the limb. The significance of parallel- and series-coupled distributing arteries is clearly demonstrated in both normal and pathophysiological states. Two general principles are derived from the experimental procedures. First, in the normal limb, altering resistance and flow in one vascular bed has little effect on pressures and flows within other parallel vascular beds. Second, in the presence of significant arterial stneosis, altering flow in one bed distal to the lesion will significantly affect pressures and flows within other parallel beds that are also located distal to the stenotic artery.

Computer-Simulated Physiology Experiments: Where Are We Coming From and Where Might We Go?

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Physiology courses at every level of instruction commonly incorporate laboratory exercises as a means of achieving a number of goals (7, 8, 11). These include *1*) reinforcement of content (facts, concepts, etc.) acquired through reading, lecture, and discussions; *2*) demonstration or illustration of dynamic phenomena that cannot readily be presented in a static mode on the blackboard or in the textbook; *3*) demonstration of the integrated behavior of complex systems; *4*) development of the scientific method of inquiry; *5*) development of problem-solving skills; *6*) acquisition of technical skills (use of apparatus, surgical skills, manipulation of data); and *7*) development of an appreciation for the fragility of biological tissue and the variability of its responses.

In spite of the great importance that has been attached to laboratory exercises over the years, it is clear that there has been a trend toward the reduction of laboratory time in *medical* physiology courses (8, 9). Two factors have been of primary importance in prompting this change. One has been the growing competition for time in an ever more crowded curriculum. The growth of biomedical science and the concurrent addition to the medical curriculum of behavioral, social science, and humanities courses have filled nearly every available hour with some scheduled activity (see Ref. 3 for a comprehensive discussion of this problem). Some of these newly added hours have come from reducing the number of laboratory exercises in physiology and other basic science disciplines.

A second factor in reducing laboratory time has been the growing expense of such activities. The total investment in space, equipment, animals, and faculty time now required for the traditional sequence of laboratory experiences in physiology is difficult to justify to cost-conscious administrators, even if we achieve the maximum educational return that can be expected from such teaching exercises.

Paradoxically decreased exposure to laboratories is occurring at the same time that medical education is placing greater emphasis on promoting active learning and problem-solving (skills that are well reinforced by laboratories) as opposed to rote memorization of the ever increasing biomedical data base (3)! One partial solution to this paradox in which there appeares to be growing interest (5, 6) is the use of computers as a teaching tool; this permits, in fact requires, a level of active learning not present in many of the more traditional educational approaches.

Physiology Labs at Rush: "Wet Labs" and Computer-Simulated Experiments

The evolution of the Medical Physiology course at Rush Medical College can illustrate the trends described above. In the early 70's we scheduled approximately nine experiments, of which five or six utilized animals (frogs, cats, dogs). As the demands on student time grew, attendance at laboratories decreased, usually in an unpredictable manner. The growing cost of the laboratory was thus being expended on the education of fewer and fewer students. Recognizing this trend we reduced the number of experiments but attempted to maintain a set of core experiments that we felt had uniquely important benefits for the students. Within a few years we had abandoned all animal experiments but had continued three experiments in which students served as subjects (see below).

However, during this same period a small number of us in the department began to develop computer-based experiments for use in the Medical Physiology course. This was the product of both available technology and faculty interest. The first exercise that was written allowed the students to explore the responses of simple dynamic systems, including models for negative-feedback systems such as operate in living organisms.

We next began to use two computer simulations written at McMaster University; MacMan, a simulation of

the cardiovascular system (2), and MacPuf, a model of the respiratory system (1). We also developed a simulation of the thermoregulatory system. These simulations permit the students to carry out a set of "experimental" procedures on a system much as one would do with an animal preparation. However, some of the experiments that can be performed with these models would be impossible for students to do in an actual laboratory because of the difficulty and/or expense of the procedures required, the length of time needed, or the irreversibility of the procedures carried out on the preparation.

All of these computer-based exercises were used in a laboratory-like setting with associated laboratory manuals and with faculty present to interact with the students. Although such experiments lack the advantages of exposing the students to an actual biological preparation, these computer labs were similar to the traditional "wet lab" in their ability to foster active learning and the development of problem-solving skills. Thus our physiology laboratories have come to consist of a mix of human experiments (cardiac cycle, spirometry and chemical control of ventilation, and urinary concentration and dilution) and computer-simulated experiments (mechanical properties of muscle, baroreceptor regulation of arterial pressure, and regulation of respiration).

This effort was initially a strictly departmental one, with both the software and the hardware made available by interested members of the faculty. However, in the middle to late 70's Rush made a substantial institutional commitment to the support of computer-based education through the establishment of an Office of Computer-Based Education serving the needs of all teaching programs in the Medical Center. The PLATO system (4) was installed, and there are now more than a dozen terminals connected to a large computer at the University of Illinois in Champaign-Urbana and a number of microprocessor systems that may be operated as stand-alone units. Within the last few years the Office has added an Apple III and four IBM PC computers to its hardware.

Currently, the computer-simulated experiments used in the Medical Physiology course are supported by the Office of Computer-Based Education, which has been responsible for programming all of the PLATO exercises and the provision of the required hardware. The physiology "content" of these exercises continues to be written by a nucleus of interested faculty within the Department of Physiology. This division of labor allows our physiologists to function most effectively as teachers of physiology—a task for which their training has prepared them—and allows our CBE staff to concentrate on what they have been trained to do—writing programs for teaching.

Our focus now is on producing simulated experiments with a high level of didactic interaction (dialogue) built into the program so that the student is continually challenged to think about the physiology being explored (7, 10). Such exercises have the added benefit of being useful in an unsupervised (by faculty) mode, thus permitting repeated ad lib. scheduling of their use by the students.

During the past three years additional effort has gone into the development of computer-simulated experiments for use on personal computers (7). Once again, this work has reflected the individual interests and commitment of the faculty involved and has received only peripheral support from the institution. Our goal continues to be the development of interactive exercises that can be used as independent learning resources, whether as supplements to a traditional medical curriculum or as integral parts of an alternative curriculum track based on a problem-oriented approach that stresses independent learning. When available on personal computers such learning resources can be used in laboratory-like settings, in the library, or even at home. Several simulated experiments (muscle responses, regulation of blood pressure) are now available for both the PLATO system and the personal computer.

Computer-Simulated Experiments: Where Are We Now?

What do computer-simulated experiments have to offer the teacher of physiology? In what ways do they potentially offer us at least one answer to some of our educational dilemmas?

To the extent that we have made learning "to think" and the ability to "solve problems" important goals of the physiology portion of the medical curriculum we must assist the students in acquiring these skills. The computer-simulated experiment offers the student an exercise with which he or she can practice the required skills. Through an interactive dialogue these programs can require the student to reveal his or her understanding of the system being studied at every step of the experiment. As the user is required to predict, whether quantitatively or qualitatively, the behavior of the system, those problem-solving skills that we think are so important are being continually honed.

It is of course true that the traditional "wet lab" can be used in the same way to develop the students' ability to "think about" physiology. However, computer-simulated experiments have a number of features that make them particularly attractive at a time when there exists many pressures to drop laboratories.

Computer-simulated experiments allow the student access to essentially any experiment thought to have instructional value, without being restricted by considerations of practicality, the availability of the required experimental animal preparation, the probability of success in a "real" experiment, or the time required for the experiment. Generation of such simulated experiments appears to be limited only by the imagination of the designer. Furthermore, simulated experiments can be used whenever and perhaps wherever the student desires; repeated attempts at the experiment are possible as well. And each attempt at the experiment will yield a worthwhile learning experience (not always the case in the traditional laboratory).

These characteristics make computer-simulated experiments well suited for inclusion in today's rapidly changing curriculum in which programs are becoming increasingly flexible and tailored to individual needs.

Of course, to the extent that the goals of one's course include experience working with living biological preparations, learning to use today's complex experimental apparatus, or practice in designing one's own experiment, simulated experiments cannot substitute for the real thing—the "wet lab."

Computer-Simulated Experiments: Where Do We Go From Here?

What ought to be the future of computer-simulated experiments in physiology? Such exercises clearly have great value in their own right. However, the expansion of such computer-based teaching is likely to continue at a slow pace not only at Rush but at most institutions. The reasons for this have been articulated by the participants at two workshops on computer-based education sponsored by the American Physiological Society (5, 6). Three of the most important issues appear to be *1*) lack of resources for development and research, *2*) lack of adequate professional rewards for the faculty involved, and *3*) technical problems related to computer compatibility and program transportability.

Although Rush is not unique, it is certainly an exception in having an institutionally funded Office of Computer-Based Education with significant hardware and personnel resources. In many more instances computer-based educational activities are supported by individual departments or faculty members using their own time and equipment. Funds are needed for hardware and for programming support so that as exercises are conceived by physiologists, they can be implemented. In addition, resources need to be committed to the development of additional new approaches to computer-based education in physiology and to the study of the effectiveness of existing and newly developed approaches as teaching tools. Such funds (whether institutional or from external sources) are presently very limited.

An equally important problem, perhaps more important in the long run, is the fact that there are few academic rewards for faculty who choose to involve themselves in this activity. Promotion, tenure, and salary increments are still awarded primarily for productivity in the research laboratory not for efforts to develop and/or test innovative teaching techniques. There is very little external grant support for computer-based education. There are few refereed journals widely acknowledged within the discipline as being of high quality in which one can publish. Thus two of the most important measures (grants and publications) by which accomplishments are judged and rewards are apportioned do not accrue to CBE practitioners. This is, of course, a particular problem for junior faculty who feel (quite rightly) that they must devote themselves to climbing the academic ladder. But, in many cases, these are often the people who might make a significant contribution to the field.

Finally, there are a number of technical problems that are limiting more wide-spread development and use of computer-based education. For example, there are a growing number of different hardware and software (operating) systems competing in the marketplace, most of them incompatible with one another. One of the most important features of computer-based exercises, the use of graphics, poses one of the most serious compatibility problems. This had made the problem of "portability" of programs (exchange) between members of the CBE community extremely difficult. There may well be at least partial solutions to these problems, but funds are simply not available to support attempts to reach solutions.

Summary and Conclusions

The ready access to computers in educational settings has come about at the same time that two contradictory trends are at work in medical education. On one hand there is a growing emphasis on problem-solving and active learning in the basic science curriculum. On the other hand one of the traditional exercises for fostering just this kind of learning, the laboratory experiment, is gradually being squeezed out of the curriculum. Computer-simulated experiments would seem to offer an educational tool that may allow us to foster the students' development of problem-solving skills without many of the currently unacceptable "expenses" of the traditional laboratory. However, greater resources must be made available if this new development is to progress in a useful way.

Many of the ideas expressed here have arisen during many years of collaboration in the area of computer-based education with Dr. Allen Rovick. The assistance of Dr. Lisa Brenner, Director of the Office of Computer-Based Education, Rush University, in implementing our ideas on the PLATO system is also gratefully acknowledged.

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The Case of the Missing Outward Current

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Holmes: Mmmmm.

Watson: Well, Holmes, I judge by the way you closed that book and started lighting your pipe that you have completed another case to your satisfaction.

H: Your deductive powers are improving, Watson, for you are correct. I've been working on a problem in physiology.

W: Physiology wasn't my strong point—I rather liked anatomy.

H: A typical surgeon, Watson? No matter, there is little left but to title this mystery. Perhaps "The Case of the Missing Outward Current" would be appropriate for this didactic problem.

W: Doesn't sound like one of your usual cases. Who is your client?

H: A group of medical students at Barts originally posed the problem to me. They felt that there was something missing from the teaching of axonal physiology.

W: Medical students? Why didn't they just ask their instructor?

H: Oh, they did, but the answer really didn't satisfy them, since it seemed basically inconsistent. And under such circumstances, I'm often inclined to trust that the students have discovered a flaw in the presentation. You see, I've been impressed by Professor Murphy's laws of teaching.

W: The Murphy that teaches at the medical school in Dublin?

H: The very same. You will recall that he discovered the first law of teaching in his first year as assistant. He phrased it, I think, "If anything can go wrong in a demonstration, it will." It was some years later, after he had done some lecturing, that he formed his second law, "If there is a flaw in a line of reasoning, the students will discover it."

W: I must admit to having found a few inconsistencies in my own student days!

H: The important part is the corollary to Murphy's second law, which can be stated, "If bright well-motivated students do not understand an explanation, it is probably either inconsistent or incomplete."

W: Well, what inconsistencies did the students discover in the presentation of axonal physiology?

H: They found it difficult to understand how the transmembrane potential could be depolarized by either an *outward* current (at the cathode when externally stimulated) or by an *inward* sodium current during an action potential. Thus the membrane seems to be depolarized either by an inward or an outward current, which seemed inconsistent to them.

W: Mmmm. That does sound contradictory. How did their instructor deal with it?

H: He made a good, but unsuccessful, attempt to explain the discrepancy by pointing out that when a resistor is hooked up to a battery, current (which in physiological usage is defined as the plus charge) passes from the anode to the cathode through the resistance, while the current *within* the battery is passing from the cathode to the anode. Thus, since the sodium pores, through which the sodium ions pass, can be considered the "battery," he felt that this could account for the different direction of the two currents.

W: Well, that sounds all right to me.

H: Yes, but one of the apparently contradictory statements concerning current flow is wrong because it is incomplete, so that the discrepancy is not really resolved.

W: Oh? Then let me guess that the correct statement is the one in which the sodium ions enter during the action potential and neutralize the internal negativity.

H: Too bad, Watson, but with a fifty-fifty chance, you've guessed wrong. Don't you recall that all currents must flow in complete circuits?

W: Oh, yes, I have heard that said, but I also remember very well examples of electrical phenomena that didn't involve complete circuits. For example, as a charged ebonite rod was moved toward the gold-foil electrometer, the charge on the rod displaced the gold leaves; this is equivalent to the sodium current moving into the cell.

H: Alas, Watson, sometimes phenomena that appear simple have more complex explanations! In the case of the ebonite rod, there *is* a complete circuit, but it is not immediately apparent. A capacitor is an insulator that separates two conductors. In the case you cited, the charging of the ebonite rod by rubbing has already separated charge between ground and the ebonite rod, and hence the rod forms one "plate" of a charged capacitor consisting of the rod, the earth, and the insulating air between them. The electrometer itself is a capacitor consisting of an inner and outer charge-carrying portion with glass and air separating the two. Thus, as the ebonite rod approaches the electrometer, the circuit is really three capacitors in series (counting the air between them). All the electrometer does is show the movement of some of these charges within this circuit as the magnitude of

the middle capacitor is diminished when the rod is brought closer to the electrometer. The true nature of the circuit is shown when the ebonite rod is grounded and the charge separation disappears.

W: Well, I don't fully understand your explanation, but I'll trust that it has been verified by someone with more scientific training than I. I gather that the problem with the depolarization due to sodium current is that there is no complete circuit.

H: Exactly, Watson.

W: Well, if inward current is carried by sodium through the pores, then where does the outward current go?

H: Why, through the membrane capacitance, Watson.

W: What membrane capacitance?

H: Remember that a capacitor is just two conductors separated by an insulator. Both the intracellular and extracellular fluids, containing ions, are excellent conductors, while the membrane is composed of fatty layers, which are good insulators. In fact, their insulating properties are very close to that of glass of similar dimensions. So the membrane itself acts as a capacitor. Indeed, the vast majority of the membrane is a capacitor since much less than 0.00001% of the membrane is composed of pores (2, p. 44).

W: Why can't the current come in through one pore and go out through another pore? Then the active pore is the "battery" and the inactive pore, with an outward current, acts like a resistance. In this way, it would be the current through the resistance that depolarizes the membrane.

H: That's ingenious, Watson, but unfortunately the experimental evidence argues that the membrane capacitance must be significant. If changes in the membrane potential involved only the membrane resistance, then potential changes would occur instantaneously following any imposed current and would not outlast the activating stimulus. However, as shown in Figure 1, the membrane potential does not follow instantaneously, and the effect on the membrane potential outlasts the driving current. The simplest explanation for this is that the membrane potential, as usually measured intracellularly, is essentially the charge on the membrane capacitor. Indeed, if the pores of a polarized membrane are inactivated pharmacologically, the membrane potential is still present, just as your ebonite rod maintains its charge. Current does not have to flow to maintain a membrane potential in the short run.

W: Do the experts agree with this explanation?

H: Indeed they do. Here is a quote from Hodgkin (1, p. 31): "Electric current . . . flows in a local circuit between resting and active nerve. This current reduces the membrane potential . . . by drawing charge out of the membrane's capacity." Westerfield, Joyner, and Moore (3) have said: "Specifically, an action potential is initiated in a particular part of the axon when enough current is supplied to charge the membrane capacitance of that patch to . . . above threshold." The complete circuit for current flow inward at a depolarized node of Ranvier, through both intracellular and extracellular fluids and the membrane capacitance, is shown in Figure 2. Indeed, as shown in both Figures 2 and 3, some of the inward pore current exits near to pore, depolarizing the membrane capacitance locally.

So, you see, Watson, trying to explain the depolarization of the membrane during an action potential solely in terms of the inward sodium current is like saying that a buggy is moved by oats, without indicating the intermediary action of the horse. In the case of the nerve, the depolarization is caused by the outward capacitative current.

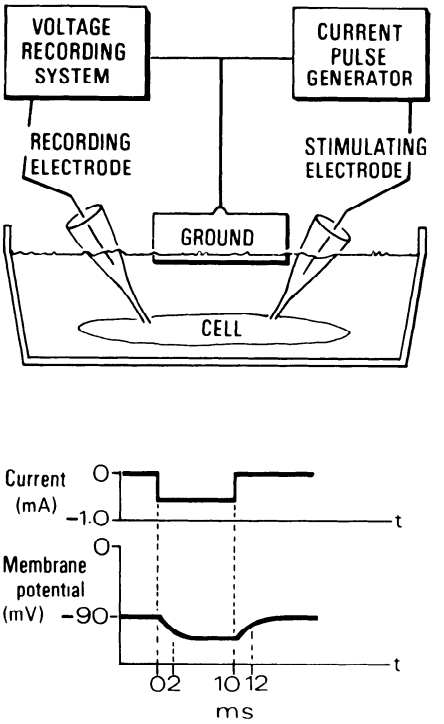

Figure 1

Effect of applied current on membrane potential in hypothetical experiment. Negative current passing inward across the membrane hyperpolarizes the cell, but not instantaneously. Furthermore, the effect outlasts the stimulus. Results of this type cannot be explained on the basis of resistances alone. These effects can be attributed to the membrane capacitance. (Reproduced, with permission, from Ref. 2.)

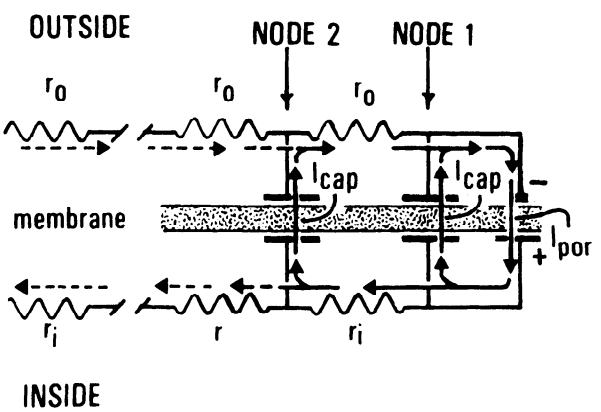

Figure 2

Current flow paths in complete circuits during depolarization of node of Ranvier 1. Current enters through sodium channels (labeled I_{por}) and leaves through membrane capacitance (labeled I_{cap}) at the same node and other nodes, using the intracellular and extracellular fluids r_i and r_o) as resistive paths. (Reproduced, with permission, from Ref. 2.)

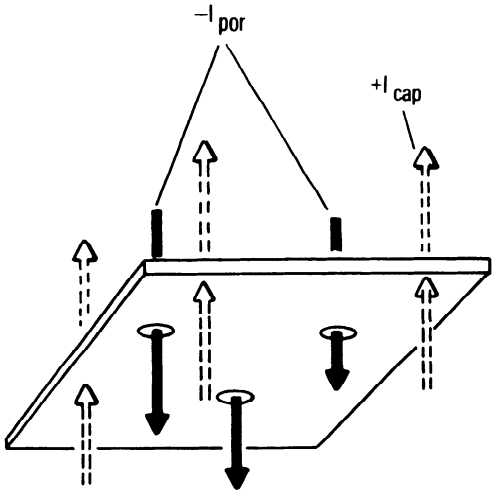

Figure 3
Internal view of a 1,000-$Å_2$ of squid axon membrane depolarized beyond threshold. Current enters the axon through pores (labeled $-I_{por}$) and leaves through membrane capacitance (labeled $+i_{cap}$). (Reproduced, with permission, from Ref. 2.)

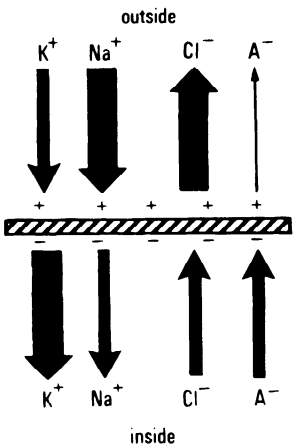

Figure 4
Possible ionic composition of inward capacitative current (hyperpolarizing). Width of each arrow is proportional to estimated contribution of that ion to the total current, based on availability (concentration) and ability to move in solution (mobility). Note that the relative contribution of a given ion is different on the two sides of the membrane, reinforcing the idea that ions that carry the capacitative current do not necessarily cross the membrane. (Reproduced, with permission, from Ref. 2.)

W: Well, Holmes, despite the experts, I still don't fully understand. In Figure 3 the sodium ions pass inward through the sodium pores, but how can current pass through the insulator in the membrane capacitor?

H: Like many things in science, what you call something determines how you think about it. It is true that no ions pass through the membrane capacitor, but this does *not* prevent current from passing through! This seems paradoxical at first, but recall that just as with your ebonite rod, charge that moves on one side of a capacitor affects the charge on the other side, across the insulator, and this change in charge *is* a current. Although a capacitor cannot carry current indefinitely, it need only carry current for a millisecond in order to depolarize the membrane during the action potential. So it is important to distinguish between the current (which is just units of charge per unit time) and the individual charged current-carrying ions. It may help to think of another example. If money is deposited at one teller's window at a bank at the same time money from the same account is being withdrawn from another window, there is a "money flow" even though no coin passes from one window to the other.

W: I think I've got it straight now. The inward sodium current through the pores during the action potential depolarizes the membrane, since it generates an outward sodium current through the membrane capacitance.

H: Not quite right yet, my friend. The sodium ion current becomes transformed in a process similar to the laundering of money.

W: They launder money?

H: Merely an expression of the criminal elements of the upper classes, Watson. The basic process is to change from one form to another while maintaining the flow. The specific inward sodium current through the sodium pores generates a *nonspecific* outward current through the membrane capacitance. This outward current is carried by a variety of species, different on either side of the membrane, as indicated in Figure 4.

W: How were these nonspecific currents determined?

H: Good point, Watson; a healthy skepticism is needed to make medicine scientific. The nonspecific currents can't be experimentally determined, so the figure is based on presumptions related to the availability of an ion and its mobility (2, p. 57).

W: Can you sum up the case for me?

H: Gladly. What has been missing from the teaching of axonal physiology is the nonspecific capacitative current that is driven either by external sources when there is an electrical stimulation or driven by inward sodium current during an action potential. If this capacitative current is kept in mind, then the inconsistency is resolved and students can devote their energies to more productive concerns. Regrettably, most textbooks ignore the capacitance, and this generates confusion.

W: Your capacity to solve such puzzles should not be underestimated!

H: There is potential for many puns here, but perhaps we should end the current explanation before we encounter resistance in our readers.

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Book Review

High Altitude and Man.

J. B. West and S. Lahiri (Editors)

Bethesda, MD: Am. Physiol. Soc., 1984, 207 pp, 109 illus., $39.00 (nonmembers), $31.00 (members).

High Altitude and Man, edited by John B. West and Sukhamay Lahiri, is a two-hundred page, multiauthored monograph that is the outgrowth of a symposium on man at high altitude which was sponsored by the American Physiological Society and held during the fall meeting in San Diego in 1982. The volume includes sixteen chapters grouped into three sections: *1*) man at extreme altitude, *2*) sleep and respiration at high altitude, and *3*) physiology of permanent residents at high altitude.

The symposium on man at high altitude was really an opportunity to present and discuss some of the data collected during the 1981 American Medical Research Expedition to Everest. This book also reports some of those data, but by and large the chapters are very uneven. The most interesting ones are those presenting findings from the Medical Research Expedition; the others are essentially review articles, albeit not very comprehensive ones. Moreover, they do not contain much information that has not previously been presented.

John West wrote the Introduction and the first chapter, entitled, "Man on the Summit of Mount Everest." This chapter is an excellent summary of several original articles published in the *Journal of Applied Physiology* and *Respiration Physiology.* It is the only one that is entirely based on the findings of the Expedition. Chapters 2, 3, and 4 all describe some data from the Expedition as well as findings from previous studies. Two of them are especially interesting: Chapter 2 by Schoene discusses the relationship of the ventilatory response to hypoxia with exercise performance. It demonstrates that the level of hyperventilation at the top of Everest was higher than expected, a factor which led to greater performance than was predicted. Chapter 3, by Townes et al., describes "Human Cerebral Function at Extreme Altitude." This is a relatively unexplored field of research, and there is no doubt that this particular study will stimulate further investigations. The other eleven chapters are reviews of prior studies conducted in various parts of the world: the Andes, the mountains of Colorado, or the Himalayas. In at least one instance (Chapter 12), the site of the study is not named, but it may be assumed that the experiments reported were conducted on Mount Logan in the St. Helen range of Canada. Some of the chapters make token reference to data from the 1981 Medical Research Expedition. Chapter 15 reports measurement of ventilatory function made in Tibet. Although there is nothing unique about these measurements, the chapter gives an interesting glance at some physiology research in the People's Republic of China.

High Altitude and Man is not just another book on high-altitude stress and adaptation, because it reports some of the findings of the American Medical Research Expedition. It would have been better and of more lasting value as a book if it had been exclusively about this expedition. It is unlikely that an expedition like that one will ever be repeated; thus its participants and its leaders should have endeavored to give students of high-altitude physiology a true reference book about the expedition rather than a collection of review articles. Nonetheless, this is a good book that is easy to read!

C. Lenfant
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Proceedings of the Sixth Annual Meeting of the IUPS Commission on Gravitational Physiology

18–21 September 1984
Lausanne, Switzerland

International Union of Physiological Sciences
Commission on Gravitational Physiology

PRELIMINARY ANNOUNCEMENT

IUPS Commission on Gravitational Physiology — Seventh Annual Meeting 13–18 October 1985 Niagara Falls, New York, USA

The Seventh Annual Meeting of the Commission on Gravitational Physiology of the International Union of Physiological Sciences is being planned for Niagara Falls/State University of New York, Buffalo, NY, USA, 13–18 October 1985. The meeting will be held in conjunction with the Fall Meeting of the American Physiological Society.

The Commission Meeting will comprise open sessions for slide presentations of voluntary papers dealing with the effects on physiological systems of humans, animals, and plants of changes in magnitude or direction of the force environment. Included are the effects of the weightlessness during space flight, acute and chronic acceleration, vibration, and the various forms of simulated weightlessness. Also included is consideration of the evolutionary consequences of gravity and the role of gravity in the manifestations of scale effects in animals and plants. The Commission Meeting will also include symposia by invited speakers on several topics in gravitational physiology.

It is planned to publish the Proceedings of the Seventh Annual Meeting in *The Physiologist.* As previously, the Proceedings will contain the voluntary papers and symposium papers presented at the Meeting.

Your participation in the Commission Meeting is welcomed. If you are interested in the particulars, please contact Dr. Orr E. Reynolds, Commission Business Officer, American Physiological Society, 9650 Rockville Pike, Bethesda, MD 20814, USA, by 15 February 1984.

Dedication

Charles Robert Darwin (1809–1882) to whom this volume is dedicated is and probably always will be best known for his *Origin of Species.* Nevertheless, after publication of the *Origin* in 1859, Darwin continued to publish on biological topics. The *Origin* has even been called an "heuristic prologue" to Darwin's chiefly botanical studies published in the last two decades of his life (1). He wrote six books after the *Origin,* two of which dealt with causes and purposes of plant movements. *The Movements and Habits of Climbing Plants* (1875) was an extension of a journal article published earlier, and what has been called his "most influential botanical work" (2), *The Power of Movement in Plants* (1880), with his son Francis as coauthor, is for gravitational physiology a 19th century classic (3).

Had Darwin not published the *Origin* when he did, he would not have enjoyed the scientific credit nor borne the brunt of criticism for the secular, evolutionary, "new science"—impossible to reconcile with special creation. Instead those honors would have gone to Alfred R. Wallace, his fellow naturalist. Nevertheless, Darwin's original experiments and observations in the sensory physiology of plants ensured for him an important place in the early development of gravitational physiology, and he would be well remembered for those seminal contributions alone.

Darwin's formal education, first at Edinburgh University, where for two years he found medical lectures, as he put it, "intolerably dull" and then three years at Cambridge to study for the clergy where his " time was sadly wasted," did not prepare him uniquely for tackling physiological problems. In those years, however, he indulged a taste for natural science by taking field trips, collecting minerals and beetles, learning first hand about countryside geology, and, as he specifically noted, making good use of the library.

More significant than formal course work were Darwin's opportunity to study on his own certain aspects of botany, to develop his natural talent as a keen observer, and most important of all to serve as the (unpaid) naturalist on the historic around-the-world voyage of H.M.S. Beagle.

Among the attitudes that we now believe importantly shaped Darwin's way of thinking and pursuing his scientific goals were his insistence that observation be coupled with speculation (or, as we would say today, experimentation cojoined with testable theory) and his frankly teleological concept of biological designs, which served him well in the years that he was marshaling evidence for the *Origin of Species.* These views help us to understand the personal background for his contributions to what we now call gravitational physiology.

Darwin lived about a century too early for him to have achieved solutions (in our modern sense) to basic problems of gravitational physiology; his achievement was to discover some of those problems. By his own rueful admission Darwin had no talent for mathematics. He was neither inclined nor able to construct mathematical models to account for biophysical mechanisms that interested him. In the 1860s and '70s what we now call biochemistry practically had not truly begun; its subject area was not much advanced beyond herbal medicine. The nature of enzymes and their mode of action were beginning to be understood only decades after Darwin's death. Nevertheless, his botanical publications provided original, thoughtful, and seminal observations on two kinds of plant growth movements—tropistic responses to photic and gravitational stimuli and presumably nastic oscillations, which Darwin recognized were responsive to gravity but, as he thought, not dependent on it. In both of these examples he identified new areas for physiological research that are important for us today.

Darwin recorded relatively slow growth movements of plants without the benefit of our modern, time lapse, cinematography. He attached a finely drawn out filament of glass to the tip of a growing organ and observed it through a fixed glass plate. By sighting along the direction of the filament a dot was made on the glass with a sharp pointed stick dipped in thick Indian-ink; afterward the series of dots made at different times would be joined by straight lines. Thus a record was obtained of the course of movement, which often was patently oscillatory. Darwin coined his own term for these movements, *circumnutation,* which was the principal subject of his *Power of Movement of Plants.* As he wrote, "Circumnutation is of paramount importance in the life of every plant; for it is through its modification that many highly beneficial or necessary movements have been acquired" (3).

Darwin's genius identified new areas for physiological research. He was the first to observe— and he explicitly recorded it as original—that the plant's gravity sensors were highly localized in the tips of growing roots and shoots but that the effect of their stimulation was to alter growth rates of tissues some millimeters or even centimeters away. As he summarized it, ". . . we now know that it is the tip alone which is acted on, and that this part transmits some influence to adjoining parts, causing the latter to bend" (3).

There followed a series of experiments by physiologists in a number of European laboratories who tried to understand the kinetics of transmission of that "influence." Ultimately it was associated with a naturally occurring substance, which, by definition, was a hormone. The substance, at first called "Auxin," later was identified chemically as a relatively simple organic compound, indole-3-acetic acid.

The progress of understanding at each step of that succession of investigations was in a way unusual, for it all seems as near as biological science ever approaches to a simple, logical sequence of experiments. From the beginning (Darwin's 1880 monograph) to the separation of the first known plant growth regulating hormone in the 1920s and its chemical identification in the 1930s, each experiment was designed as a follow-on from a previous result; there were almost no accidental or serendipitous discoveries along the way. Thus one may confidently trace the growth of this research field all the way back to its Darwinian origin.

Today we know of dozens of naturally occurring organic compounds, commonly grouped in five distinct classes, that have growth-regulating power, although we still are not able to explain to our full satisfaction how any of them regulates plant growth.

In a very practical sense today's multimillion dollar chemical growth-regulator industry was established on the foundation of Darwin's astute observations of plant growth responses to gravitational and other stimuli. This relationship should not be overlooked by those among us who share responsibilities for allocating public or private resources for research. Darwin was financially independent, and he surely felt no obligation to justify his work on any but intellectual grounds, but had it been otherwise it seems most unlikely that, during his lifetime, he could have anticipated any financial rewards stemming from his researches.

After more than a century Darwin's classic monograph on circumnutation (3) still is read and often cited by gravitational physiologists, and since it is nearly devoid of pedantic technical terminology, it stands as a quite readable reference and inspiration for our students with some curiosity about the history of our science.

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Proceedings of the Sixth Annual Meeting of the IUPS Commission on Gravitational Physiology 18–21 September 1984, Lausanne, Switzerland

The "Sixth Annual Meeting of the IUPS Commission on Gravitational Physiology" was held at the Institute of Plant Biology and Physiology of the University of Lausanne, Switzerland, September 18–21, 1984. More than 100 registrants from 14 countries attended the presentation of 70 research papers on topics in gravitational physiology.

The meeting opened with four invited symposium papers covering recent spaceflight results and future plans for space life sciences research in the USSR, USA, Western Europe, and Japan, followed by two papers from Japan and the USSR on the neural regulation of cardiovascular function in rabbits and dogs, respectively, during changes in body orientation. In the afternoon of the first day, four invited symposium papers from the USA on plant bioregenerative systems were presented.

The second and third days of the meeting, plus a night session on the last day, were devoted to 46 voluntary papers on gravitational research results from plant and animal forms ranging from *Arabidopsis* to man. The topics included cardiovascular function, cell division, circadian rhythmicity, circumnutation, embryonic development, endocrine function, energy metabolism, fluid and electrolyte balance, gravitropism, muscle function, population dynamics, respiratory function, skeletal function, temperature regulation, and vestibular function.

On the final day of the meeting, the morning session comprised four invited symposium papers from Western Europe and the USA on cardiovascular and vestibular effects of spaceflight in man, together with two papers from the USSR on motor and vestibular function in the Cosmos 1514 monkeys and on results from the pregnant rats flown in Cosmos 1514. In the afternoon eight invited symposium papers from Japan, Western Europe, and the USA were given on the topic of gravity and plant reactions.

The sessions were lively and were characterized by much discussion, and the consensus was that the meeting was highly successful.

The follow pages are presented as the Proceedings of the meeting by arrangement with the American Physiological Society. In the interest of timeliness and economy they are published without editorial review. Financial support for the preparation of the Proceedings has been provided by the US National Aeronautics and Space Administration, for which the Commission is grateful.

Travel support for many of the participants was generously provided by the National Aeronautics and Space Administration, the European Space Agency, and the American Physiological Society.

The seventh annual meeting of the IUPS Commission is scheduled to be held in conjunction with the Fall Meeting of the American Physiological Society in Niagara Falls, New York in October 1985, and the eighth annual meeting is to be held in Tokyo, Japan in early November 1986. All are welcome, and detailed announcements are forthcoming.