THE PHYSIOLOGIST

The American Physiological Society was founded in 1887 for the purpose of promoting the increase of physiological knowledge and its utilization. The APS Constitution and Bylaws appears in the FASEB Membership Directory. Officers: *President,* John B. West, University of California, La Jolla, CA; *Past President,* Alfred P. Fishman, University of Pennsylvania Hospital, Philadelphia, PA; *President-Elect,* Howard E. Morgan, Pennsylvania State University, Hershey, PA; *Council,* John B. West, Howard E. Morgan, Alfred P. Fishman, Franklyn G. Knox, Harvey V. Sparks, Jr., Norman C. Staub, Aubrey E. Taylor; *Executive Secretary-Treasurer,* Orr E. Reynolds, 9650 Rockville Pike, Bethesda, MD 20814.

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Cover: Orr E. Reynolds, APS Executive Secretary-Treasurer, p. 132.

Editorial

Retirement of Orr E. Reynolds as Executive Secretary-Treasurer

The following are remarks from the President's "State of the Society" Address at the Business Meeting, Anaheim, 24 April, 1985.

One of the most significant impending events for the Society is the retirement of Orr Reynolds as Executive Secretary-Treasurer and his replacement by Dr. Martin Frank. There must be few of us here who do not have reason to be grateful to Orr for the myriad of administrative actions he has taken since 1973 when he became Executive Secretary. It is important to realize that in a Society whose president changes each year, a great deal of responsibility falls on the executive secretary to maintain an orderly advance. Orr has guided the Society through good times and bad, but the net result has been a remarkable degree of progress over the last 12 years. I shall not try to cover all the changes, some of which were detailed in an editorial in the December 1984 issue of *The Physiologist*. However, Orr's retirement as Executive Secretary-Treasurer serves as an opportunity to briefly review some of the changes in the Society during his tenure.

Figure 1 shows some of the changes in membership and meetings over the last 12 years. As can be seen, there has been a substantial increase in membership, and in addition two new categories have been introduced—corresponding membership for foreign members and student memberships. The Spring meetings of the Society are thriving; indeed the present meeting is one of the largest ever. However, the Fall meetings are more problematical; the meeting in Lexington, Kentucky, last year had one of the smallest registrations for the last 10 years, though we should not assume that because a meeting is small it is not worthwhile. Nevertheless, the Program Committee and the Long Range Planning Committee are giving a lot of thought to the format of the Fall meeting, and it is likely that it will become more structured and focused on several themes.

Figure 2 shows the progress that has been made in Society journals; this is most impressive. However, a worrying feature is that the number of subscriptions has not increased, and indeed there has been a slow but steady fall over the last several years. An interesting statistic is that if the production costs of the journals are calculated in 1973 dollars to remove the effects of inflation, the costs have not increased as fast as the number of manuscripts or published pages.

Figure 3 shows changes in the Society's budgets. The general subscriptions have increased, though much less than you might think when calculated in terms of 1973 dollars. Again, the subscriptions have not increased as much as the Society Operating Fund or the Publications Operating Fund. A statistic that should give us pause is that the Publications Reserve Fund, which is meant to buffer the Society against hard times, has actually fallen fairly substantially when calculated in terms of 1973 dollars.

Council has decided to institute an annual award in honor of Orr Reynolds. Our Society has been fortunate

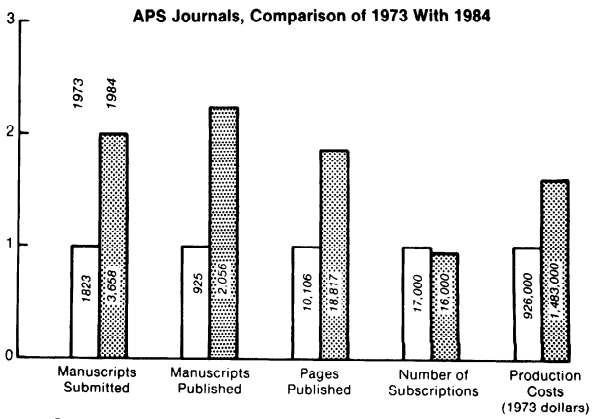


Figure 2
Changes in the Society's journals over the last 12 years.

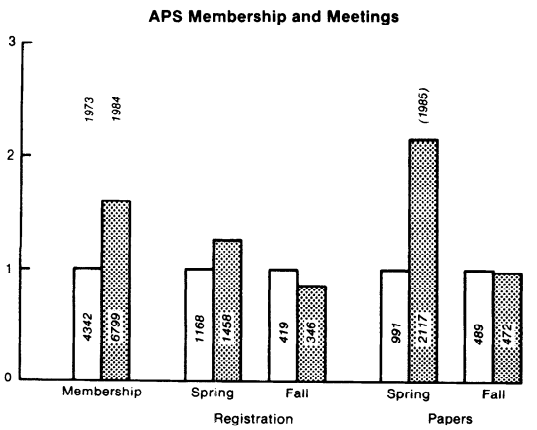


Figure 1
Changes in membership and meetings over the last 12 years.

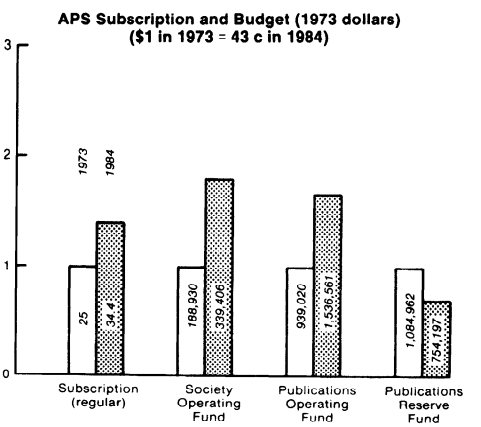


Figure 3
Budgets in 1973 and 1975, calculated in 1973 dollars.

in the long tenure of its Executive Secretaries. Milton O. Lee was Executive Secretary from 1948 to 1956, and his name is commemorated in the Milton O. Lee Building on the Bethesda campus. Ray Daggs was Executive Secretary from 1956 to 1972 and of course his name is remembered in the annual Daggs Award, which has just been presented. Orr Reynolds has made contributions in many areas but perhaps preeminently in those of the education mission of the Society and recording its history. After consultation with Orr, we have decided to institute an annual Orr Reynolds Award for an article by a member of the Society on some aspect of the history of physiology including the American Physiological Society. The article will be published in one of the Society journals after appropriate peer review, and the award will be given annually at the Spring Business Meeting at the same time as the Daggs Award. If the Program Committee and the recipient wish, an oral presentation will be made at one of the Spring or Fall meetings at the beginning of an appropriate scientific session. The fact that the award article will be published in one of the Society journals means that it will continue to remind us of the contributions made by Orr Reynolds.

We were honored to learn that President Ronald Reagan had written a letter to Orr Reynolds on the occasion of his retirement as Executive Secretary. The letter is reproduced on p. 138 of this issue and is eloquent testimony of the regard in which Orr is held in high places.

In addition, on behalf of the Council and the Society as a whole, I am very glad to present Orr with an inscribed sterling silver dish that we hope he will put on his mantelpiece as a reminder of his long association with the Society. The inscription reads:

O.E. Reynolds and J.B. West

To Orr Reynolds, Ph.D., in appreciation of his service to the American Physiological Society, Anaheim, 1985.

Finally, I am very pleased to introduce Dr. Martin Frank who has been selected as the new Executive Secretary-Treasurer of the Society, effective 1 July, 1985. Those of us who have had the opportunity of getting to know Dr. Frank are all impressed by his energy and wealth of new ideas. We welcome him in anticipation of his taking up his new position in July.

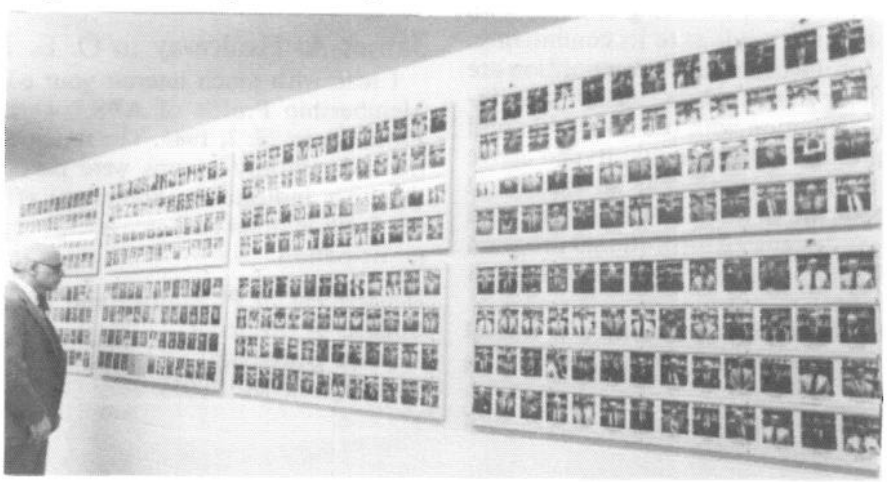
[At the conclusion of these remarks, Dr. David Bruce Dill, one of the most respected senior members of the Society made a brief statement referring to the Society's great debt to Dr. Reynolds, p. 143.]

John B. West, President

Portrait Gallery of Physiologists

In 1960 the Department of Physiology at the University of Buffalo (now State University of New York at Buffalo) started the custom of taking Polaroid Land camera portraits of distinguished visitors including lecturers invited for our Departmental Seminars. Over the last 25 years the number has grown to about 1,000 portraits. These are mounted on boards as shown in the accompanying photo. Each board contains 52 portraits, and all 20 boards hang in the hallway of the Department. Each individual portrait is identified by name, institution, and month and year of visit. A registry is available that allows one to quickly locate the picture of each visitor. A good number of scientists have made repeated visits, and this offers an opportunity for the study of changes in physiognomy with time. Dr. Charles Paganelli looks over the photographs.

Hermann Rahn



Public Affairs

Public Health Service Makes Major Shift in Animal Policy

The Public Health Service (PHS) has made a major shift in its policy regarding the care and use of laboratory animals.

A new directive, which is to become effective in November, shifts the PHS policy from making recommendations to researchers to a policy of placing requirements on both individuals and institutions using laboratory animals.

"This change in policy gives us added assurance that PHS-supported institutions will provide proper care and use of laboratory animals," James B. Wyngaarden, director of the National Institutes of Health (NIH), said in announcing the new PHS policy.

Most of the requirements in the new "Policy on Humane Care and Use of Laboratory Animals by Awardee Institutions" focus on the role and responsibilities of the local Institutional Animal Care and Use Committee (IACUC), including a requirement that all research projects involving animals must receive the committee's approval before it is to be funded by the federal government.

The committee also is required to conduct self-assessments of the animal research programs at those institutions not accredited by the American Association for Accreditation of Laboratory Animal Care. The self-assessments are to be based on the "NIH Guide for the Care and Use of Laboratory Animals."

Deficiencies found by the committee in the institution's program or facility will be reported to NIH and the institution will have to correct the deficiencies within a designated time to avoid termination of the project.

Although only NIH can order the termination of any program, the new policy gives the committee the authority to suspend a research program involving animals until a final determination can be made as to its continuance.

The requirements for the committee's composition are that it must have at least five members, including an individual who has no affiliation with the institution and who represents the prestige of the community; an active scientist who uses animals in research; an individual whose primary interests are in a nonscientific area; and a veterinarian who has designated institutional program responsibilities and who is trained or experienced in laboratory animal care.

Each institution is also required to identify an offical who has the ultimate responsibility for the institution's animal programs.

The new policy also requires that the institution must provide detailed information regarding the institution's program for the care and use of research animals which is to be used to determine the institution's commitment to animal welfare and its ability to comply with the PHS policy.

The new policy covers any live vertebrate animal used or intended for use in research, research training, experimentation, or biological testing or for related purposes. The policy cover all agencies of the PHS including the Alcohol, Drug Abuse, and Mental Health Administration, the Centers for Disease Control, the Food and Drug Administration, the Health Resources and Services Administration, and NIH.

The new policy ends a two-year review of a PHS policy that has been in effect since 1979.

House Bill Designed to Reduce LD_{50} Testing

A bill designed to virtually eliminate the use of the LD_{50} test has been introduced in the Congress by Rep. Barbara Boxer (D-CA). The proposal, entitled "Humane Products Testing Act" (HR 1877), states that the LD_{50} test has been shown to be inaccurate and unnecessary and other methods have been developed that are less costly and more humane.

The LD_{50} test is a procedure wherein toxicity is measured in terms of the median dose that will kill 50% of the test animals that receive the product being tested.

The bill, if enacted, would require each relevant federal agency to promulgate regulations specifying tests to be used in lieu of the LD_{50} test. In cases where no viable alternative exists the agency would publish an explanation of the other options considered and the justification for continuing the use of the LD_{50} test in those cases.

No date has been scheduled by the House Committee on Energy and Commerce Subcommittee on Health and the Environment for consideration of this bill.

William M. Samuels, CAE

Letter to the Editor

James A. Holloway to O. E. Reynolds:

I read with much interest your editorial, "Change in Membership Profile of APS," which appeared in *The Physiologist* 28: 2, 1985. The statistics on the representation of minority groups were particularly revealing in that they indicate the additional effort which must be put forth in order to increase the proportion of minority participation.

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Orr E. Reynolds . . .

Reflections Upon the Past to Provide a Vision of the Future of the American Physiological Society

In a way it is typical that Orr Reynolds will be out of the country on APS business when he retires June 30th of this year. It is typical because for 15 years, the last 12 as executive secretary, he always has placed the needs of the Society before personal considerations.

It also is typical that Dr. Reynolds will continue to work for APS as a volunteer staff person in preparing the Society for its participation in the International Union of Physiological Sciences Congress in 1986 and for its Centennial Year celebration in 1987. His last official act as executive secretary is to represent US physiologists at international scientific gatherings in Hungary and Russia.

The retirement of Orr Esrey Reynolds as APS executive secretary marks the end of an era within the Society inasmuch as he holds the unique distinction of having known personally 50 of the 60 presidential officers and both chief executive officers, Milton O. Lee and Ray Daggs, who preceded him.

Furthermore, he represents an era when many significant changes took place in the Society's structure, including greater membership involvement in APS affairs, such as mail ballots to elect officers and Council members, sectionalization of members into areas of interest, establishing membership categories for both foreign and student members, providing avenues for women in physiology, creation of program advisory committees with representation for all sections, and the organizing of a Public Affairs Advisory Committee with representation from all states.

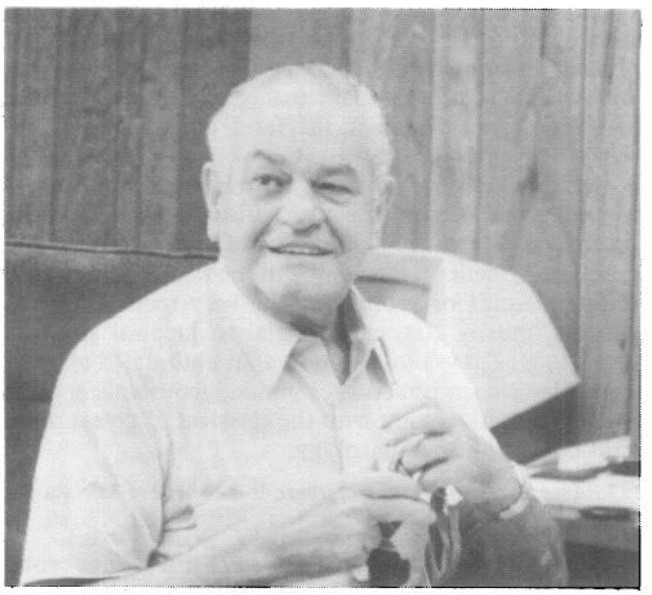
Also of significance during Dr. Reynolds' tenure is the threefold growth in the number of pages published in APS journals and periodicals and the 300% increase in attendance at the fall scientific meeting.

After earning his degrees at the University of Maryland, Dr. Reynolds began his career in 1943 as an assistant physiologist at the National Institutes of Health. He then served two years with the US Navy, and in 1946 he became the civilian head of the Physiology Branch of the Office of Naval Research. He was named director of the Biological Sciences Division in the Office of Naval Research in 1948.

He was appointed director of the Office of Science in the Defense, Research, and Engineering section of the US Department of Defense in 1957. Five years later he was selected as the director of Bioscience Programs for the National Aeronautics and Space Administration.

Dr. Reynolds joined the APS staff in 1970 as education officer and was appointed executive secretary upon the retirement of Dr. Daggs.

Just prior to his departure for the scientific meetings in Hungary and Russia, Dr. Reynolds was asked about the Society and his role as its executive secretary.



What prompted you to retire after 12 years as the Society's executive secretary?

I reached 65 years of age this year and, therefore, I would be retiring soon in any event. I had planned to stay on through the Centennial Year and decided I might as well serve the last two years as a volunteer, allowing the Society an opportunity to bring in my successor now so that I can devote full time to the centennial program.

When you were appointed executive secretary, what were your personal goals for the Society?

Ever since I served as director of a survey of physiology conducted by APS in the 1950s, I have felt the Society would be strengthened *1*) by broadening the membership to comprise a larger fraction of the world's physiologists and *2*) by involving more members in the Society's business by the dispersal of responsibility for Society programs more widely among the members.

Have you reached these goals?

I believe the Society has made several important steps toward both goals since the 1950s. Perhaps attainment of these goals has accelerated somewhat in the past decade, with sectionalization of the membership and the journals. Both of these actions provide a greater opportunity for member participation in Society affairs. Also the new categories of membership help broaden our base. There is still plenty of room for further advancement in this respect, however.

How would you characterize APS evolution during your tenure as executive secretary?

The progress toward the goals I have discussed characterize most of the evolution. In more general terms, I believe the influence of the individual member on the Society has increased and, in turn, the Society's role in influencing the course of events in the world has increased.

Your knowledge of the issues affecting APS commands a great deal of respect. What three issues would you label at this time as top priorities for APS?

I would say the most immediate issue is the preservation of the opportunity to perform research using animals, because the forces opposing this freedom of inquiry are so militant and unrelenting, as well as unrestrained by reality and truth. Second is the maintenance of a spirit and image of physiology as being in the forefront of modern biology. This is the key to attracting young scientists to the Society, thus ensuring the long-term health of the Society as well as that of physiology as a discipline. Third is the problem of the teaching. Teaching of undergraduate and graduate students and teaching of medical students pose different kinds of problems. The very requirement of teaching mostly classical material to medical students seems to give physiology a somewhat antiquated appearance. Medical student courses should incorporate enough modern material along with the classical to give a more vital impression of physology.

In looking ahead to the future, where do you believe APS should be headed?

As alluded to in a previous answer, I still believe broad representation among physiologists in America is an important goal of the Society. Many people teaching physiology to undergraduates in the the colleges or doing physiological testing and product development in government and industry are not members of our Society. Yet they are probably the biggest interface our field of science has with the public. Most indicators show that this group of nonresearcher physiologists is at least equal in number to the membership of the Society. By excluding them from membership we decrease the likelihood that what they do reflects well on the image of physiology both to the general public and also the scientific and medical public. A way should be found to bring these nonresearchers into the Society for the benefit of the science itself.

In addition to being executive secretary you also serve as treasurer of APS. How does the financial health of the Society today compare with 1973 when you were named APS chief executive officer?

The financial health of the Society is essentially unchanged. The Society has for many years had a dichotomy in its finances with respect to publications and general Society operations. This is reflected in the two operating funds, the Publications Operating Fund (POF) and the Society Operating Fund (SOF). The POF is primarily dependent on subscriptions and book sales for income; the SOF is dependent on membership dues and net income from the meetings plus personal and corporate contributions.

The publications income is by far the more stable of these, and over the years has built up a sizable reserve, which generates additional income. The SOF has always been a marginal fund, with no reserve and a continuing tendency for new programs to be started which eat up any excess that it develops. Frequently insufficient funds have been available in the SOF for these programs so that the use of interest received on the POF reserve fund has been necessary to stay in the black.

A few years ago a Financial Development Committee was formed to find ways to make the SOF less dependent on dues as its principal source of income. Although the Committee has been successful in about doubling nondues income, primarily by stimulating contributions, the dues are still the main source of revenue. I fear this will be the case perennially unless the Society finds a way of increasing and sequestering meeting income. Products that can be sold to a clientele broader than the membership would be another source of income. But our experience with teaching materials, for example, has not shown much success.

What significant changes have you seen in the membership?

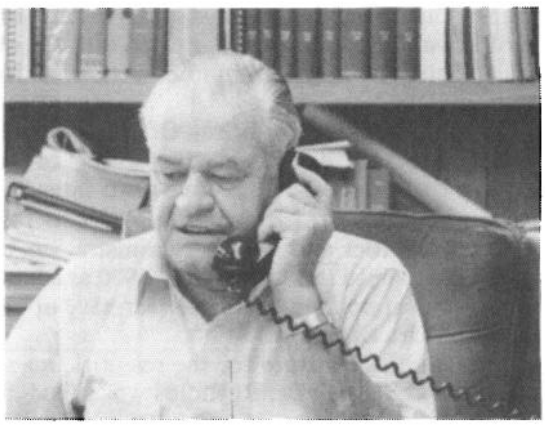
The most significant changes have been the addition of two new categories of membership. Corresponding membership for foreign physiologists is improving the Society's international communications and Student membership has the potential, not yet fully realized, of bringing a more stimulating atmosphere to the Society's scientific meetings. The growth in the proportion of women members is a notable change, and this reflects the increase in the number of women entering science, in general, and physiology, in particular.

What new trends do you foresee developing in APS membership?

Unless some very active steps are taken to promote particular aspects of membership, I do not see a likelihood of much change except the gradual eroding of breadth as new specialty societies compete for young scientists, in the way that biophysics and neuroscience societies have done in recent years and the other Federation societies did in former times.

In the next ten years what issues will be the most important to the membership?

I believe the most important issues affecting our membership will be those largely out of the Society's control. All have fiscal implications. One is likely to be an increas-



ing competition for research money from government as the growth of federal funding for research tends to plateau. Another is the development of electronic communications, which is likely to revolutionize the classical publishing system, within the next two decades. A third may be a revision of tax laws, which may well compromise nonprofit institutions. The flat tax proposal, for example, could greatly change the finances of currently tax-exempt organizations by its effect on postal rates and charitable deductions.

All three of these issues are of course directly involved in Society finances and may well have a bearing on the services the Society can provide its members. It is easy to predict a doubling of costs to members for their present services, without considering inflation. One way of preventing such a cost increase would be to greatly enlarge membership, cutting down the per member cost of largely fixed expenditures (executive office salaries, for example).

Another way might be to reduce services, but that would be counterproductive. The requirement for public affairs activities on behalf of the membership, for example, is likely to be greater as we move to a more competitive enviroment.

What do you see as the advantages for an individual to be a member of the American Physiological Society?

The advantages for an individual member depend greatly on that individual's use of Society services. If the member attends the meetings and buys the publications, he or she benefits both financially and in terms of scientific communications. If the member does neither, the benefits are largely in terms of status, either individually or as a part of that segment of the scientific community the Society represents. If the member is very active in Society committees or boards, he or she helps to affect the future of the Society, in particular, and physiology, in general.

Another recognized strength of the Society is its publications. What has led to this development?

For many years the APS publications have benefited by being managed by Society members who have been very sensitive to the needs of physiologists for publication outlets. The organization of the journals and the standards of editorial review have been kept as close to the needs of authors and readers as the responsible committee and editors could make them. This is an advantage as compared with journals with strictly commercial management and has resulted in the fine reputation these journals now have. With the changing technology of electronic publishing on the horizon, it will be a challenge to maintain the qualities that have made the journals so widely appreciated while deriving full advantage from the new technology. Also some new ground must be plowed on the financial side to incorporate the new technical capabilities without losing the income that makes the editorial process possible.

Aside from its publications, what are the other strengths of the Society at this time?

Running the two large meetings a year provides a very important service for the members. The Society organization that develops the program for these meetings has been rather carefully developed during recent years in a direction that maximizes the opportunity for the individual members to influence the character of the meetings by working through section representatives on the Program Advisory Committee. Through this mechanism the meetings can be tailored to the memberships' wishes, new types of meetings can be developed, etc.

Another important strength of APS is the rather large amount of biographical information we maintain on the individual member. With this database we can provide customized lists of individuals with particular specialties or other attributes for use in forming Society committees, lists of candidates in response to governmental office requests (study Section membership for example), and statistical data for various surveys of scientific manpower. Because of the very high proportion of our members who have supplied such information, APS seems to be practically unique among similar scientific societies in being able to provide such data.

In the Public Affairs arena APS has concentrated on the effort to maintain the access to experimental animals in the face of strong opposition from animal rights groups of several persuasions.

APS has had a strong tradition of fostering humane principles in dealing with laboratory animals and its Animal Care and Experimentation Committee and Council have given much consideration to the issues, resulting in clear and defensible policies for dealing with regulation and legislation. As a result the governmental agencies, including the Congress, have a considerable respect for APS as a source of criticism and advice concerning pending federal actions. This constitutes a major benefit because it means the Society is consulted early and paid attention to in these matters, far beyond what would be expected for the number of members the Society has. No small part of this respect is due to the very well considered and pointed letters our members write to their legislators on issues involving laboratory animals.

What programs of the Society need to be strengthened or, perhaps, eliminated because they no longer provide a service useful to the membership?

This tends to be an autoregulatory situation. An activity of the Society that does not meet the needs of the Society does not survive very long in the competition for funds in the budgeting process. New programs are always waiting in the wings and deferred for lack of funds. A program that has outrun its intellectual support soon also runs out of financial support.

Who Would You Like To Know?

The purpose of this feature is to provide members of the Society with insights to a variety of issues and, hopefully, to give the answers to questions you would like to ask such individuals.

If you have someone in mind you would like to see featured in a future "People You Should Know" interview, please let us know.

William M. Samuels, APS

Are there any new areas in which the Society should explore as possible membership services?

I believe the Society should consider some outright recruiting campaigns for membership. It would probably require some restructuring of the present membership categories and probably some bylaw changes, but I feel that the Society will be in much better position to deal with the problems it faces in the future if it has a broader membership base, including those whose physiological contribution is not in fundamental research but, rather, in teaching, applied research, and development and testing.

In the early history of the Society, applications of physiological knowledge were almost exclusively clinical medical. That is, they were directed toward the individual suffering from disease. Application of physiology to maintenance of health and well-being was probably first recognized as an adjunct to human hygiene. Many states still have statutes requiring education in "physiology and hygiene" in the public schools. Most physical education majors in our colleges of education still have a course in physiology as a requirement, and, therefore, physiology tends to be taught, if at all, by the athletic department rather than the biology department in high school.

During World War II, especially because of the physiological problems caused by higher performance aircraft, the military role in physiology became obvious, and a large and expanding specialty of applied physiology developed. This has been extended to sports and general fitness. The Society has never accomodated to this changing role of the science, and physiologists not actively producing new knowledge by research have been excluded from membership. The societies in some fields, such as chemistry and microbiology, have been more inclusive in membership policy and as a result are much stronger in their effect on the future of their disciplines.

Such a change for APS would probably involve some new services addressed to the needs of the new types of members. But the impact of the Society would be broadened, the financial base more secure, and the overall cost per member reduced.

What did you find to be the most demanding aspect of your job as executive secretary?

The most demanding aspect of the job is also one of its greatest satisfactions. That is dealing with the individual members. The range of subjects in which one becomes involved in dealing with members' problems and ideas is somewhat staggering, ranging from an incorrect mailing address to an international meeting involving denial of visas to scientists. For one who considers every request from a member to be entitled to attention, this flow offers a wide variety of stimulation. The most difficult part of the job is that of maintaining the more or less routine and scheduled functions of the office while juggling a dazzling array of unscheduled projects. But that is also where a lot of the fun is.

What do you believe you will miss most when you step down as APS' executive secretary?

I think I will miss dealing with colleagues in the Society more than anything else. Although I expect to keep in touch to the extent that I can, it will certainly be different from being at the center of a communication system, which is true of the executive secretary's role.

What do you want your tenure as executive secretary to be remembered for?

Perhaps it has been a mistake, but I do not believe I have given a moment's thought to that question over my period of tenure. I believe that what I have tried hardest to do is to make every member feel like the Society is a "we" rather than a "they." I have tried to make every member feel that he or she had a right to ask the Society for what he or she wanted and that the Society would comply if it could and did not infringe on another member's rights. Also I guess I would like to be remembered for a "can-do" philosophy for Society affairs in general. I have envisioned my role as an implementer of Society objectives coming from the membership through the committees and council to my office for execution. My job is to figure out how to do it, not whether it should be done.

THE WHITE HOUSE

WASHINGTON

April 17, 1985

Dear Dr. Reynolds:

Nancy and I are delighted to join with all those gathered to congratulate you on your retirement. Your years of service to the American Physiological Society have been marked by outstanding dedication and achievement, earning the respect and admiration of your friends and colleagues alike. We are happy to share in this special time in your life and to send our best wishes for good fortune and happiness in the years ahead.

Again, congratulations on this memorable occasion.

Sincerely,

Ronald Reagan

Dr. Orr E. Reynolds
The American Physiological Society
Bethesda, Maryland

Departmental History

Physiology Department Creighton University School of Medicine Omaha, Nebraska

Creighton University was founded in 1878. The medical school was founded in 1892 as the John A. Creighton Medical College. It was coeducational from the beginning. St. Joseph Hospital, long associated with the Creighton Medical School, was founded in 1870 and further developed by John A. Creighton in memory of his wife, who had donated to the Sisterhood of St. Francis the sum of money which made the hospital possible. It became the teaching hospital of the medical school at its foundation but has never been owned to this day by the University.

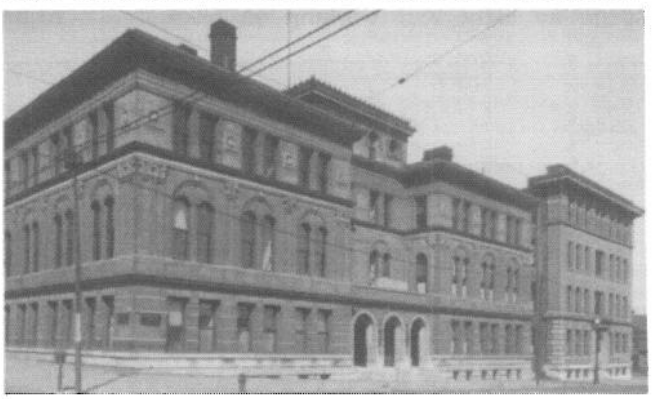
The idea of the Creightons was to leave a sufficient endowment to provide free tuition in the college and associated high school. This ambition was realizable until 1924.

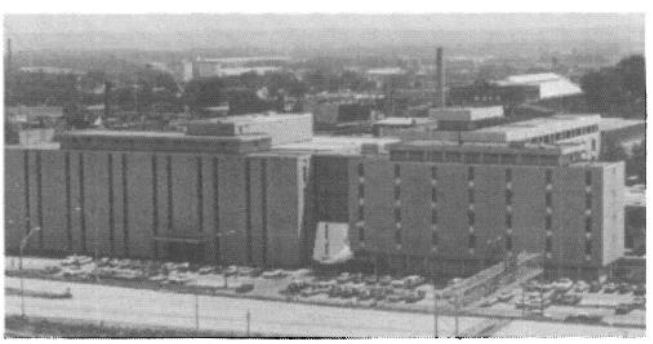
The Department of Physiology started with B. F. Crummer as professor of both Physiology and Pediatrics. There was one assistant. Teaching was entirely didactic with "diagrams, plates, models and vivisections." The duration of the course is not specified. It included Physiological Chemistry. In 1894 the St. Joseph Hospital's pathologist had become Professor of Physiology, Histology, and Pathology, without any assistant. He gave three lectures per week to first- and second-year students. By 1896 a laboratory had been introduced. Oral examinations were required at the end of each subject and a final examination at the end of the course. The required text was *Kirke's Physiology* (13th ed.). In 1896 also, the medical curriculum was extended to 4 years. In the 1898–99 session the course is described as 3 hours per week for 7 months. Starting in the 1906–07 session students were required to prepare papers to be read before the whole class. By 1910 Professor Foote, who had taught Physiology and Biological Chemistry alone since 1894, was assisted by the Professor of Pharmacology and Materia Medica, who now assumed a title in Physiology. Lectures were increased by 20%. The first mention of laboratory exercises in Physiology and Pharmacology is in 1912. Sixty-four hours are listed for the former. The course covered 2 years.

In 1914 Professor Foote gave up Physiology and was succeeded by Professor Muirhead, who the previous year had added Physiology to his Professorship of Pharmacology. In 1914 Physiology-Pharmacology got its first assistant since 1893, and Professor Muirhead became Dean. Physiology was now 96 hours of lectures in the first year plus 64 lectures and 64 laboratory hours in the second year. By 1915 the assistant evidently had enough of Physiology, and it was dropped from his title.

In 1916 the name Physiological Chemistry first appears in the *University Bulletin.* It was taught in the first year, and Physiology (350 hours of it) was taught entirely in the second. In 1917 Sergius Margulis, Ph.D., was appointed Professor of Physiology and Biochemistry. He has the distinction of being the first full-time basic scientist employed by the medical school. Indeed, he might well be the first full-time professional employee, since to this point the entire faculty seems to have consisted of part-time teachers employed either in private or hospital practice or by the city and county health departments. At the same time Margulis was given an assistant in Biochemistry (W. A. Perlzweig). These were the only Ph.D.'s on the faculty roster to this point. The *Bulletin* description of the course was now expanded from six lines to two pages and is divided into *1*) General Physiological Chemistry, *2*) Neuromuscular Mechanisms, and *3*) Special Senses, Circulation, Respiration, Digestion, and Secretion. Class time was 16 hours per week for half a semester—except for Physiological Chemistry, which had 10 hours per week for a whole semester. In addition there was an advanced course. "The facilities of the laboratories will be given freely to those who may desire to either work up some special topic or extend their study beyond the elementary course." This invitation was extended also to physicians. The following year V. E. Levine joined the department as Assistant Professor of Biochemistry.

In 1919 the department added Pharmacology, with Muirhead now no longer Dean. Nineteen twenty-two seems to have been a year of upheaval. Two of the three Ph.D.'s in the department were replaced by James F. McDonald, M.D., in Physiology, and H. F. Gerald, M.D., in Pharmacology. The latter had a title in Physiology from 1914–15. This left Levine the only full-time employee in the department and perhaps in the school. The description of the course was now back to half a page, and the advanced course was no more. Biochem-





Top: Original Medical School and College of Pharmacy.
Bottom: New Medical School and Medical Research Building (*right*).

istry and Physiology were run as separate entities. By 1927 Professors Gerald and McDonald were running Physiology-Pharmacology between them without assistants. The clinical faculty in the meantime consisted of 75 people. In addition, there was a full-time anatomist, a full-time biochemist, and an assistant in Chemistry.

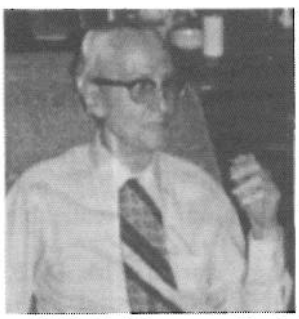
In 1931 **Charles M. Wilhelmj** with Ward Peterson as assistant joined the department as Professor of Physiology and James McDonald left. The former came here from the Mayo Clinic, where he had been a member of the permanent staff, and the University of Minnesota, where he had been instructor in Physiology. The latter was a Creighton Medical School graduate. The joint Physiology-Pharmacology Department now consisted of two professors, one assistant and a student assistant. Wilhelmj introduced a student research fellowship, a course in Applied Physiology (Physiology of Symptoms), and a History of Medicine Club with weekly seminars on the subject. In 1933 Biochemistry was increased by the arrival of Nicholas Dietz from the University of Pittsburgh.

In 1937 E. R. Whalen joined the department as a fellow in Physiology and Pharmacology. This continued until 1947, at which time Drs. Struck and Ferguson joined the joint department as assistant professors. The course continued as before, but now there appeared as an addition a course in experimental surgery, research courses in Physiology and Pharmacology, and two thesis courses.

In 1949 for the first time specific courses were listed for students wanting to obtain an M.S. degree in Physiology. Many medical students in Wilhelmj's time did spend an extra year working on research for M.S. degrees. The last of these was in 1966 and the first in 1933. Between 1933 and 1984 a total of 50 students were awarded M.S. degrees in Physiology. Until 1966 almost all of these were medical students. After 1966 these were students who had failed to get into medical school. All subsequently gained admission. Wilhelmj was never department chairman, but he assumed the deanship between 1940 and 1948.

In 1950 Dr. R. K. S. Lim replaced Dr. Gerald as Chairman of Physiology and Pharmacology. Lim had left China a year earlier with the collapse of the Koumintang government and remained with A. C. Ivy at the University of Illinois, Chicago, before being appointed to the Creighton chair. Unfortunately, he remained only one year. The department now consisted of two professors, two assistant professors, and two instructors.

In 1955, **Dr. J. Raymond Johnson** became chairman of the department, which had now grown to six. By 1964 there were nine, four of them pharmacologists. Every member of the department had a research grant, and NIH funds had been obtained, which resulted in the construction of a research building on the main university campus.



By 1965, J. R. Johnson had retired from the Chair and D. F. Magee arrived from the University of Washington as chairman and the staff was further increased to thirteen. The University agreed in 1968 to permit the institution of doctoral degrees in the basic medical sciences. We have graduated six Ph.D.'s in Physiology since then.

In 1967 a new teaching building was constructed, which became the home of the department. The old off-campus building was abandoned and demolished to accommodate the construction of Interstate 80. The sudden infusion of life into the department was due to the availability of research and construction funds and to the vision of Richard Egan who became dean in 1960. The need to turn the school into an academic institution was apparent to him and to the LCME accreditation committee. Academic medicine had not heretofore been considered as a vital part of the medical school's mission. After a few years the school was removed from probation, which it had been on for several years previously.

The decrease in research funding and an administrative upheaval that preceded the building of a new hospital hurt the department greatly. Pharmacology was split off as a separate department in 1976. Physiology became responsible for teaching in all four of the health science schools, and our faculty declined to its present level—four. Teaching laboratories were abandoned, research grants became scarce, equipment deteriorated, and graduate education came to a virtual standstill. Despite this, the department has continued to publish. At present a change in administration and the sale of the teaching hospital has brought about an evident improvement of the department. By July 1985 we will be back up to seven full-time faculty.

D. F. Magee

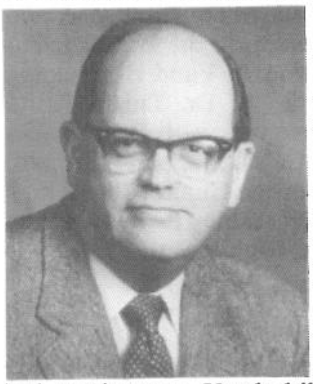
Orr E. Reynolds Award

Manuscripts are solicited for consideration for the Orr Reynolds Award, a newly instituted award to honor Dr. Reynolds who is retiring as Executive Secretary-Treasurer in June 1985. The award will be given annually for an article by a member of the Society on some aspect of the history of physiology, including the American Physiological Society. The article will be published in one of the Society journals after appropriate peer review. The choice will be made by a committee set up by Council. The deadline for this year is December 1 and the award will be presented at the Spring meeting in St. Louis. The award is open to all members of the Society except professional historians, i.e., those members whose Ph.D. is in the history of science or medicine. If the awardee wishes, and there is a suitable place on the program, an oral presentation will be made at the Spring or subsequent Fall meeting at the beginning of an appropriate scientific session. The value of the award is $500 plus expenses to attend the Spring meeting. To obtain operational details write to APS Headquarters.

Fifty-Eighth President of APS

Howard E. Morgan, M.D., is the 58th President of the American Physiological Society. Dr. Morgan, who has been a member of the Society since 1965, succeeds Dr. John B. West as APS' chief elected officer.

A native of Bloomington, Illinois, Dr. Morgan attended Illinois Wesleyan University and earned his M.D. at the Johns Hopkins University School of Medicine. Dr. Morgan started his career with clinical training in obstetrics and gynecology in which he did his residency at Vanderbilt University. Immediately following his clinical training, he began his research career as a physiologist, initially as a fellow and then as an investigator of the Howard Hughes Medical Institute at Vanderbilt University, where he rose through the academic ranks to Professor of Physiology. In 1967, he became Professor and Chairman of the Department of Physiology at the Milton S. Hershey Medical Center of Pennsylvania State University, a position which he holds to the present. In 1973 he was given the additional position of Associate Dean for Research, and in 1974 he was named Evan Pugh Professor of Physiology.



Dr. Morgan has been actively involved with the Society's publications since 1967, having served on editorial boards from that time until 1973 when he was named editor of *Physiological Reviews.* He later served as editor of the *American Journal of Physiology: Cell Physiology,* and since 1981 he has been the chairman of the Society's Publications Committee.

Dr. Morgan's entire research career has been devoted to studies of cardiac physiology and biochemistry. One of his very important contributions was the development, characterization, and validation of the isolated working rat heart model, which he used to investigate the effects of preload, afterload, and cardiac work on oxygen consumption and substrate utilization. This model has been used by many investigators around the world for studies of cardiac function and metabolism in normal and pathophysiological states. Another area in which he has made important contributions is his studies of the mechanisms of cardiac hypertrophy. He has shown that stretch of the ventricular wall is the mechanical parameter most closely correlated with an acceleration of protein synthesis and that the rate of synthesis is closely linked to the number of ribosomes and other enzymatic components of the protein synthetic pathway. Dr. Morgan's contributions to our understanding of the factors leading to growth of the heart will yield better insight into pathophysiology of certain types of heart disease and suggest new approaches to management of some of these problems.

In addition to his many important scientific contributions and his role with APS, Dr. Morgan has played leadership roles in many scientific societies and advisory bodies dealing with heart research. He is currently Chairman of the Basic Science Council of the American Heart Association and President of the International Society of Heart Research. He is past President of both the Association of Chairmen of Departments of Physiology and the Cardiac Muscle Society. He has served on the Physiological Chemistry Research Study Group of the American Heart Association, the Metabolism Study Section and the Cardiology Advisory Committee of the National Heart, Lung, and Blood Institute. He has just completed a term as a member of the NIH-NHLBI Advisory Council.

Dr. Morgan has received numerous awards for his many important contributions, including the Award of Merit from the American Heart Association, the Carl J. Wiggers Award of the Cardiovascular Section of the American Physiological Society, and being named the Hughes Scholar of the Howard Hughes Medical Institute and Honorary Fellow of the American College of Cardiology.

APS Election Results

Dr. **Franklyn G. Knox,** Department of Physiology & Biophysics, Mayo Medical School, Rochester, MN, was elected President-Elect. The two new Councillors are Dr. **Norman C. Staub,** Professor of Physiology, University of California, San Francisco, for a 4-year term and Dr. **Shu Chien,** Professor of Physiology, Columbia University, College of Physicians and Surgeons, New York, NY, to complete Dr. Knox's term expiring in 1986.

H. E. Morgan and F. G. Knox

133rd APS Business Meeting

Time: 10:15 A.M., Wednesday, April 24, 1985

Place: Anaheim Room, Convention Center, Anaheim, CA

I. Call to Order

President John West called the meeting to order and welcomed the members to the 133rd Business Meeting of the Society. Distributed with the agenda were the ballot for the election of new members and a list of future meetings.

II. Report on Membership

Dr. H. E. Morgan, President-Elect, reported on the status of the Society membership and deaths since the last meeting.

A. Summary of Membership Status. As of March 1, 1985, the APS membership reached 6,231 of which 4,526 are Regular members, 604 Emeritus, 10 Honorary, 125 Corresponding, 757 Associate, and 209 Students.

B. Deaths Reported Since the Last Meeting. In tribute to the 23 deceased members whose names were read and the membership observed a moment of silence in tribute to them (p. 158).

III. Election of Members

A. Appointment of Tellers. Tellers appointed by President West were E. R. Buskirk, F. S. Grodins, P. C. Johnson, and S. Permutt, who collected the ballots for the election of new members.

It was noted that on the recommendation of the Honorary Membership Committee, three distinguished physiologists, Bernard Katz, Erik Torsen, and Karl-Julius Ullrich, are included on the ballot for election to Honorary membership.

B. Election of Members. Dr. Reynolds, Executive Secretary-Treasurer, announced that all candidates nominated were elected to membership.

IV. Election of Officers

Reporting on the Election of Officers by mail ballot, Dr. Reynolds announced that the new President-Elect is **F. G. Knox**, and the two new Councillors are **N. C. Staub**, for a four-year term, and **S. Chien**, to complete Dr. Knox's term expiring in 1986. The total number of ballots cast were 1,633 for President-Elect and 1,572 for Councillor.

V. Awards

A. Ray G. Daggs Award (see p. 144).

B. Caroline tum Suden Professional Opportunity Awards. The Caroline tum Suden Professional Opportunity Awards, open to graduate students or postdoctoral fellows presenting papers at the Spring FASEB meeting, consists of a $500 check to attend the meeting, free registration, and access to the FASEB Placement Service. The Chair of the Women in Physiology Committee, Dr. Marie Cassidy, joined Dr. West in presenting awards to **Lynn M. Baxendale** (University of Illinois), **Fredric R. Boockfor** (Iowa State University), **Hannah V. Carey** (University of Nevada), **Michael A. Gropper** (University of California), **Robert T. Mallet** (George Washington University), and **Karen M. Wilson** (University of Florida).

C. John F. Perkins, Jr. Memorial Award. The Perkins Memorial Fellowships provide supplemental support for the families of foreign physiologists who have fellowships or sabbatical leave to carry out scientific work in the United States. The awards are for the purpose of developing the full potentialities for culture benefit associated with scientific exchange. U.S. physiologists requiring supplemental assistance to work abroad are also eligible. Awards range from $3,000 to $7,500 depending upon the needs of the family over and above the amount already available to the visiting scientist. In 1985, the Perkins Memorial Fund is providing partial support for the families of Dr. Tatsuo Tanita from the Tohoku University to work with Dr. Norman C. Staub at the University of California, San Francisco, and Dr. Massimo Miniati from the Clinical Physiology Institute, Pisa, to work with Dr. Aubrey E. Taylor at the University of South Alabama, Mobile.

D. Orr E. Reynolds Award (see p. 139).

VI. State of the Society

"This year," remarked President West, "has been a busy one for the Society and over the course of the next few minutes I would like to touch on some of the most important events.

"One far-reaching change is the impending transformation of *The Physiologist*. As I indicated at the last Business meeting in Lexington, Kentucky, *The Physiologist* will remain as the house organ of the Society and it will continue to be edited by the Executive Secretary. The size will be 16 pages, at least initially, and it will contain news of forthcoming events, and other contemporary issues of interest to members. The scientific and educational aspects of *The Physiologist* will be assumed by a new journal *News in Physiological Sciences*. This will be jointly managed by the American Physiological Society and the International Union of Physiological Sciences, and we are very fortunate that Knut Schmidt-Nielsen has agreed to be the first editor. He will be assisted by an eminent international group of associate editors. With Dr. Schmidt-Nielsen's broad interests across several areas of physiology, his writing skills, and his international contacts, I believe that the journal will get off to a very strong start. The journal will concentrate on brief reviews and news of current advances in physiology and should prove to be a valuable and interesting education journal. Many of you will be familiar with *Trends in Pharmacological Sciences* and *Trends in Biochemical Sciences*, which have been extremely successful.

"The Society is also considering becoming involved in electronic publishing. Discussions are underway with

the BRS/Saunders organization to have the *Journal of Applied Physiology* as part of their data base. This would mean that information in the Journal would be available via a computer terminal in anybody's private office. At the present time this data base includes the *Annals of Internal Medicine*, *New England Journal of Medicine*, *Lancet*, and *British Medical Journal* as well as a number of full texts of books. A feature of the system is that every word is indexed and can be used as a basis for a search. We are also discussing the possibility of putting the *Handbook of Physiology, The Respiratory System*, on the same data base. There are many implications of this entry into electronic publishing and not all the consequences can be predicted at the present time. However, this is an exciting and innovative development.

"Animal rights is another critical issue for the Society which threatens the future of experimental physiology. I will not go into details of present changes here; many of these can be found in recent issues of *The Physiologist*. Also, a symposium on 'Use of animals and adjuncts in biomedical research' will be held later today. It should be emphasized that the Society has a considerable financial investment in moderating the effects of animal activists and seeking a reasonable solution to the problems. Bill Samuels devotes a substantial amount of his time to this area on behalf of the Society.

"Preparations for the Centennial celebrations of the Society in 1987 are proceeding apace. These will occur at the Spring FASEB meeting, and the general theme will be 'A Century of Progress in Physiology.' The goals are to have a birthday celebration of this oldest of the FASEB societies, and at the same time to emphasize the vital dynamic aspects of contemporary physiology in an effort to attract more of the bright young minds into this area. A number of keynote lectures will be scheduled, and I hope they will be as stimulating and successful as the one we have just heard from Roger Guillemin."

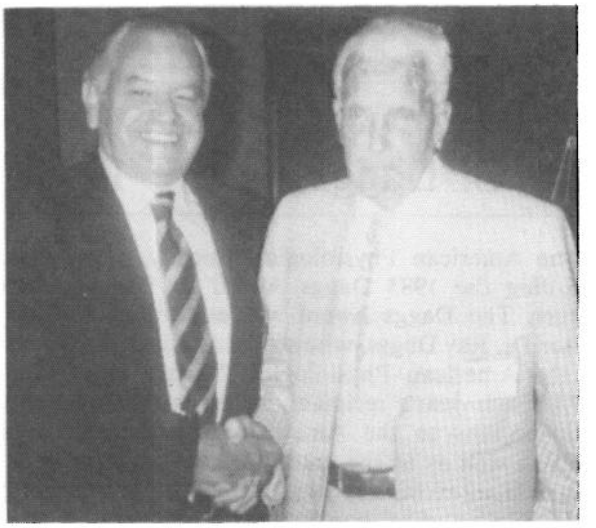
[The remainder of the President's remarks concerned the retirement of Orr Reynolds as Executive Secretary-Treasurer and his impending replacement by Dr. Martin Frank. These can be found in the editorial on page 132.]

Following a standing ovation, Dr. Reynolds said, "I pride myself in keeping aware of what is going on, and I must admit that all of these things come as a complete and utter surprise to me. I cannot imagine with as many people on Council and the staff who were involved in this, that I had so many surprises. I am awestruck in more ways than one.

"I feel extremely fortunate to have had the opportunity to serve the Society that I have been in love with for fifty years and to serve as its executive officer for the last twelve years. I feel even more fortunate that I am being given the opportunity to help in the organization of the Society's 100th birthday party. I hope you will all be there. Thank you very much."

In introducing a very distinguished member, David Bruce Dill, who was President of the Society in 1950, Dr. West commented, "I had the privilege on Monday of presenting some of Dr. Dill's primary data on lactate and high altitude produced in 1935 and as far as I can determine, no one has gotten any better data since then. Dr. Dill indicated he would like to say a few words on the occasion of Dr. Reynolds' retirement."

"I am very happy at this privilege of paying tribute to my warm friend, Orr Reynolds," stated Dr. Dill. "His



O.E. Reynolds and D.B. Dill

characteristics that I have found to exist during the years are: he is wise; he is judicious; he is kind; he is diplomatic; and those characteristics put together have enabled him to become extremely skillful in humane relations. Thank you Orr Reynolds. It has been my great privilege to have been associated with you over these years, and I trust that your future endeavors including those with the Society will be very fruitful indeed. Again, thank you Orr."

In response to his introduction as the incoming Executive Secretary-Treasurer, Dr. Martin Frank said, "I think it is unique that Orr Reynolds has been Executive Secretary-Treasurer of the Society for as long as I have been a professional physiologist. I guess I am part of the commemorative activities as such in honor of Dr. Reynolds' retirement. I look to all of you for assistance and guidance in continuing the greatness of the American Physiological Society, and I hope that I can be to each and every one of you the same as Orr Reynolds has been over the past twelve years."

VII. New Business

A member of the Education Committee, Dr. Howard Modell, announced that the Learning Resource Center has been a gathering place for physiologists who share common problems in teaching but whose research areas are diverse. Because of the interest generated by these discussions, it was decided that a broader forum for exchanging ideas relevant to physiology teaching was needed. More than the required number to establish a Section on Education met to develop a Statement of Organization and Procedures for presentation to Council in the Fall. The proposed section is intended to compliment and not conflict with the Education Committee, and Dr. Modell invited APS members to contact him if they were interested in adhering to the section.

Dr. Modell also inquired as to whether the new NIPS publications will absorb the education articles currently appearing in the Physiology Teacher Section of *The Physiologist*. Dr. West responded that although all the details have not been worked out, NIPS will include a number of educational articles with emphasis on teaching.

With no other business, the 133rd Business Meeting was adjourned at 11:15 a.m., April 24, 1985.

Howard E. Morgan, President-Elect

Ray G. Daggs Award, 1985

The American Physiological Society takes pride in awarding the 1985 Daggs Award to Dr. **A. Clifford Barger**. The Daggs Award was established in 1973 to honor Dr. Ray Daggs, who served as Executive Secretary of the American Physiological Society from 1956 to 1972. Each year's recipient is chosen for outstanding contributions to the American Physiological Society itself as well as to the entire field of physiology. Cliff Barger is an exemplary person in both his leadership in our Society and in the world of physiology.

Let us first list only a very few of Cliff's many contributions to the American Physiological Society: Cliff served as president in the year 1970-71, and he was a member of Council from 1968 to 1972. He served two stints on the Publications Committee from 1961 to 1963 and 1966 to 1969, and he was chairman of the committee in the years 1962-63 and 1966–69. Almost single-handedly he has maintained the viability of the Porter Development Committee, having served on this committee for an incredible period of 17 years and during all of this time as its co-chairman. From 1979 to 1981 Cliff was a member of the Financial Development Committee of the American Physiological Society, helping in the all-important task of developing a sound financial basis for our Society, and presently he is a member of the Committee for Liaison with Industry, having served in this capacity since 1983. Cliff has also been very deeply involved in the fight by our Society and its members to maintain access to appropriate animal models for our physiological research, working especially closely with the Society for Medical Research and the IUPS.

In addition to Cliff's contributions to the American Physiological Society, he has also been a leader both in physiology education and in basic physiological research. As a member of the Physiology Department of the Harvard Medical School for almost 40 years, serving as professor in that department for the past 24 years and as chairman of the department from 1974 to 1976, Cliff has played a very personal role in the training of literally thousands of physiology students. More specifically his own research laboratory has been the source of inspiration and outstanding research training for dozens of graduate students and fellows who now occupy important positions in physiology throughout the world.

J. B. West and A. C. Barger

As a research scientist, Cliff has received worldwide recognition for his research on the cardiovascular system. Though it is not proper to emphasize one area of Cliff's research over his many other areas, nevertheless he will be remembered especially for very precise characterization of the hemodynamics and endocrinology of congestive heart failure, and more recently for extended and intricate studies on the relationship of the kidneys and the renin-angiotensin system to the genesis and maintenance of hypertension.

It is difficult to terminate this recitation of Dr. Clifford Barger's many contributions to the world of physiology, but it is an honor both to the American Physiological Society and to Dr. Ray Daggs that Dr. Barger has been selected as this year's recipient of the Daggs Award.

Response

I am deeply honored that my colleagues have deemed me worthy of the Award which honors Ray G. Daggs, a long-time Executive Secretary and my wise mentor during my term as President of the American Physiological Society. His devotion to the Society and his willingness to tutor each incoming president provided the continuity which has made the Society function smoothly.

The timing of the Award is also propitious, for I shall have the last plaque that will be signed by our second Executive Secretary, Orr E. Reynolds, whom I helped attract to Beaumont House and who will soon retire. Thus, I am doubly honored and now look forward to serving under our third Executive Secretary, Martin Frank. I hope I may be able to continue to contribute to the American Physiological Society under his leadership and to repay the Society in a small way for all it has meant to me.

A. Clifford Barger

Recipients of the Ray G. Daggs Award

1974	J. H. Brookhart
1975	M. B. Visscher
1976	J. D. Hardy
1977	J. H. Comroe
1978	H. Rahn
1979	J. R. Pappenheimer
1980	J. R. Brobeck
1981	A. C. Guyton
1982	R. W. Berliner
1983	C. L. Prosser
1984	E. F. Adolph
1985	A. C. Barger

Committee Reports

Physiology and FASEB 1985

The meetings of our Society have come and gone, and, in the main, have been forgotten until the next "Call for Papers" is delivered to the membership by the postman. Perhaps it is opportune to reflect on what constitutes the scientific program of the American Physiological Society's segment of FASEB 85 and how the contributions of physiological scientists are organized to accommodate them through the media of slide and poster sessions, symposia and special scientific sessions.

An analysis of the scientific program of the 1985 Spring Meeting of FASEB and APS follows. The six FASEB member societies met in consort this year in Anaheim, along with several guest societies. The foundation for this unusually large interdisciplinary biologic forum stems from the submission of 8,904 abstracts of volunteered papers, an all time high for FASEB.

Of this total, 2,104 papers represent submissions by the APS membership and the three APS guest societies – The Society for Experimental Biology and Medicine (SEBM), The Biomedical Engineering Society (BMES), and The Society for Mathematical Biology (SMB). The physiology component of FASEB 85, then, represented 21.38% of the science encompassed in the short communications presented by APS members and guests. Of the APS-sponsored papers, 396 or 18.82% represented the scientific efforts of women physiologists and 156 or 7.41% of non-American physiologists.

Noticeably, 94 of the non-American contributions came from Canada. However, 18 were accepted form the Federal Republic of Germany; 5 each from Beirut, France, and The Netherlands; 4 each from Belgium and Kuwait; 3 each from Finland, Japan, The People's Republic of China, and Sweden; 2 from Venezuela; and singles from Australia, Hong Kong, Israel, Italy, Norway, Singapore, and Switzerland. Although Puerto Rico is a self-governing commonwealth in union with the United States, it is appropriate to note here the 8 submissions by its physiologists. Unfortunately, we did not maintain statistics of this type for FASEB 84. Had we done so, along with those for prior years, we might have been able to show some trends in the APS outreach to non-North American scientists from the view of adding Corresponding Members to our ranks, increased reciprocity in scientific exchange, and diminishing some of the constraints to more facile international collaboration in physiological science.

An immediate reaction to the figures 8,904 and 2,104 might be, "How can this mass of volunteered papers ever be accommodated sensibly into meeting sessions representative of current interests and significant advances in the science of physiology?!" Simply, the task is enormous, difficult, and multi-variant in detail, but it is not insurmountable. It is accomplished by an excellent system that was designed and developed some 10 years ago.

Looking back to 1976, the Council of the Society approved and adopted the recommendations of an ad hoc Committee for expanding the composition and functions of *the original* APS Program Committee [*Physiologist* 19(2): 93–94, 1976; and *Physiologist* 19(4): 471–475, 1976]. The system, still extant, centers about the roles and functions of a Program Advisory Committee (PAC) and a Program Executive Committee (PEC). The PAC maintains liaison with the many constituent specialty groups within the Society and is charged with the responsibility for the organization and control of the Society's scientific programs. The activities of the PAC are overseen by the PEC, which relates directly to Council with respect to scientific events. The PEC is composed of a Chairman (an ex officio member of Council) and two members recommended to Council by the Committee on Committees. The PAC is made up of representatives of each of the 12 APS Sections, the Muscle and Epithelial Transport Groups, and the Subcommittee on Clinical Science of the APS Publications Committee. The PAC and the PEC meet during the APS Spring (FASEB) and Fall Meetings for the purpose of developing symposia, analyzing, and establishing thrusts in physiological science, consideration of opportune special sessions, and looking into the needs, in general, for the well-being of the scientific communication of the Society. During these intervals, program plans are developed by the PAC and the PEC for implementation in the respective meetings one year hence.

Relative to the APS scientific segment within the framework of FASEB 85, what follows stems principally from the PAC and the PEC activities and functions for the APS scientific contributions, formally implemented at the time of FASEB 77 [*Physiologist* 20(1): 6, 1977].

In this context, the programming of abstracts of volunteered physiological papers for FASEB 85 was accomplished through the diligent and dedicated efforts of the PAC and the sectional/specialty consultants with whom they work to facilitate integration of papers into attentive and meaningful topical sessions. Final scheduling of sessions was achieved through a unified effort of the Chairman of the PEC, the Executive Secretary-Treasurer, and the staff of the Membership Services Department. The need to avoid conflicts between topical presentations of volunteered papers and symposia along with special requests for time slots, dates, and locations of presentations imposed mostly by travel constraints of speakers made sessions scheduling difficult.

Of the 1,929 APS member-sponsored abstracts, 23.32% were designated by the authors for inclusion in topics programmed by other FASEB Member Societies (Table 1). Only one-third of the SEBM papers were designated for presentation in physiology sessions.

TABLE 1: DISTRIBUTION OF APS- AND GUEST SOCIETY-SPONSORED ABSTRACTS OF VOLUNTEERED PAPERS FOR FASEB 85

SPONSOR	RECEIVED	RETRACTS	SOCIETAL PROGRAM DESIGNATION						
			APS	ASBC	ASPET	AAP	AIN	AAI	TOTAL
APS	1929	12	1470 76.68%	54 2.82%	193 10.07%	111 5.79%	67 3.50%	22 1.15%	1917
SEBM	122	1	41 33.88%	11 9.09%	25 20.66%	24 19.83%	9 7.45%	11 9.09%	121
BMES	35	1	30 85.71%	·	1	2	·	1	34
SMB	6	·	5 83.33%	1	·	·	·	·	6
OTHER	12	·	3	1	3	1	1	3	12
TOTAL	2104	14	1549 74.11%	67 3.21%	222 10.62%	138 6.60%	77 3.68%	37 1.77%	2090

JFO 2-7-85

TABLE 2: SOURCES OF VOLUNTEERED PAPERS PROGRAMMED BY APS FOR FASEB 85

SCIENTIFIC DISCIPLINE	TOTAL PAPERS	FASEB ELEMENTS					
		APS	ASBC	ASPET	AAP	AIN	AAI
THEME.....	11	5	•	6	•	•	•
CARDIOVASCULAR	497	402 (81.0%)	11	71 (14.2%)	8	5	•
CELL & GENERAL	146	47 (32.2%)	43 (29.5%)	43 (29.5%)	3	5	5
COMPARATIVE	44	39	1	3	•	1	•
ENDOCRINE & METABOLISM	249	99 (40%)	54 (22%)	31 (12%)	15 (6%)	43 (17%)	7 (3%)
ENVIRON. THERM. & EXER.	135	121 (89.6%)	•	13 (9.6%)	•	1	•
EPITHELIAL TRANSPORT	95	88	•	7	•	•	•
GASTROINTESTINAL	72	53 (73.6%)	2	10 (13.9%)	•	5	2
MUSCLE	114	81 (71.1%)	5	25 (21.9%)	3	•	•
NERVOUS SYSTEM	64	22 (34.4%)	9 (14.1%)	32 (50.0%)	1	•	•
NEUR. CONT. & AUTONOM. REG.	98	69 (70.4%)	1	26 (26.5%)	1	1	•
RENAL	109	79 (73.0%)	5	19 (17.1%)	3	3	•
RESPIRATION	392	368	2	13	4	1	4
WATER & ELEC. HOMEO.	38	33	•	3	1	1	•
BIOMEDICAL ENGINEERING	37	30	1	3	1	•	2
TEACHING	16	7	5	3	•	1	•
TOTAL	2117	1543 (72.9%)	139 (6.6%)	308 (14.5%)	40 (1.9%)	67 (3.1%)	20 (1.0%)

JRS 2-2-85

TABLE 3: ABSTRACTS OF VOLUNTEERED PAPERS PROGRAMMED BY THE APS SECTIONS FOR THE FASEB 85 MEETING

	RECEIVED	WITHDRAWN	ABSTRACTS PROGRAMMED (2)				SESSIONS				TOTAL SESSIONS
			SLIDE	POSTER	TOTAL	% POSTER	SLIDE	POSTER DISCUSSION	POSTER TITLES	SYMPOSIA & SPECIAL	
APS	1929 (1)	12	782	1287	2069	62.20	69	3	62	27 (4) / 5 (4)	161 / 5 (4)
BMES	35	1	10	27	37	72.97	1	•	1	5	7
SEBM	122	1	•	•	•	•	•	•	•	•	•
SMB	6	•	•	•	•	•	•	•	•	1	1
THEME	12 (1)	•	11	•	11	•	1	•	•	9	10
TOTALS	2104	14	803	1314 (3)	2117 (3)	62.07	71	3	63	42 / 5 (4)	179 / 5 (4)

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(1) - RECEIVED IN APS CENTRAL OFFICE AS APS-VOLUNTEERED AND/OR SPONSORED.

(2) - APS TOPIC DESIGNATED... INCLUDES TRANSFERS TO APS FROM OTHER FASEB SOCIETIES.

(3) - INCLUDES 7 APS, 5 ASBC, 3 ASPET AND 1 AIN POSTERS FOR TEACHING/LEARNING RESOURCES PROGRAM.

(4) - INCLUDED ARE:
- APS-FASEB SPONSORED SYMPOSIUM ON "THE USE OF ANIMALS AND ADJUNCTS IN BIOMEDICAL RESEARCH."
- HONORS IN PHYSIOLOGY LECTURE.
- PHYSIOLOGY IN RESPECTIVE LIGHTS.
- HISTORY OF PHYSIOLOGY SERIES LECTURE.
- NIH-APS-ASPET WORKSHOP.

(5) - INCLUDES 2 SESSIONS ON APS-FASEB SPONSORED "COMPUTER-BASED EDUCATION IN BIOMEDICAL SCIENCE" AND THE APS-FASEB SPONSORED SYMPOSIUM CENTENNIAL SYMPOSIUM.

When collation of the 8,904 abstracts was completed according to the FASEB Unified Societal Topic Category List, the APS had amassed a total of 2,117 papers for final programming into its scientific sessions. Going back as far as 1962, we found the 2,117 volunteered papers for this meeting to be monumental! APS-sponsored papers did not eclipse the 1,000 mark until 1974. In the interval from 1962 to 1974, the average number of volunteered papers per FASEB meeting was 833. The 1,500 papers level was not surpassed until 1979, with 1,665 contributions. Since then, the average number of papers volunteered annually stands at 1,801. Thus, over the next 10 years, could 1985 have begun a promising trend?

As indicated in Table 2, 27.1% of the volunteered papers to be programmed by the APS were the products of members of the other FASEB Member Societies, with ASPET members providing the majority. The contribution of papers by the pharmacologists and toxicologists was significant in 9 of the major areas of physiology and, especially, in the nervous, cell, neural control, and muscle areas. The contributions of the biochemists (ASBC) are noticeable in the fields of cell and general physiology, nervous system, and endocrinology and metabolism. Considerable input for the latter area came from the nutritionists (AIN).

Table 3 shows the distribution of volunteered papers programmed by the APS and its Guest Societies into slide and poster sessions in conformance with discrete physiological subject areas. 1,314 or 62.07% of the 2,117 papers in physiological science were designated by the PAC for poster sessions, either by virtue of author preference or programmer choice for better conformity with a poster topic vis-a-vis an "out-of-context" presentation in an otherwise integrated slide session. The percent of posters this year is just slightly less than during FASEB 84, 62.63%, and well above the annual average of 44.72% since the inception of poster presentations during FASEB 75. Over the years, there has been an increase in tendency among APS members to choose poster presentations over slide-type deliveries, 22.83% posters in 1975 to 62.07% in 1985.

Upon completion of the programming of volunteered papers by the PAC, the disposition of papers resulted in 71 slide sessions, 3 poster discussions (each with 20 posters), and 63 poster session titles. The latter range from as few as 3 to as many as 49 papers per poster session title. The average was 20.

The PAC-PEC are credited with the development for FASEB 85 of 36 of the 42 APS symposium sessions and one Special Session on "The Use of Animals and Adjuncts in Biomedical Research." The latter was proposed and ultimately organized through the efforts of the APS Committee for Liaison with Industry (now with representation on the PAC) and sponsored by FASEB. The APS-managed theme for this year consists of 9 symposium sessions on "Ganglionic Control of Autonomic Effector Systems." Thus, with a total of 184 physiology sessions during FASEB 85 (Table 3), the APS has achieved another scientific milestone.

Inspection of Table 4 reveals the contribution of members of APS Sections to activities in their respective disciplines of physiological science. In comparison to 1984, significant declines in submission of volunteered papers are observed in water and electrolyte homeostasis (38 vs. 77) and in nervous system (64 vs. 92). Contributions in the other disciplines are either unchanged from last year or on the increase.

Nevertheless, the scientific interest and pursuit in the disciplines of physiological science continue to be intense. And, of course, the Society continues its effort toward coming as close as possible to meeting all of the needs of its members. Yet there appear to be tendencies in certain areas of physiology toward a decline in the submission of papers. A review indicates that 92 or 57.14% of the 135 meeting-paper topics in physiology are of primary interest and choice to 5 or fewer individual investigators/authors. This does not preclude, however, that a senior physiologist might have sponsored numerous papers in a variety of areas, cardiovascular

TABLE 4: PROGRAMMING BY APS SECTIONS OF ABSTRACTS OF VOLUNTEERED PAPERS FOR FASEB 85

APS SECTION	ABSTRACTS PROGRAMMED					SCIENTIFIC SESSIONS				
	TOTAL (a)	% OF TOTAL	SLIDE	POSTER	% POSTERS	SLIDE	POSTER DISCUSSION	POSTER TITLES	SYMPOSIA	TOTAL
THEME.....	11	0.52	11	•	•	1	•	•	9	10
CARDIOVASCULAR	497	23.47	231	266	53.80	20	1	19	3	43
CELL & GENERAL	146	6.89	35	111	76.03	3	•	8	1	12
CLINICAL	•	•	•	•	•	•	•	•	3	3
COMPARATIVE	44	2.08	24	20	45.45	2	•	1	•	3
ENDOCRINE-METABOLISM	249	11.76	105	144	57.83	9	•	6	•	15
ENVIRON. THERM. & EXER.	135	6.37	64	71	52.89	7	•	3	3	13
EPITHELIAL TRANSPORT	95	4.49	35	60	63.16	3	•	2	1	6
GASTROINTESTINAL	72	3.40	11	61	84.72	1	2	2	1	6
MUSCLE	114	5.38	•	114	100.00	•	•	3	•	3
NERVOUS SYSTEM	64	3.02	29	35	54.69	3	•	1	5	9
NEUR. CONT. & AUTONOM. REG.	98	4.67	47	51	52.53	4	•	2	•	6
RENAL	109	5.15	48	61	56.00	4	•	2	3	9
RESPIRATION	392	18.52	129	263	67.10	11	•	11	4	26
WATER & ELEC. HOMEO.	38	1.79	24	14	36.84	2	•	1	•	3
TEACHING	16 (b)	0.76	•	16 (b)	100.00	•	•	1	•	1
BMES	37	1.75	10	27	72.97	1	•	1	5	7
SMB	•	•	•	•	•	•	•	•	1	1
TOTAL	2117	•	803	1314	62.07	71	3	63	42 (c)	179 (c)

JRS 2-2-85

(a) - INCLUDES BMES AND SMB PAPERS NOT PROGRAMMED SPECIFICALLY BY THOSE SOCIETIES.

(b) - INCLUDES 7 APS, 5 ASBC, 3 ASPET AND 1 AIN TEACHING POSTERS.

(c) - INCLUDES APS-FASEB SPONSORED CENTENNIAL SYMPOSIUM AND TWO SESSIONS OF THE APS-FASEB SYMPOSIUM ON "COMPUTER-BASED EDUCATION IN BIOMEDICAL SCIENCE."

APS Volunteer Photographer Wanted

A member is wanted with a good camera and flash attachment to take one or two rolls of black and white photographs at upcoming APS Spring and Fall meetings. Among the photographs desired are those of Council, of awards presented at the Business Meeting, and of special speakers and events. Film and processing will be supplied by APS. If you would like to volunteer, please write to Toby Appel, American Physiological Society, 9650 Rockville Pike, Bethesda, MD 20814 (301/530-7105).

and respiration physiology, for instance. On the other hand, there are 29 dominant scientific topics that maintain a rather well-established momentum and enthusiasm for pursuit. Contributions in these areas range from 21 to as many as 86 volunteered papers (epithelial transport).

Finally, as we "put to rest" our administrative management of the contributed materials for our Spring (and Fall) Scientific Meetings, we cannot overlook some of our anecdotal encounters. There is the case(s) of the first author who calls us to request withdrawal of his/her abstract because "final data do not support the result and conclusions presented in his/her abstract!" Of course, numerous are the pleas for "special allocation" of time and dates because of certain *hardships.* Many requests come to us for special attention to corollary or companion presentations, otherwise one of the two or more hoped-for sequential presentations might become less significant in so-called isolation! Then too, there is the instance of "I stated a preference for presentation in a post session; however, my institution (non-American) will not sponsor my trip to the meeting unless the paper is presented in a podium (slide) session. . . ." Often the rules for presentation of papers are totally ignored or misinterpreted, especially in the situation of scientists occupying the first author position on two or more abstracts. In most cases, this matter is mediated without reprisal; yet in some instances we encounter degrees of furor. But being endowed with generous quantities of tact and diplomacy, we are able to ameliorate most of the initial unpleasantries. The "confirmation card" prompts many telephone queries—some are frenzied and some irate, but most are mild—about the title on the card not being the one of the abstract submitted! Some authors even go to the length of accusing us of *deliberately* having changed the title of their paper to suit our own needs! The confirmation card specifies the time, date and place of paper presentation *and* the name/title of the session, *not* the paper title. Once we explain, clarification is accepted with gratitude and a sigh of relief. On the whole, the typical abstract is representative of an "art form" and a medium of "effective communication." However, there are those with barriers to easy reading and comprehension because of excessive length and, even, brevity, carelessness in composition, and the exorbitant use of acronyms and abbreviations that overtax the visual musculature in constant referral.

From this vantage, the APS contribution to FASEB 85 was a striking success and scientifically rewarding, especially to those who made it possible.

J. B. Saunders

Porter Development

The report of the Porter Development Committee to the Society provides the opportunity of informing the members that fellowship funds are available for able minority students both at the pre- and postdoctoral level.

Two of the former Porter Development Postdoctoral Fellows have recently returned to the Department of Physiology at the University of Puerto Rico: Dr. Nelson Escobales, who was a fellow in the laboratory of Dr. Mitzi Canessa in the Department of Physiology and Biophysics, Harvard Medical School; and Dr. Jose E. Garcia-Arraras, who was a fellow in the laboratory of Dr. Nicole Le Dourain at the Institut d'Embryologie, Centre National de la Recherche Scientific, Nogent-Marne, France. We are also continuing the support of Dr. Jorge R. Mancillas, who is a postdoctoral fellow in the laboratory of Dr. Floyd E. Bloom at Salk Institute; Jean A. King, who is a candidate for the Ph.D. degree in the Department of Biology, New York University, in the laboratory of Dr. Fleur L. Strand; and Darlene K. Racker, who is a candidate for the Ph.D. degree in the Department of Physiology and Biophysics, Chicago Medical School, in the laboratory of Dr. Warren W. Tse.

The Committee has continued funding for the Atlanta consortium, a program organized with the assistance of the Department of Physiology at Emory Medical School. Two former Porter Development Committee Fellows, Drs. Pamela Gunter-Smith and John C. S. Fray, have been Visiting Porter Lecturers in the Atlanta Program. The Dillard Program in New Orleans has been assisted by the staff of the Departments of Physiology at Louisiana State University and Tulane University.

The Committee is also providing support for a Minority Student Research Internship Program in the Department of Physiology, Michigan State University, and for a Summer Student Research Program for Native American Indians in the Department of Physiology and Biophysics, College of Veterinary Medicine and Biomedical Sciences, Colorado State University. Errol Williams of Princeton University was a summer fellow in the laboratory of Dr. George M. Langford at Woods Hole. Dr. Harris Mackey who was a Porter Development Fellow in Dr. John G. Hildebrand's Laboratory in the Department of Biological Sciences at Columbia University has recently been awarded a Johnson and Johnson Fellowship.

A. Barger and E. W. Hawthorne, Co-Chairmen

Future Meetings

1985	
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	

Public Affairs

Since its last report to Council in August the Public Affairs Committee (PAC) has been active with federal and local issues and with the development of informational programs for the Society's membership. Highlights of these activities follow.

Federal

1) A PAC proposal making it a federal offense to break into a federally funded laboratory was presented to the Congress in September. The PAC's proposed amendment to the Animal Welfare Act was approved by Council in August.

The proposed amendment was included with the Society's testimony on HR 5725, the "Improved Standards for Laboratory Animals Act," and was presented at the public hearings conducted by the House Agriculture Committee's Subcommittee on Department Operations, Research, and Foreign Agriculture. The proposed amendment was received with favorable comment from Subcommittee Chairman George E. Brown, Jr. (D-CA) and has been endorsed by the Association of American Medical Colleges, the National Society for Medical Research, and the American Psychological Association. [For details see October issue of *The Physiologist*.]

2) PAC responded in September to a request from the House Appropriations Committee's Subcommittee on Labor, Health and Human Services, and Education for information concerning the use and the need for random source animals. The humane societies and animal rights groups were putting grass-roots pressures on the Subcommittee to prohibit funds appropriated for research to be used for the purchase of random source animals. The restriction was not added to any of the appropriations bills.

3) PAC prepared a summary report in September concerning the proposed revision of the "US Government Principles for the Utilization and Care of Vertebrate Animals Used in Testing, Research, and Training." The report was incorporated into the FASEB letter of comment and included APS' comments submitted in July concerning the proposed revision of the Public Health Service's "Policy on Humane Care and Use of Animals by Awardee Institutions."

4) In October the PAC responded to requests from APS members with Department of Defense (DOD) contracts concerning unpublicized orders by the Army and the Air Force that placed an immediate ban on the use of dogs and cats in all research and clinical investigations. The restriction was lifted within several days by the Air Force, is reported to be "under study" by the Army, and has been denied by DOD as being any change in its policy dealing with laboratory animals.

Local

1) PAC provided background information on animal rights groups to the City of Hope National Medical Center following a raid in December by the Animal Liberation Front in which 110 animals were stolen. The PAC also served as a clearinghouse for information to be shared with other associations regarding this breakin.

2) In January the PAC office coordinated an information exchange between California police agencies, the Philadelphia District Attorney's Office investigating breakins earlier last year at the University of Pennsylvania, and the D.C. Police Department's office of special investigations.

Membership

1) A workshop for Society members on "How to Meet with the Press and Media" was conducted in August. The workshop attracted 63 members and featured presentations by a television newsman, a newspaper reporter/editor, and a research physiologist. [For details see December issue of *The Physiologist*].

2) To provide the Society's membership with current views and opinions of persons involved in public affairs of interest to physiologists, PAC began a featured interview series to be published in each issue of *The Physiologist*. The interview series was started in the February issue and featured Rep. Doug Walgren (D-PA).

T. J. Shepherd, Chairman

Publications

Steady progress was made in 1984 in the easily measurable aspects of the publications program of the American Physiological Society. In addition the groundwork for projects that will lead to continued improvement and growth were underway.

The number of new journal manuscripts received and the number of articles published increased over last year. The journals were operated in the black despite the continued loss of subscriptions. Less visible but equally important were the refining of the process of selecting editors for the journals. This process now regularly includes input from the Sections of the Society and interviews with the leading contenders for the leadership role. Procedures for the revitalized Modeling Methodology Forum were worked out and it is set to be reinstated in 1985. Negotiations were underway for the founding with the International Union of Physiological Sciences of a jointly published journal.

Three books were published in 1984, but less visible was the work on eight books that are scheduled for completion in 1985. The expanding book program includes not only the *Handbook of Physiology* and the Clinical Physiology Series, but also includes books of importance to animal welfare, the history of physiology, and on physiological techniques.

The Publications Committee prepared a review of the journal activities since the 1976-77 reorganization. The results of this review were published in the December 1984 issues of the journals.

The bylaws of the Society were changed to enlarge the number of members of the Publications Committee from 3 to 5.

Journals

Manuscripts. The number of new manuscripts received for the journals increased by 325 (+9%) compared to 231 and 213 (+7%) in each of the two previous years. The number for the six journals of the *American Journal of Physiology* increased by 210 (10%). By number of manuscripts the range was from +75 for *AJP: Heart and Circulatory Physiology* to -19 for *AJP: Regulatory, Integrative and Comparative Physiology*. By percentage the range was from +20% for *AJP: Renal, Fluid and Electrolyte Physiology* to -5% for *AJP: Regulatory, Integrative and Comparative Physiology*. The *Journal of Applied Physiology* received 66 more manuscripts

(+6%), whereas the *Journal of Neurophsiology* received 49 more +19%). The total received for all of the journals was 3658 manuscripts. Rejection rates were about the same as last year, i.e., 40%.

Rapid Communications. Rapid Communications continued to be received for each of the journals of the *American Journal of Physiology* in 1984. In May this special category of manuscript was invited for the *Journal of Applied Physiology.* Rapid Communications continue to be acted on more rapidly than Special Communications. The speed of handling manuscripts was about the same in 1984 as 1983 except for the time from receipt to acceptance of Special Communications, which was about one month faster in 1984. Almost 50% more Rapid Communications were published in 1984 compared to 1983. Seven Rapid Communications were received for the *Journal of Applied Physiology*; four of these were rejected and action had not been taken on the other three by the end of the year.

Articles and Pages Published. The number of articles published in 1984 increased by 4% and the number of text pages by 1% compared to 1983, but decreased by 2% if 1983 cumulative indexes are included. The number of articles published in the *American Journal of Physiology* was up by 124 (10%). The largest increases in the number of regular articles published was for *AJP: Regulatory, Integrative and Comparative Physiology* (+50 or +28%) and *AJP: Renal, Fluid and Electrolyte Physiology* (+50 or +21%). The Editor's Pages were most heavily used by *AJP: Regulatory, Integrative and Comparative Physiology,* primarily during the first half of 1984 when F.E. Yates was completing his term as Editor of the Journal. Fewer articles were published in the *Journal of Applied Physiology* and the *Journal of Neurophysiology.* No change occurred in the number of articles published in *Physiological Reviews.* 925 (+9%) more pages were published in the *American Journal of Physiology* in 1984 compared to 1983. The largest increase was in *AJP: Renal, Fluid and Electrolyte Physiology* (+393 or +24%). The number of pages of research reports published declined in the *Journal of Applied Physiology* (-105 or -3%), *Journal of Neurophysiology* (-489 or -15%), and *Physiological Reviews* (-215 or -13%).

Printing. Printing costs increased by less than 1% in 1984 to pay for 2% fewer pages printed. The pressruns for the major journals were reduced in July as follows: AJP - 200, JAP -100, JN - 10, and PRV - 400. The pressruns for the specialty journals of the *American Journal of Physiology* were unchanged in 1984.

Subscriptions. The total number of paid subscriptions again dropped this year, from 16,529 to 16,084. This is a decline of 3%, whereas the drop was 5% in 1983. All of the major journals showed losses in the number of subscribers: consolidated *American Journal of Physiology,* -4%; *Journal of Applied Physiology,* -2%; *Journal of Neurophysiology,* -3%; and *Physiological Reviews,* -5%. The loss of foreign subscriptions was about twice that of domestic subscriptions. Member subscriptions ranged from a gain of 4% for the *Journal of Applied Physiology* to a loss of 10% for *Physiological Reviews.* The number of subscribers to the specialty journal of the *American Journal of Physiology* increased by 55 or 2% over 1983. Most (44) of the increases were in foreign subscriptions. Five of the six journals had more subscribers in 1984. The largest increase in total subscribers was for *AJP: Cell Physiology* (+13%); the only decrease was for *AJP: Renal, Fluid and Electrolyte Physiology* (-1%). Domestic subscriptions changed by +14% for *AJP: Cell Physiology* to -5% for *AJP: Renal, Fluid and Electrolyte Physiology.* Foreign subscriptions changed by +14% for *AJP: Cell Physiology* to -2% for *AJP: Gastrointestinal and Liver Physiology.* The number of member subscriptions increased by 40 or 4%. Although losses in the number of subscriptions to the major journals continues, the percentage loss was not as great as in 1983. The gain in the number of subscriptions for the specialty journals, although small, does reverse losses in 1983. Subscription prices for 1984 were increased by about 20% compared to 50% increases for the consolidated *American Journal of Physiology, AJP: Regulatory, Integrative and Comparative Physiology,* and *Physiological Reviews and 30% for the other journals in 1983.*

Page Charges. Page charges remain an important source of income for the journals. The percentage of authors arranging for page charges to be paid was 93% overall (88%) in 1983).

Reprints. The number of reprints of each article ordered continues to decline. The number of authors ordering at least 100 reprints was 95% (96% in 1983).

Advertising. The number of pages of paid advertising in the research journals again decreased in 1984. 19.25 pages of space were sold for *The Physiologist* compared with 21.50 pages in each of the previous two years.

Promotion. A brochure was developed for the Society journals that emphasized the growth of the program since reorganization and the need to recognize both the reductionist and integrative aspects of physiology. The brochure was mailed to a broad group of more than 25,000 libraries, laboratories, members of other societies, and subscribers to non APS journals. Recently prepared cumulative indexes were offered at $5.00 each. A journal, other than the consolidated *American Journal of Physiology,* was offered to new members of APS at the price of the least expensive journal, i.e., $30.00 in 1984.

Mailing. The journals usually mailed close to the scheduled date, but problems were encountered with each of the journals. The fewest delays were with the specialty journals of the *American Journal of Physiology.* In 1984 an additional step was added to the already complex assembly of the consolidated AJP, the binding in two parts. This was necessitated by the number of pages and overseas postal regulations that limit weight for second-class mailing to four pounds. Six of the issues were mailed a week or more late. In five months the *Journal of Applied Physiology* mailed more than a week late. *The Journal of Neurophysiology* was mailed late by more than a week twice. *Physiological Reviews* was mailed a month late in January and October. Plastic wrapping was introduced for the specialty journals of the *American Journal of Physiology* and the *Journal of Applied Physiology.* However, as we were dissatisfied with the results of the test mailing of the consolidated *American Journal of Physiology* in plastic wrap, the more expensive cartons and jiffy bags were retained.

The Physiologist. Discussions continued through the year within the Publications Committee and Council on the future of *The Physiologist* and the founding of a "trends" type journal. Toward the end of the year a discussion draft of a contract between the International Union of Physiological Sciences and the American Physi-

ological Society was prepared and was being circulated within each organization.

Physiology in Medicine. "Physiology in Medicine." edited by T. E. Andreoli, began to appear in *Hospital Practice* in January. Six articles on dynamic imaging of coronary circulation in health and disease were presented in the first series and five on the physiology and pathophysiology of gastrointestinal disorders in the second series. An introductory editorial on each series was reprinted in *The Physiologist.*

Financial Summary. Total income in 1984 increased by 12% (+23% in 1983). About $433,000 (+16%) additional income was realized on subscriptions from the 20% subscription price increase (30-50% in 1983) and 3% loss (5% in 1983) in the number of subscriptions. Back and single issue sales and alteration charges were higher and page charges, reprint sales, and advertising lower than last year. Subscriptions accounted for 74% of the income compared to 72% in 1983 and 66% in 1982.

Expenses in 1984 increased by 3% (+19% in 1983 when 18% more pages were published). Most expense categories were similar to last year as about the same number of pages were published in 1984 and 1983.

Books

Handbook of Physiology

The Nervous System. Volume III, *Sensory Processes,* edited by I. Darian-Smith, was completed in January. It contains 1244 pages and 636 figures in two books. The price is $275 to nonmembers and $220 to APS members. Twelve of an anticipated 14 or 15 manuscripts have been received for the next volume, *Intrinsic Regulatory Systems of the Brain,* edited by F.E. Bloom. Two additional volumes are in preparation.

The Cardiovascular System. Volume IV, *Microcirculation,* edited by E. M. Renkin and C. C. Michel, was completed in September. It contains 1124 pages and 631 figures in two books. The price is $275 to nonmembers and $220 to APS members. This completes the revision of this section.

The Respiratory System. All page proof has been returned to the printer for *Circulation and Nonrespiratory Functions,* edited by A. P. Fishman and A. B. Fisher. This volume should be available early in 1985. All manuscripts have been received for *Mechanics of Breathing* and more than 80% have been set in type. One manuscript and the preface are yet to be received for *Control of Breathing* and more than 90% of the manuscripts have been set in type. These two volumes should be completed in 1985. About half of the manuscripts for *Gas Exchange* have been accepted by the Volume Editor and forwarded to the Section Editor.

New Commitments. Manuscripts are being prepared for one new section, *Cell and General Physiology,* and the revision of two sections, *The Gastrointestinal Tract* (formerly the *Alimentary Canal*) and *Renal Physiology.*

Financial Summary. In 1984, 5,143 (1749 in 1983) copies of the Handbooks were sold, providing income of $614,230 ($123,014 in 1983). The cost of the series from 1959 through December 1984 totaled $4,564,559; the income was $4,042,819. The total deficit was $521,740. Most of the deficit is from recently published books, which have not been on the market long enough to generate much income, and from work in progress. The cost in inventory was $1,191,461.

Clinical Physiology Series

High Altitude and Man, edited by J. B. West and S. Lahiri, was completed in June. It contains 207 pages and 109 figures. The price is $39 to nonmembers and $31 to APS members.

Financial Summary. In 1984, 677 copies of the first seven books in the Clinical Physiology Series were sold (310 copies of *Secretory Diarrhea* on consignment were returned), providing an income of $12,012 ($5,852 in 1983). The cost of the series from 1977 through December 1984 totaled $251,273; the income was $234,866. The cost over income was $16,407. The cost in inventory was $83,674.

Special Publications

Technique Book. Voltage and Patch Clamping With Microelectrodes, edited by T. G. Smith, Jr., H. Lecar, S. J. Redman, and P. W. Gage, was being printed at the end of the year and should be available in January 1985. This is the first book for which the Society has accepted the final manuscripts on disks and thus rekeying was not necessary for typesetting. Final copy-editing and inserting of typesetting instructions were carried out in the Bethesda Publications Office.

Animal Welfare. All but one manuscript are in page proof for *Animal Stress.* (The book was set directly as pages, without galley proofs being prepared.) The remaining manuscript is at the printer awaiting typesetting. The book should be completed in the spring of 1985.

People and Ideas Series. Authors are preparing manuscripts for the initial three books planned in the People and Ideas Series. The books are on endocrinology, renal physiology, and membrane transport.

Financial Summary. In 1984, 1062 copies of the three books listed as Special Publications, i.e., not in the *Handbook of Physiology* or Clinical Physiology Series, were published. They provided an income of $22,660 ($16,802 in 1983). The cost of these books from 1982 through December 1984 totaled $117,868; the income was $69,621. The total deficit was $48,247. The cost in inventory was $63,142.

H. E. Morgan, Chairman

New Books

Interaction of Platelets With the Vessel Wall

Interaction of Platelets With the Vessel Wall, edited by John A. Oates, Jacek Hawiger, and Russell Ross, is the newest book in the Clinical Physiology Series of the American Physiological Society. An excellent introduction to the subject is given in the preface to the book.

The past two decades have given rise to remarkable advances in our understanding of blood platelets and of the vessel wall. The physiological integrity of the circulation depends on continuous surveying of the vessel wall by circulating platelets. During each minute of transit time within the circulatory system, $\sim 10^{12}$ platelets survey 1,000 m^2 of capillary surface carpeted with 7×10^{11} endothelial cells. Any break in the continuity of the vessel wall is met with an instant response from platelets, which

contact the zone of injury, spread, and clump. Their sufaces are transformed into batteries of receptors; their interior receives a flux of Ca^{2+} and becomes a furnace for enzymatic oxidation of arachidonic acid into endoperoxides, which are then transformed into thromboxanes, potent vasoconstrictors and platelet aggregants. The storage granules of platelets discharge their constituent molecules targeted toward other platelets and cells in the vessel wall such as smooth muscles. Spasm, migration, and proliferation of smooth muscle cells occur in response to the amines, growth factors, and enzymes secreted from platelets. The unleashing of smooth muscles to proliferate not only results from the action of growth factors secreted by platelets but also from the breakdown of heparin-like molecules in the vessel wall that keep smooth muscles in check.

The receptor function of platelets involves a set of membrane glycoproteins that provide sites for binding of adhesive macromolecules, such as von Willebrand factor and fibrinogen, and for assembly of clotting factors. The orderly surface packing of coagulation proteins propels them to generate thrombin at a rate 300,000 times higher than that in a cell-free environment. The metabolism of arachidonic acid by the vessel wall parallels that by platelets but culminates in products of opposing effects; thus a burst of the vascular prostaglandin, prostacyclin, turns off activated platelets. This ongoing interplay among platelets, plasma factors, and the vessel wall constitutes the central problem of hemostasis and is analyzed in this volume.

The book is divided into three parts: the receptor function of platelets, the metabolism of arachidonic acid and its functional consequences, and the action of platelet-derived factors and enzymes on the vessel wall. It has developed during the transition of the physiology of circulation from organ-oriented knowledge into information dealing with cell-to-cell contact mediated by molecules generated within the cellular compartments and shuttled between them or exported to another.

Interaction of Platelets With the Vessel Wall (180 pages, 74 figures) may be ordered by APS members from the Business Office of the American Physiological Society, 9650 Rockville Pike, Bethesda, MD 20814. The price for APS members is $26.00 (list price $32.50).

Effects of Anesthesia

The Clinical Physiology Series of the American Physiological Society continues with another fine addition: *Effects of Anesthesia.* This book, edited by Benjamin G. Covino, Harry A. Fozzard, Kai Rehder, and Gary Strichartz, is now available. In the preface they emphasize the close ties between anesthesia and physiology.

Anesthesia for relief of pain during surgery is one of the wonders of modern medicine. Perhaps more than any other single clinical discipline, anesthesia has been influenced by the science of physiology. Anesthesiologists can truly be considered clinical physiologists. During anesthesia the patient's vital functions must be maintained and controlled, often for several hours. This is especially true during thoracotomy and cardiopulmonary bypass, when mechanical support systems must supplant the thoracic musculature, the lungs, and the heart. The response to the profound challenges thus presented to the anesthesiologist depends on intimate knowledge of processes encompassing almost the entire field of physiology. Understanding the effects of anesthetic agents on the various organ systems is also important for physiologists because they frequently perform their experiments on anesthetized animals. This book is aimed at highlighting the intimate relationship and interdependence between anesthesiology and physiology, especially in the area of neurological and cardiopulmonary function.

Our understanding of anesthetic mechanisms is seriously incomplete. Nowhere is this ignorance more obvious than in our lack of understanding of the fundamental neurobiological mechanisms of action of the anesthetic agents themselves. The responsibility for resolving this ignorance is shared by physiologists and anesthesiologists.

The book begins with a section on the molecular and membrane basis of anesthesia. The interaction of volatile anesthetics with membranes and their influences on membrane excitability become clearer with the new techniques described by Urban and Miller. Local anesthetics have been somewhat easier to study, and our progress in identifying their various membrane interactions and receptors is reviewed by Smith and Butler, Strichartz, Cohen et al., and Colatsky. These chapters give us a brief glimpse of the field of neurobiology and the influence it has on our understanding of anesthesia.

The second section of the book examines the influence of anesthesia on respiration. It is astonishing how much anesthesia affects this natural function, demonstrating the extraordinary complexity of respiration. Hornbein lays the groundwork for consideration of the mechanics of respiration by Rehder, role of the chest wall by Froese, gas exchange by Nunn, and pulmonary circulation by Marshall and Marshall. Significant questions remain unanswered in this relatively well-studied area, and the need to understand respiration thoroughly is apparent from the responsibility of the anesthesiologist to control respiration.

The third section examines cardiac and circulatory effects of anesthesia. The major circulatory effects produced by both regional and general anesthesia are discussed by Seagard et al. and Covino. Many intravenous agents are presently used, but their effects are complex and in many instances are not understood; this subject is reviewed by Reves and Gelman. The effects of opiate agents, reviewed by Rosow, is an especially challenging area to physiologists.

The questions raised in this book will not all be answered quickly. We must take advantage of newer techniques examining anesthetic actions at a molecular level. This effort is apparent in attempts at understanding the effects of anesthetic agents on membrane excitability. We must next assemble the knowledge gained by the study of molecules, isolated membrane systems, and cells into an understanding of the integrated function of the whole organism. Our past successes in this effor have brought anesthesiology and physiology closer together, but we still have a long way to go.

Effects of Anesthesia (232 pages and 113 figures) may be ordered by Society members from the Society Business Office, 9650 Rockville Pike, Bethesda, MD 20814. The price for APS members is $31.95 (list price $39.95).

Senior Physiologists

The principal function of this committee is simply that of maintaining contact with the members of our Society who are 70 years old or older. This is carried out primarily through correspondence. Most of the business of the committee is also carried out by correspondence and telephone.

There have been two meetings of the committee during the past 5 years, one in San Diego in October 1982 and the other in St. Louis in April 1984. In each instance only 3 members of the committee attended.

Although the Society operates on a July–June 30 year, this committee functions on a calendar-year basis. Late in the calendar year the Membership Office prepares a computer printout of members who will become 70 years of age during the next calendar year plus all members who are already 70 or older.

At the beginning of 1984 there were 556 names on our list; approximately 90 correspondents for each of our 6 members [Dr. Code had resigned leaving us with only 6 members]. At the end of 1984 we had 536 names. The addition of 65 names of those whose birthday is in 1915, increased the list to 601 at the beginning of 1985. With the addition of Drs. Selkurt and Zweifach and the loss of Dr. Alexander, we now have, on average, 86 correspondents per committee member.

In 1983, fifty-two responses from senior physiologists were published in *The Physiologist*. Last year the number was 37. Beginning with the Feb. 1984 issue, a new logo for the "From Senior Physiologists" column appeared in *The Physiologist*. Most of us on the committee consider it to be an improvement.

E. B. Brown, Jr., Chairman

News From Senior Physiologists

J. Newell Stannard to Bob Alexander:

I long ago strayed from physiology into pharmacology, toxicology, radiation biology, and biophysics. Nevertheless, I have always, and still do, regard physiology as the "queen of the biological sciences" and that includes molecular biology.

I retired from the University of Rochester in 1975. In 1977 we moved to San Diego, partly because my wife had had a stroke and we were finding wheelchairs and snow more and more incompatible. I have a courtesy appointment at the University of California, San Diego, Medical School as Adjunct Professor of Community Medicine and Radiology. This involves a bit of teaching, some seminars, some professional contacts, but, most important of all, access to the magnificent University of California library system. This last has been of key importance, since in 1978 I embarked on a book-writing project to summarize, in an historical context, research and field activities involving the health aspects of radioactivity. It involved over 100 interviews, over 2 years of hunting for and pouring over old in-house unpublished reports, and hundreds of old and new publications. Now it is almost finished and is in the editorial phases. Publication is expected this summer by the Technical Information Service of the Department of Energy (that should keep the price down!). The book was done under the aegis of the Battelle Institute, and the responsible officer is my first Ph.D. student (so now I am working for him!). It is entitled *Radioactivity and Health—A History*. It will be long but should have enough summaries and outlines to steer the reader to what he wants (I hope).

In addition to the above I chair a national committee of the National Council on Radiation Protection and Measurements (Bethesda) and am a member of two other NCRP committees. The one I chair is charged with the development of new or revised standards for occupational and population exposure to radioactive materials. It has 13 Task Groups with more coming so it involves input from over 50 scientists throughout the country. They lead me a "merry chase" at times. Perhaps I should mention that I was recently appointed to an advisory committee to examine and advise on the biological and environmental progress at the Battelle Pacific Northwest Laboratories and became a corresponding member to a Task Group of the International Commission on Radiological Protection. All of the above should be an indication that I have managed to keep out of mischief in "retirement." Things do not get done as easily as they used to, especially without full-time secretarial help, but it is great to be active and, thankfully, to be able to continue in biomedical science. I would urge a reduction in competitiveness among young scientists and more single-minded devotion to seeking the truth, even if it means a smaller grant. They will feel better about themselves.

Department of Community Medicine
University of California, San Diego, School of Medicine
17441 Plaza Animado, #132
San Diego, CA 92128

Bradley T. Scheer to Edward Adolph:

Your birthday card on behalf of the Committee on Senior Physiologists was most welcome. I'll respond with some autobiographical details. I am now a living paradigm in many respects. First, my weight remains, with some effort on my part, at the paradigmatic 70-kg level. I am also a paradigm of the aphorism that "old physiologists never die; they just lose their research grants." Finally, I am a living demonstration that one can survive loss of the right temporal lobe of the cerebrum with no impairment of brain function. In October 1971 I suffered a severe cranial fracture in consequence of a fall from my bicycle. After appropriate surgery, including removal of the aforesaid temporal lobe, and prolonged hospitalization, I was able to return to customary activities, with no change other than an increased emotionality and a somewhat decreased work capacity and ability to do several things at once.

As for research grants, in 1976 my grants from NSF and NIH, both of which had supported my work for more othan 20 years, expired. I submitted what I still consider to have been an excellent proposal, soundly based in my own work an that of others, and it was rejected by both agencies. The only explanation I could obtain was the doubts of my ability to do the work proposed had been raised and the proposal was not consistent with current research in the field. So I decided to retire from the University of Oregon after 27 years

and devote my efforts to writing and to the ministry. I am probably the only member of the Society who is in orders in the Episcopal Church.

My wife chose Santa Barbara for retirement, and I have found her judgment as usual to have been excellent. We disposed of our property in France, purchased in 1970 as a possible retirement site, and bought a house here in a very similar climatic and geographical location, but a more congenial cultural environment. After a summer of writing, I formed connections here with Westmont College, where I am Adjunct Professor of Biology, and Trinity Episcopal Church, where my ministry is primarily directed at the "senior citizens" in this gerontological paradise. I can't afford to attend meetings, and in any case have nothing new to say. You may pass along any of the above to my friends and colleagues, and if any of them are in this region, I should be glad to see them.

1905 Mission Ridge Rd.
Santa Barbara, CA 93103

Roland A. Coulson to Edward:

The university stops paying me on June 30, 1986, by which time I will be 70½, but I hope that does not mean a forced retirement from the laboratory. At least until then, I will keep at work. For the past several years my principal area of interest has been in enzyme kinetics in vivo, a field unexplored by either Biochemists or Physiologists. Slowly, almost painfully, a theory has been evolved to the effect that the rate of a catabolic reaction is determined primarily by the rate at which a substrate flows over its enzyme and that this is fixed within the cells. Metabolic rate, which is defined by the rate of catabolic reactions in the body, is controlled by the number of times the blood volume is circulated each hour. Within narrow limits, each time the 80 ml of blood found in an "average" kilogram pass through that kilogram, a constant amount of any given substrate is removed whether the animal under study is a mouse, a dog, a man, a turtle, or an alligator. For example, ~0.1% of methionine will be removed at each circulatory pass in man or mouse, and ~1.8% of serine will be extracted at each pass from both. Since the percent of substrate removed per cycle is a constant, the velocity of the reaction is determined by multiplying that percent by the number of circulations per hour. Where the percent removed per cycle is fixed in catabolic reactions in a resting animal, in anabolism the percent removed is quite variable. "Demand" at rest seems to be a misnomer, since the rate of the reactions depends on the likelihood of a collision between a substrate and its enzyme, which in turn, is proportional to blood flow. Flow rates are determined by hydraulics: the longer the blood vessel, the greater the resistance and the lower the capillary pressure, and therefore the flow. In a 2-g shrew, the average distance from the aorta to an "average" capillary is about 1 cm. In the whale, it is measured in meters. Since aortal pressure is about the same in both, capillary flow is fast in a shrew and slow in a whale, and so forth. If I am boring you, remember you asked for it.

Department of Biochemistry
Louisiana State University Medical Center
1100 Florida Ave.
New Orleans, LA 70119-2799

John P. Lambooy to Edward:

I must apologize for not having responded to your kind birthday card on my 70th! Except for a sleep-time, morning-time lower back pain, I'm in great shape and expect I could keep on cranking out research for another 10 years. However, my plans are quite different. I have always had certain abilities and much pleasure in working with wood and metal (glass-blowing skills have gone for the lack of need), and over the years I have accumulated, as a result of lack of any real restraint, a considerable number of machines and tools. Furniture making, wrought iron work (some gadget making), gemstone cutting and polishing, silversmithing, and seemingly endless care and repair of a couple of old cars are going to be my principal activities.

The process of retiring is taking a great deal of time. Since most of my equipment will be useless here, I have distributed it to other campuses of the University of Maryland and as far away as the University of Arizona. About all I can do in my lab at present is to heat water for coffee. My last two papers are "in," one in press (*Chem. Biol. Interact.*) and the other has gone off to *Int. J. Biochem.* I cleared my last student last year and gave up my chairmanship of the Graduate Committee of the Combined Program in Biochemistry. And as you might expect, after having done it so long, no one else knew how to do it! It's great to be able to go home without a briefcase full of paper and problems. I am doing my last poster on flavoprotein enzymes (ASBC). This reminds me that your greeting as a senior physiologist was a little off the mark. I resigned from APS and AIN as of the end of 1984. I anticipate not continuing any of my scientific society memberships after July, 1985, with the possible exception of Sigma Xi; I continue to enjoy the American Scientist but I have participated in the Society only as a Member-at-Large for some time.

Finally, a story about retirement. I was talking to one of our several Associate Deans the other day because he heard I was going to retire. He said he was looking forward to retiring. When he asked how long I'd been at it I said that the first time I had anything to do with teaching college students was as a teaching assistant in 1934. His response was, "My God, I was born in 1934." Can you believe he is thinking about retiring now? Maybe he isn't enjoying his career as much as we did.

Department of Biochemistry
University of Maryland Dental School
Baltimore, MD 21201

Giles Filley to E. B. Brown:

Thanks for your hand-written note on the Senior Physiologists letter. I am indeed very busy with both theoretical and practical acid-base matters. Carbicarb, our alkalinizing ion-generating agent of possible clinical usefulness, has been approved by the US Patent Office, sponsored by a vigorous if small drug house and currently being tested in severely shocked dogs to get FDA approval for human use. Because the drug generates HCO_3^- from CO_2 in the blood plasma, it increases the osmolality of circulating blood, perhaps most rapidly in peripheral capillaries supplying hypoxic tissue and containing slow-moving blood loaded with lactic acid. If so, the drug would be not simply a better alkalinizer but also a useful adjunct for the treatment of hypovolemic

shock. To achieve this has brought me in contact with those fascinating people, surgeons, under conditions which reveal how they think. It is quite a challenge working with them. If anything useful comes of this research, it may justify having an M.D. like me learn some physiology at various people's expense.

Webb-Waring Lung Institute
Denver, CO 80262

Clinton N. Woolsey to Roy:

Thank you for your kind note on behalf of the American Physiological Society on the occasion of my 80th birthday.

In June 1983 I attended a Symposium in Stockholm, Sweden in memory of Yngve Zotterman. I chaired the first session and later gave a review of our Comparative Evoked Potential Studies on Somotosensory Cortex of Mammals. Some 50 different species have been studied in this manner since our first study of the monkey with Marshall and Bard, begun in 1937 and published in 1942. The symposium has just appeared as Vol. 41 of the Wenner-Gren International Symposium Series: *Somotosensory Mechanisms* edited by C. von Euler, O. Franzén, U. Lindblor and D. Ottoson and published by Macmillan Press, London, in 1984.

I am currently preparing for publication studies on cortical localization in the chimpanzee carried out with the assistance of some 45 collaborators on nine chimpanzees over an 11-year period from 1951 to 1961. Experiments were done under Nembutal anesthesia and carried on around the clock continuously for from three to eight days each. Figurine maps have been prepared of the precentral motor area, the supplementary motor area, somatosensory areas I and II, and the supplementary sensory area on the medial wall of the hemisphere. Studies were also made of tonotopic localization in the auditory cortex and gross definition of the visual cortex on the lateral occipital surface of the hemisphere. We have also prepared figurine motor maps of one chimpanzee, one orangutan, and one gorilla studied by Leyton and Herrington (1917) and of three chimpanzees studied by Marion Hines (*J. Neurophysiology,* 1940). Other studies on chimpanzees were made on cerebellar-cerebellar connections and on the definition of dermatomes. When the chimp task is finished I have other experiments which need to be prepared for final publication. Perhaps other investigators have unpublished studies to keep them busy in retirement.

Department of Neurophysiology
University of Wisconsin
Madison, WI 53705

Robert S. Dow to Roy:

I am still in good health and practicing clinical neurology as I have for 45 years. I still collaborate on an occasional paper also. Willetta and I celebrated our 50th wedding anniversary with a cruise to Alaska and a week at a beautiful fishing lodge. We also attended the Asian Oceanic Congress of Neurology in Taipei in December 1983. We visited and gave a lecture in Bangkok and Tokyo. I am chairman of a fund development committee and have been quite successful in raising funds for the Neurological Sciences Center at Good Samaritan Hospital and Medical Center, where the growth and productivity of the research program at the Center give me great pride and satisfaction. I enjoy reading the notes sent in by old friends and look forward to keeping active for some more years and my advice to colleagues is to not be too eager to retire!

The Neurological Clinic
2222 N.W. Lovejoy St.
Portland, OR 97210

Jack Finerty to Roy:

Thank you for the greetings on my 70th birthday. I retired in July 1984 and bought a home next door to my daughter in Houston. Thirty years in Deans' offices did not keep me current in active endocrine research, so most of my activity now is helping Mildred take care of our second homes in Forest County, WI, and Green Valley, AZ, and working seriously at lowering my golf handicap.

1110 Bethlehem St.
Houston, TX 77018

Joseph Katz to Arthur Otis:

I attained age 70 in January of this year. I still continue my work just as before and hope to be active for a few more years, provided my grant support does not dry up and that Cedars-Sinai is continuous with its support.

Cedars-Sinai Medical Center
Box 48750
Los Angeles, CA 90048

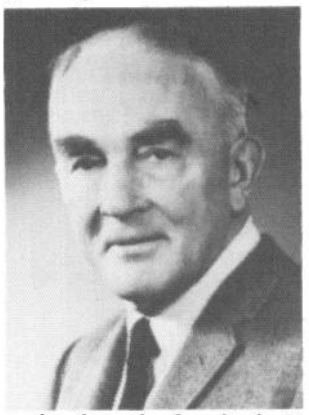
Fifty-Year Members and Year of Election

W.F. Adolph, 1921
E.C. Albritton, 1933
W.M. Allen, 1934
S.H. Bartley, 1935
J.W. Bean, 1932
R.J. Bing, 1922
T.E. Boyd, 1925
E. Bozler, 1932
C.McC. Brooks, 1933
P.C. Bucy, 1933
E.B. Carmichael, 1931
K.K. Chen, 1929
M.F. Crawford, 1933
R.G. Daggs, 1935
M.C. Damour, 1934
H. Davis, 1925
H.H. Dukes, 1934
L.B. Flexner, 1933
F.E. Franke, 1934
M.H. Friedman, 1929
C.L. Gemmill, 1928
F.A. Gibbs, 1935
A.S. Gilson, Jr., 1927
P.O. Greeley, 1931
A.B. Hastings, 1927
J.M. Hayman, 1928
F.A. Hellebrandt, 1933
E.C. Hoff, 1933
H.E. Hoff, 1933
C.B. Huggins, 1932
J.L. Johnson, 1934
J.S.R. Johnson, 1925
F.T. Jung, 1930
N. Kleitman, 1923
E.M. Landis, 1928
A. Lieberman, 1931
H.S. Mayerson, 1928
A.T. Milhorat, 1934
E.S. Nasset, 1932
H.C. Nicholson, 1932
H. Pollack, 1933
C.L. Prosser, 1935
P. Reznikoff, 1927
O.W. Richards, 1934
C.P. Richter, 1924
D.M. Rioch, 1931
J.J. Sampson, 1932
C.F. Schmidt, 1929
F.O. Schmitt, 1930
J.A. Shannon, 1933
H. Silvette, 1933
P.W. Smith, 1933
S. Soskin, 1930
I. Starr, 1929
E.U. Still, 1928
M.L. Tainter, 1929
S.S. Tower, 1932
G.E. Wakerlin, 1933
J.T. Wearn, 1921
R.W. Whitehead, 1932
L.C. Wyman, 1927

Edmund Sigurd Nasset (1900–1985)

On March 16, 1985, the American Institute of Nutrition and the American Physiological Society lost one of their distinguished members, Edmund Sigurd Nasset.

"Sig," as he was known to his colleagues, was born of Norwegian parents in Willmar, Minnesota, in 1900. He grew up on a ranch in North Dakota where the work ethic was dominant. His academic education was obtained at Dickinson State College (North Dakota), St. Olaf College (Minnesota), Pennsylvania State University, University of California at Berkeley, and he received his doctorate in physiological chemistry and physiology in 1931 from the University of Rochester School of Medicine, where he was the pupil of John R. Murlin. He remained on the faculty in Rochester, became Professor of Physiology, and taught there until he retired. In 1967 he returned to Berkeley and for the next six years was associated with the University of California and the Bruce Lyon Memorial Research Laboratory of Children's Hospital Medical Center in Oakland, California.



He served on many national committees and was associated with the National Academy of Sciences, and the US Department of Health, Education, and Welfare. Under the auspices of the Food and Agricultural Organization of the United Nations, he was Nutrition Advisor to the Government of India from 1961 to 1963. He held visiting professorships at George Washington University, Louisiana State University, and the University of Lucknow (India), and twice he was the recipient of Fulbright Awards. He received honorary doctorates from Woosok University, Seoul, Korea, and from his alma mater, Dickinson State College in North Dakota. In 1968 St. Olaf College gave him the Distinguished Alumnus Award.

During World War II, Sig served with the 9th Tactical Air Force Command in Europe, receiving the Bronze Star Medal and four battle stars. Before leaving active duty in 1945, he served in Belgium as nutrition officer with the Supreme Headquarters Allied Expeditionary Forces.

His skills as a writer and editor were put to good use by the American Physiological Society and the American Institute of Nutrition. He served on the editorial boards of both societies and made a large contribution to the literature. In addition to his technical writing, in 1951 he published a book *Food and You*. Originally the book was intended to give his two young daughters a nontechnical description of the physiology and biochemistry of nutrition. The book proved so popular that a second edition under the title *Your Diet, Digestion and Health* was published in 1958. A third edition, *Nutrition Handbook*, appeared in 1982. The flavor of this book can be sampled from the following quotation taken from the chapter "Common Sense About Food" in the third edition: "Pure cussedness in regard to food habits is found in individuals of all nations. Many such persons were reared on limited diets and in provincial environments. To them, departures from their customary diets are considered inconvenient, unpleasant, or foolish and, hence, are carefully avoided. The result of denying oneself new adventures in eating is a lifelong continuation of a stereotyped pattern of food and drink."

In 1928 he married Elizabeth H. Custer and 54 years later he wrote: "I owe a special debt to my dear wife, Elizabeth Custer Nasset, for her perusal of the entire manuscript and her pertinent criticisms of both content and style. Her reading the manuscript aloud enabled me readily to detect and emend my most egregious solecisms."

He is survived by his wife and two daughters, Laura Cronewett of Denver, Colorado, and Susan Stanford of Salem, Oregon, and seven grandchildren.

Now on a personal note. I first met Sig in 1935 when, as an undergraduate, I worked part-time in his laboratory. In 1937 he persuaded me to start graduate work in physiology, for which I shall forever be in his debt. I believe I was his first graduate student, and I have some wonderful memories of the years I spent with him. For instance, he was the star second baseman of the faculty team, much to the dismay of the medical students. He had some unexpected side-line research projects, such as blending various pipe tobaccos until we found the perfect mixture in experiment #36 and discovering how to prepare a week's supply of brewed coffee without it turning rancid or bitter.

Enology was one of his extracurricular research subjects. While still in Rochester he started to make wine in the basement of his home. It was one of his more popular courses. Betty participated actively in this *Arbeit*. When fermentation was complete, it was her job to put her head in the barrel and remove grape stems, etc. According to her, it produced an alcoholic daze without imbibing. This claim became a family legend.

Above all, I remember Sig's extraordinary patience and his unique teaching skills. Some examples: One day he did not show up on time for surgery, and I was forced to make the Thiry-Vella fistula on my own for the first time. As I was closing he came in and asked what would happen when I took the stitches out! And there was that black day when after two months of hard work I accidentally ruined the precious hormone, and he said not a word. Or that hot summer day when I was to determine the nitrogen content of beer. I took a cold bottle of beer from the refrigerator and was carefully and not very successfully drawing it into a 50-ml pipette. Sig quietly and gently instructed me how to pipette beer without having to drink it. Such, such were the days.

M. J. Schiffrin
Port St. Lucie, Florida

Membership Status

Regular	4,526
Emeritus	604
Honorary	10
Corresponding	125
Associate	757
Student	209
Total	6,231

NEWLY ELECTED MEMBERS

The following, nominated by Council, were elected to membership in the Society at the Spring Meeting, 1985.

Regular

ALPERN, ROBERT J.
DIVISION OF NEPHROLOGY
UNIV. OF CALIFORNIA
SAN FRANCISCO, CA 94143

ANDERSON, DEBRA F.
DEPT. OF PHYSIOLOGY, L334
OREGON HEALTH SCIENCES CENTER
PORTLAND, OR 97201

ASTERITA, MARY F.
INDIANA UNIV. SCH. OF MEDICINE
3400 BROADWAY
GARY, IN 46375

BARNEY, CHRISTOPHER C.
DEPT. OF BIOLOGY
HOPE COLLEGE
HOLLAND, MI 49423

BERSOHN, MALCOLM M.
CARDIOLOGY SECTION (111C)
SEPULVEDA V.A. MEDICAL CENTER
SEPULVEDA, CA 91343

BEYER-MEARS, ANNETTE
DEPT. OF PHYSIOLOGY
UMDNJ-NJ MEDICAL SCHOOL
NEWARK, NJ 07103

BKAILY, GHASSAN
DEPT. OF BIOPHYSICS
UNIV. OF SHERBROOKE
SHERBROOKE PQ J1J 5N4 CANADA

BOLLI, ROBERTO
CARDIOLOGY SECTION
BAYLOR COLLEGE OF MEDICINE
HOUSTON, TX 77030

BUCHANAN, JACK W., JR.
349 CLINICAL SCIENCES 229H
UNIV. OF NORTH CAROLINA
CHAPEL HILL, NC 27514

CANESSA, MITZY L.
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Deaths Reported Since the 1984 Fall Meeting

Bockman, E.L., Bethesda, MD (3/01/85)
Chamber, L.A., Houston, TX (8/22/84)
Comroe, J.H.,Jr., Hillsborough, CA (7/31/84)
Edholm, O.G., Berkshire, UK (1/18/85)
Evonuk, E., Eugene, OR (6/84)
Gerstner, H.B., Oak Ridge, TN (7/13/84)
Hendley, C.D., Highland Park, NJ (3/12/84)
Herrin, R.C. De Forest, WI (4/21/84)
Hurtado, A. Lima, Peru (10/24/84)
Koppanyi, T., Washington, DC (2/28/85)
Lowenbach, H., Durham, NC (3/01/85)
Lowenstein, L.M., Wellesley, MA (3/06/84)
Melampy, R.M., Ames, IA (5/27/84)
Merrill, J.P., Boston, MA (4/05/84)
Mettler, F.A., Blairstown, NJ (1/30/85)
Phillips, H.J., Omaha, NE (7/13/84)
Ravin, M., Lexington, KY (9/17/84)
Stone, H.L., Oklahoma City, OK (11/16/84)
Szepsenwol, J., Miami Beach, FL (2/22/85)
Wakim, K.G., Terre Haute, IN (2/06/85)
Waugh, D.F., Cambridge, MA (1/14/85)
Whitney, J.E., Little Rock, AR (1982)
Windle, W.F., Granville, OH (2/20/85)

Teaching Cardiovascular Integrations with Computer Laboratories

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One goal in teaching physiology is to foster in the minds of the students a mental model that allows synthesis of knowledge in a way that facilitates its use in solving physiological problems. Methods such as stem questions and clinical examples are often employed in striving for this goal. Although they are successful to some extent, they rely exclusively on *practice* in the use of knowledge as a means for synthesis. They do not address the difficult problem of defining for the student an *explicit route* to knowledge integration.

This report describes a computer-based instructional unit in cardiovascular physiology that makes an explicit attempt to provide the student with intellectual tools for conducting knowledge synthesis. The pedagogical approach emphasizes the dynamic hierarchy in the cardiovascular system. The primary intellectual tool is aggregation, i.e., the substitution of a simple approximate mental model for a collection of detailed models of interacting system components. Aggregation is used to form a hierarchical set of abstractions of system behavior and properties that parallels to a high degree the system's dynamical hierarchy. The program provides the student with physiological information in a setting that facilitates acquisition of this set of models and then provides problem-solving exercises for decomposing that hierarchy of models. All of this is done using simulated laboratory experimental techniques. Whereas aggregation develops the knowledge constructs, decomposition develops skills for the use of that knowledge in solving problems.

Our current effort bridges the gap between two previous efforts and goes considerably beyond them. The first of these (3) used a minicomputer to examine whole system behavior and reveal some of the mechanisms working within the system to bring about changes in the system's behavior. The second effort (9, 10) represents a more advanced use of the computer. It uses a personal computer and simulated laboratory to teach isolated left ventricular mechanics. The program uses two types of simulation: *1)* the laboratory apparatus and *2)* the organ being studied. The student interface consists of graphically rich cathode-ray tube (CRT) displays that portray the isolated left heart and the experimental laboratory apparatus. A simple seven-key keyboard controls the program. The student manipulates the laboratory apparatus to control inputs to the numeric simulation and recreates experiments that demonstrate essential aspects of left ventricular pumping behavior.

Our new program adds three new simulated laboratory environments to the previous program: heart-lung blood pump, systemic circulation, and a complete cardiovascular system. Taken individually, the isolated left heart, heart-lung, and systemic circulation laboratories can teach basic concepts of the excised system components. The cardiovascular system laboratory is, by its nature, a vehicle for examining whole system sensitivity to parametric variations. These variations may be made singly to observe isolated changes such as blood transfusions, variation of heart rate, contractility, or total peripheral resistance. The student may also change the parameters in a coordinated fashion to represent syndromal changes as would occur in cases of chronic hypertension or congestive heart failure.

The primary purpose of our most recent program extends beyond that of its four component laboratories. Three types of integrations are part of the program; these integrations weave the isolated laboratories into a novel learning setting. They are *1)* a set of models which share the same parameters and model structure—in essence, a single individual in several different laboratory preparations; *2)* a software design approach which permits data to be shared between laboratories for comparison; and *3)* a student manual designed to allow the student to explore integrative physiology and discover a hierarchical approach.

Previous workers have also recognized the potential learning benefits of a complete pulsatile cardiovascular system model. One project was based around an analog simulator which calculated pressure, flow, and volume data in real time (1). That machine did not make provision for the freeze-frame and off-line data analysis that is incorporated in the present report. Another approach used a minicomputer to present a complete circulatory system model (3). That program provided off-line analysis. Neither of these examples permitted the complete model to be easily subdivided into its component laboratories. A third project (8) was developed on a microcomputer and permitted three hierarchically arranged laboratory views: isolated muscle fiber, isolated ventricle, and complete circulatory system. Because of limited processing power in the particular machine chosen, the model was required to be much simpler than the one presented here.

Design Goals

The average student in the medical sciences is unprepared to use formal systems theory to analyze the cardiovascular system. Therefore, we felt it was necessary to devise a less formal approach that would embody the essential features of this theory as it applies to the cardiovascular system. We created an experimental environment on the computer in which students are guided to discover hierarchical organization in complex systems without recourse to formal mathematics. Throughout

the computer program we used a laboratory metaphor because it fitted the previous classroom experiences of the students. Our hypothesis was that an intuitive understanding of time scales, component interaction, and system decomposition strategies would be developed through experimentation on several cardiovascular subsystems and a complete system model.

Our previous computer program has been viewed as a supplement to the animal laboratory, a tool which can prepare the student for a richer and more productive experimental session with real animals. Our new program, however, offers much more than laboratory enhancement. The set of laboratories presented is designed to achieve a larger goal: through software integration, these laboratories permit us to teach physiological integrations in a way that cannot be captured by lectures, textbooks, or even real laboratories. An essential aspect of this design is the means by which the software integrates the multiple parts of a rather large numeric model. The models, laboratories, and data presentations are all part of one software package. This encourages comparison of data collected from the different laboratories. Comparisons lead to observations which demand integrative explanations.

Although we conceived of the program as a laboratory for hands-on student experimentation and feel that it meets those objectives well, it may also be used successfully as a lecture aid. The pace of the program allows the instructor to make a point while the computer seeks a new steady-state condition. The students may watch the transient behaviors or take notes as the experiment progresses.

Numerical Models

An overview of the construction of the four laboratories is presented in Figure 1. The details of the models are presented in Figure 2, assembled into the circulatory system model. Figure 3 presents the three elements of experimental apparatus used in the laboratories: controlled pressure, flow, and hydraulic afterload. Model parameters under student control are indicated in Figures 2 and 3 with an asterisk.

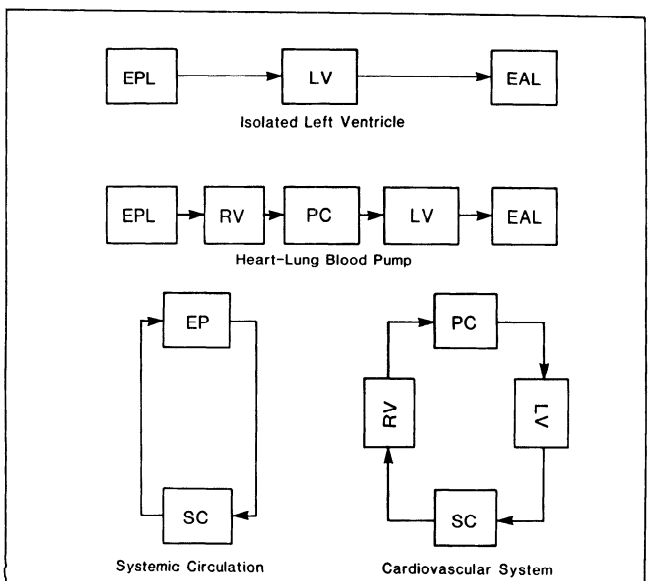

Figure 1
Schematic of 4 models showing interconnections of physiological elements and experimental apparatus. Components: EPL, experimental preloading apparatus; EAL, experimental afterloading apparatus; EP, experimental pump; RV, right ventricle; LV, left ventricle; PC, pulmonary circulation; SC, systemic circulation.

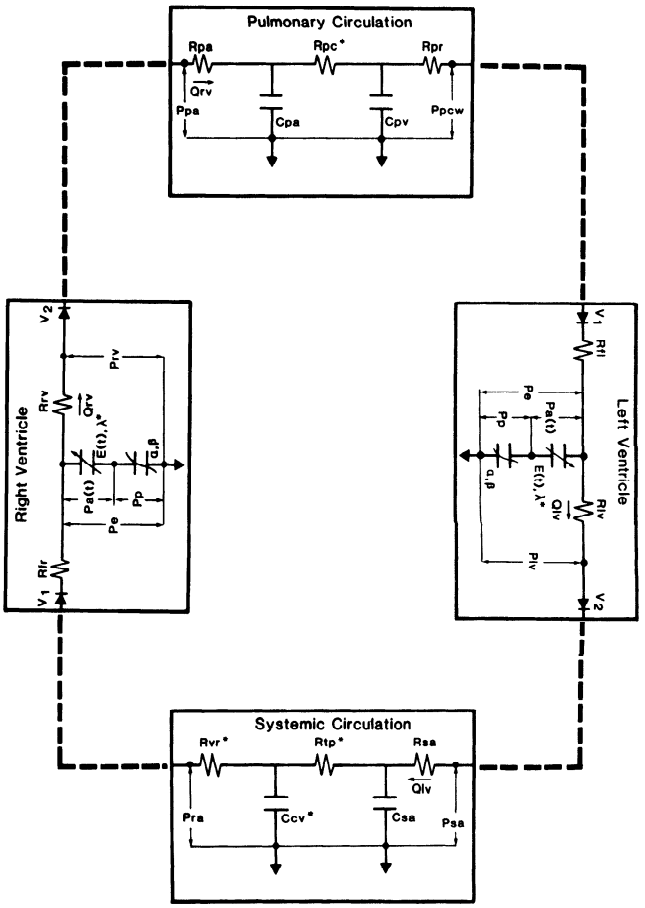

Figure 2
Detailed schematic showing electrical analog representation of physiological components of the laboratories. Terms are defined in the text. Component values are specified in Table 1.

Isolated Left Ventricle Laboratory

The isolated left ventricle laboratory consists of three elements: an apparatus for experimental control of preload; the left ventricle (LV) itself, and an experimental apparatus for control of afterload. As we have presented a detailed description of the components of this model previously (10), we will only summarize here. The LV is composed of two series-connected elastances: one is active (linear and time varying) and one is passive (nonlinear and time invariant). The active element is based on the Suga-Sagawa time-varying elastance concept (13). Pressure, Pa(t), from this element is described by

$$Pa(t) = E(t)\ (V - V_D)$$

where E(t) is a time-varying stiffness, V is the instantaneous volume contained in the ventricle, and V_D is a dead space volume. Values for these terms are indicated in Table 1. Contractile properties were introduced to the ventricle with a multiplier, λ, applied to E(t). Values of the multiplier > 1.0 represent increased contractility; values < 1.0 represent depressed function. The passive nonlinear elastance comes from the diastolic pressure-volume relationship, Pp

$$Pp = \alpha \exp\ [\beta\ (V - V_D)]$$

where α and β are constants. Facility is provided for changing the parameters, α, β, and V_D to simulate

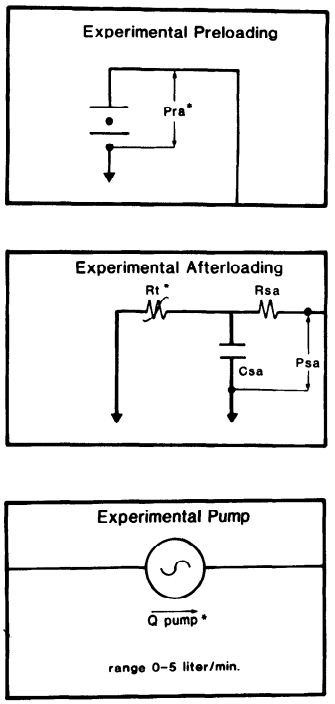

Figure 3
Detailed schematic showing electrical analog representation of the experimental control apparatus.

changes in diastolic compliance that accompany hypertrophy, dilation, and stiffening.

The pressures arising from the two compliances Pa(t) and Pp must be added to represent the total pressure due to the series elastic elements, Pe. The active element is the major determinant of systolic behavior. The passive element, while always present, is most significant during diastole, when the E(t) function is zero valued. An internal resistance, Rlv, has been shown to be important in predicting the pressure-flow behavior of the ventricle (11) and in accounting for responses to a variety of perturbations (6). The instantaneous left ventricular pressure, Plv, is calculated from the elastance pressure, the ejected flow, Qlv, and outflow resistance, Rlv

$$Plv = Pe - Qlv * Rlv$$

Filling resistance, Rfl, has been reported (7) and was observed to be necessary in the simulation to prevent over-rapid filling of the ventricle. The valves V_1 and V_2 are modeled as perfect one-way flow devices, having zero resistance when the pressure on the left exceeds the pressure on the right and infinite resistance at all other times.

The nominal values of E(t) were determined from data collected in our research laboratory. The parameters of the passive pressure-volume relationships were taken from the literature. The parameters of the LV model were fine-tuned to produce realistic pressure-volume loop displays over a wide range of preloads and afterloads and to produce realistic Frank-Starling curves with an ascending limb, plateau, and descending limb over a wide range of preloads. Heart rate was varied through a combination of changes in the integration step size and number of integration steps per cardiac cycle (see Figure 4). The combined effect preferentially shortened diastole for high heart rates.

The experimental afterloading system is a modified Windkessel load, composed of an input impedance, systemic arterial resistance and compliance (Rsa and Csa), and a nonlinear Starling resistor (Rt). The flow through the resistor, Q, is governed by its conductance and chamber pressure

$$Q = (P - Pc) * 1/Rt$$
$$(\text{if } Q < 0 \text{ then } Q = 0.0)$$

where P is the inlet pressure, Pc is the chamber pressure, and 1/Rt is a constant conductance. If arterial pressure (P) should fall below the tube-closing pressure (Pc), an incorrent negative flow would result from the equation. This is prevented by setting negative valued results to zero.

Heart-Lung Blood Pump Laboratory

The Heart-Lung Laboratory contains five component models: an experimental apparatus for control of right ventricular (RV) filling, the RV, a pulmonary circulation, the LV, and an apparatus for experimental control of the hydraulic afterload.

The RV and LV have been reported as phenomenologically equivalent (2), differing only in their parameter values. Therefore, the description of the equations for the RV will not be repeated. The parameter values may be found in Table 1. The pulmonary circulation is modeled analogously to the systemic circulation. It consists of an input impedance, pulmonary arterial resistance and compliance (Rpa and Cpa), and a venous compliance (Cpv) separated by a pulmonary capillary resistance (Rpc). The outflow of the pulmonary circulation to the left heart is mediated by a resistance to pulmonary return (Rpr). The apparatus for control of RV filling and LV afterload are identical to those used in the isolated LV laboratory.

The parameters of the LV component are those used in the isolated left heart laboratory. The parameters of the RV and pulmonary circulatory components are taken from earlier published research work and from the literature. Final parameter tuning of these latter two components was done to yield a left atrial input pressure which was equivalent to the nominal value used for tuning the LV model. The performance of the assembled system is shown in Table 2 and as the solid lines in Figures 5 and 6. Finally, the heart-lung model was tested with the protocol of the Herndon-Sagawa experiment (5). For this purpose a servo feedback was connected to monitor mean arterial pressure and control the chamber pressure

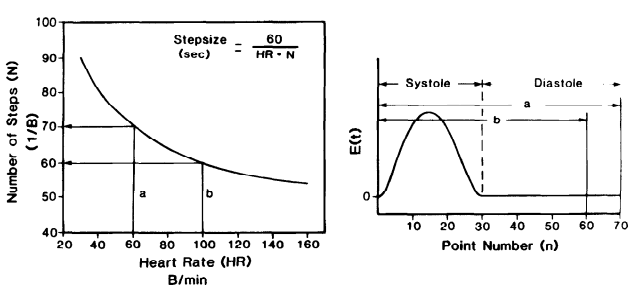

Figure 4
Technique for varying heart rate (HR) by varying integration step size and number of integration steps (N). Steps which are added or deleted from E(t) are the last ones, all zero valued, in the diastolic period. Desired heart rate is input; number of integration steps and step size are outputs.

Table 1
Canine parameters used in all models

	Isolated Left Heart	Heart-Lung Blood Pump	Systemic Circulation	Complete System	Units
Left Heart					
E(*t*) max	9,646.0	9,646.0		9,646.0	$dyn \cdot cm^{-5}$
E(*t*) min	0.0	0.0		0.0	$dyn \cdot cm^{-5}$
α	220.0	220.0		220.0	$dyn \cdot cm^{-2}$
β	0.1	0.1		0.1	cm^{-3}
Rfl	36.8	36.8		36.8	$dyn \cdot s \cdot cm^{-5}$
Rlv	90.0	90.0		90.0	$dyn \cdot s \cdot cm^{-5}$
VD	6.0	6.0		6.0	ml
Right Heart					
E(*t*) max		2,962.0		2,962.0	$dyn \cdot cm^{-5}$
E(*t*) min		0.0		0.0	$dyn \cdot cm^{-5}$
α		170.0		170.0	$dyn \cdot cm^{-2}$
β		0.095		0.095	cm^{-3}
Rfr		14.7		14.7	$dyn \cdot s \cdot cm^{-5}$
Rrv		100.0		100.0	$dyn \cdot s \cdot cm^{-5}$
VD		8.0		8.0	ml
Pulmonary Circulation					
Cpa		0.9E-3		0.9E-3	$dyn^{-1} \cdot cm^{5}$
Cpv		0.3E-2		0.3E-2	$dyn^{-1} \cdot cm^{5}$
Rpa		100.0		100.0	$dyn \cdot s \cdot cm^{-5}$
Rpc		134.0		134.0	$dyn \cdot s \cdot cm^{-5}$
Rpr		18.0		18.0	$dyn \cdot s \cdot cm^{-5}$
Systemic Circulation					
Csa			1.0E-3	1.0E-3	$dyn^{-1} \cdot cm^{5}$
Ccv			22.3E-3	22.3E-3	$dyn^{-1} \cdot cm^{5}$
Rsa			150.0	150.0	$dyn \cdot s \cdot cm^{-5}$
Rtp			2.97E3	2.97E3	$dyn \cdot s \cdot cm^{-5}$
Rvr			20.0	20.0	$dyn \cdot s \cdot cm^{-5}$
Hydraulic Afterload					
Csa	1.0E-3	1.0E-3			$dyn^{-1} \cdot cm^{5}$
Rsa	150.0	150.0			$dyn \cdot s \cdot cm^{-5}$
Rt	1,000	1,000			$dyn \cdot s \cdot cm^{-5}$

Table 2
Model performance measures

	Isolated Left Heart	Heart-Lung Blood Pump	Systemic Circulation	Complete System	Units
Flows*					
SV left	20.2	21.1		22.2	ml
SF left	52.0	52.0		54.0	%
SV right		20.2		22.2	ml
SF right		52.0		56.0	%
CO	2.02	2.1	2.2§	2.2	l/min
Volumes					
EDV left	38.9	40.8		41.3	ml
EDV right		38.5		39.9	ml
Total active†	38.9	108.0	212.0§	315.0§	ml
Pressures					
Pla‡	4.5§	5.3		5.6	mmHg
Pra‡		2.4§	3.4	2.6	mmHg
Arterial					
Mean	90.0	93.0	92.0	89.0	mmHg
Max	114.0	118.0	110.0	117.0	mmHg
Min	80.0	81.0	82.0	79.0	mmHg
Pulmonary art					
Mean		13.0		14.0	mmHg
Max		26.0		27.0	mmHg
Min		7.0		7.0	mmHg

*Small transients may not be totally damped. The criterion for steady-state conditions is an error between beats k and $k + 2$ for each node of $<1\%$. This condition is checked prior to calculating a new beat, near physiological end diastole. †Total volume is the sum of volume on the appropriate nodes of Figure 3 (RV, Cpa, Cpv, LV, Csa, Ccv); includes dead space volume in RV and LV. Isolated heart and heart-lung afterload volumes were excluded to prevent confusion with the volume in the real arteries. ‡End-diastolic pressure is indicated; Pla, Pra, left and right atrial pressures. §Inputs to the models are indicated; all other values are calculated outputs.

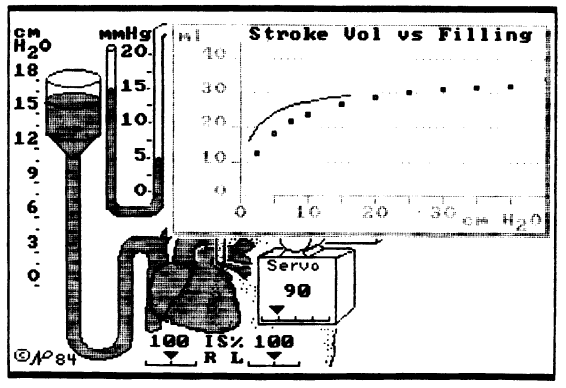

Figure 5
Results of 2 preload experiments. Isolated left ventricle model (*open boxes*) and heart-lung model (*solid line*). Heart-lung blood pump is more sensitive to preloading changes; its curve is above and to the left of the isolated left ventricle curve.

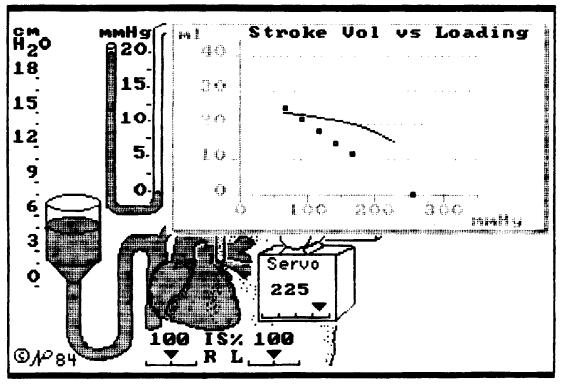

Figure 6
Results of two afterload experiments. Isolated left ventricle model (*open boxes*) and heart-lung model (*solid line*). Heart-lung blood pump is less sensitive to changes in the afterloading variable; its curve is above and to the right of the isolated heart curve.

of the Starling resistor. The design of this (computer simulated) servo system permitted mean arterial pressure to be held at preset control levels independent of a variation in cardiac output. Data points were collected for steady-state conditions or when flow became "unmeasurably" small (LV stroke volume less than 1.0 ml) over a wide range of right atrial and mean arterial pressures. In the cases where flow became unmeasurable, the arterial loading was released before steady state was achieved, as in the original protocol. The qualitative performance of the model over its full range of operation (Figure 7) agrees well with the results reported by Herndon and Sagawa (inset to Figure 7).

It is important to elaborate on what would appear to be significant differences between the surface created by simulation and that reported by Herndon and Sagawa. The original figure shows a plateau in the range of 10–20 mmHg preload and 30–180 mmHg afterload. Our model shows this region to be sloped in two directions. The text of their report stresses the relative insensitivity of aortic flow to mean arterial pressure in the range of 30–180 mmHg for heart-lung preparations in contrast to the steady decrease in flow for similar experiments performed in a left heart preparation (12). Our models show this same behavior in Figure 6. In contrasting their results to the isolated left heart work, they do report a slight slope saying, "Comparable curves from the present studies . . . extend *almost* (our emphasis) horizontally to MAP [mean arterial pressures] of 180–200 mmHg, after which AF (aortic flow) fell more rapidly than seen in the case of the left ventricular curves."

Herndon and Sagawa go on to speculate concerning the mechanism responsible for isolating the right heart from the rise in left atrial pressure which occurs secondary to elevations of mean arterial pressure. They discuss a waterfall between the pulmonary capillaries and veins as possibly responsible for providing the pressure isolation. This effect would operate at low left atrial pressures and continue until left atrial pressures have risen to some threshold. Above the threshold the blood pressure in the pulmonary veins would be communicated to the pulmonary artery. If such a mechanism is significant, it is not represented in our model, which uses a simple linear resistor in the pulmonary capillaries. In our model, pulmonary venous pressure is always connected to pulmonary arterial pressure.

Systemic Circulatory Laboratory

The peripheral circulation model possesses two compliance elements: a systemic arterial compliance, Csa, and a venous compliance, Ccv. These are separated by a peripheral arterial resistance, Rtp. The characteristic impedance of the arterial system is represented by an input resistance, Rsa. Following the Guytonian model, the blood returns to the right atrium through a resistance to venous return, Rvr.

The pump which circulates blood between the veins and arteries is modeled as an ideal flow source with no compliance. Its actions are pulsatile, consisting of one-half sine wave during ejection (first third of the pump cycle) and another half sine wave of lower frequency and

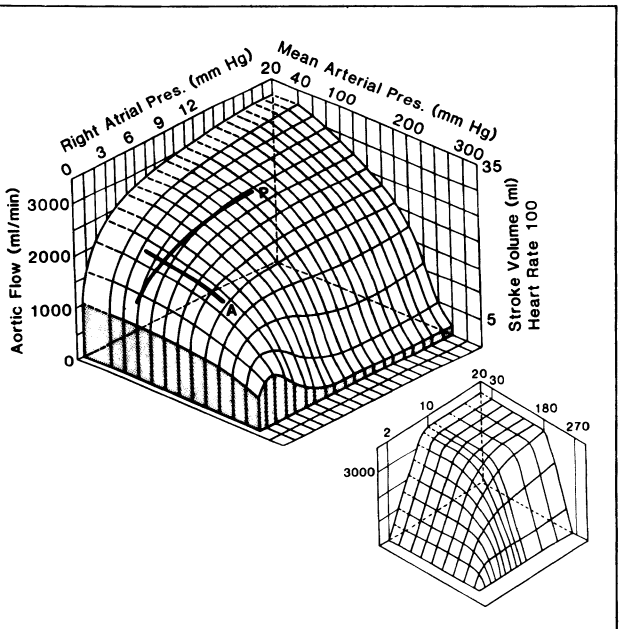

Figure 7
Results from simulation of Herndon-Sagawa experiment in heart-lung blood pump. Preload is on *left axis*, increasing from outer edge of figure toward the center. Afterload is on the *right axis*, increasing to the right. *Vertical axis* measures stroke volume of the LV in steady state, or when ejected flow becomes unmeasurable. Surface agrees qualitatively with the results reported in the canine; differences are discussed in the text.

negative sign during filling (two-thirds of pump cycle). The pump filling is insensitive to venous return pressure and it always ejects exactly as much volume as it fills.

The systemic circulation model was tuned by setting the pump at the nominal cardiac output of the heart-lung model. Parameters and blood volume were adjusted to yield a pressure at the pump inlet (equivalent to right atrial pressure) equal to the nominal preload used in tuning the heart-lung model. Arterial pulse pressures and mean arterial pressure were also required to match those seen in the heart-lung preparation with its experimental afterload. Finally, the circulatory system properties were required to yield a stop flow pressure of 7 mmHg. Table 2 gives the performance data.

Cardiovascular System Laboratory

The cardiovascular system model is an assemblage of the heart-lung model, less preload and afterload apparatus, and the systemic circulation model, less pump apparatus. In the whole system model, the facility for interaction of the cardiovascular system with intrathoracic pressures is given. This is done by making Rvr, Rpc, and Rpr nonlinearly dependent on intrathoracic pressure. Further, the transcompliance pressures for all compliant element in the thoracic chamber (i.e., Cpa, Cpv, Csa, and the two ventricles) are dependent on the intrathoracic pressure. These dependencies make possible demonstration of features such as respiratory cycle-induced variation in cardiac output and arterial pressure. The Valsalva maneuver is also possible.

The total active blood volume in the assemblage is the algebraic sum of the mean volumes contained in each subsystem. When assembled, the whole system performed almost identically to its parts, as shown in Table 2.

CRT Displays

The outputs and data displays from the left heart model have been covered in detail in a previous publication (10). They include both raw data displays, in the form of animated strip charts, and processed data displays. The strip charts show instantaneous LV pressure, volume, outflow, and instantaneous arterial pressure. Processed data displays include pressure-volume loops, instantaneous isovolumic LV pressures (presented in the format of the classic figure published by Otto Frank), cardiac function curves (similar to Figure 5), and afterload response curves (similar to Figure 6).

The data from the systemic circulation model may also be displayed in two formats. Animated strip charts show pulsatile arterial and venous return pressures. These operate at two display speeds: fast, showing pulsatile events clearly; and slow, showing transient changes in partially damped signals. Processed data showing venous return curves and arterial pressure curves is also available, as shown in Figure 8.

In the remaining two models, heart-lung blood pump and cardiovascular system, we chose to limit the data access to more highly processed types of displays. This is in keeping with our goal of presenting cardiovascular behavior in a hierarchical fashion; raw data showing pulsatile events may only be seen in the laboratories that are at the bottom of the conceptual hierarchy.

In the heart-lung blood pump we permit the student to observe pressure-volume loops for the LV and RV, since these are useful in understanding the interactions of the LV with the RV and pulmonary circulation.

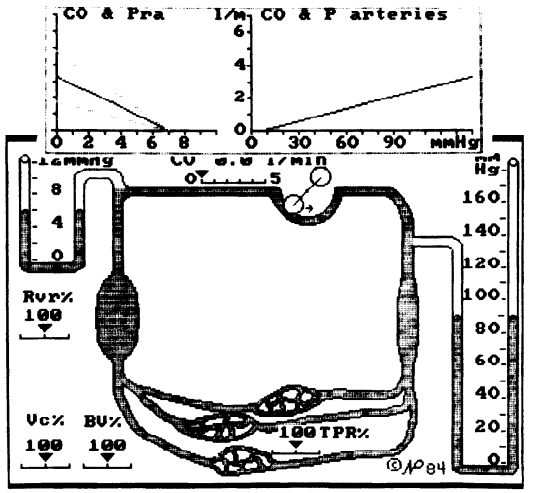

Figure 8
Overall: view of the systemic circulation laboratory, showing student controlled variables for resistance to venous return (Rvr%), central venous compliance (Vc%), active blood volume (BV%), total peripheral resistance (TPR%), and flow velocity (CO). *Left inset*: venous pressure response to circulation velocity (equivalent to cardiac output). *Right inset*: arterial pressure response to circulation velocity.

Figures 5 and 6 are also part of the repertoire of the heart-lung blood pump model. They show this experimental preparation in an abstract form: a model consisting of two curvilinear functions. One relation is the cardiac function curve and the other is the afterload response curve.

The cardiovascular system model is represented by one data display, showing the steady-state relationships among cardiac output, right atrial pressure, and mean arterial pressure. Figure 9 presents these data as two boxes. In addition, four curvilinear relationships calculated in lower laboratories have been imported into the display. We have purposely restricted the data view at the top level of the hierarchy to preclude access to pulsatile data. Our purpose is to reinforce the student's thinking about the system in terms of the abstract models derived from the heart-lung and systemic circulation laboratories.

Instructional Uses of Program

Obviously, the program may be used to teach many aspects of cardiovascular mechanics and physiology. It can teach about the components of the system and the whole system's sensitivities. It is unique among existing programs in offering this capability. Classical experiments may be recreated and experiments of the student's own design conducted. However, the goal of the program, its organization and design, is to allow the teaching of integrative cardiovascular physiology by allowing a synthesis of knowledge about the system.

In a very general sense, the steps to a synthesis of knowledge about a system with a dynamic hierarchy are as follows. *1)* Develop mental models of system components at their atomistic level. These will be detailed models having many descriptive features that will express behavior on the fastest time scale of interest. *2)* Simplify these descriptions so that only those features of a component are retained that are essential to relating it to the environment in which it interacts with its component neighbors. Often, this simplification will require the

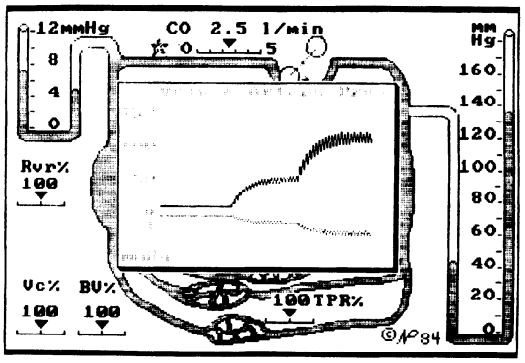

Figure 9

Strip chart showing transient response of arterial pressure (*top trace*) and venous return pressure (*bottom trace*) to stepwise increases in cardiac output from mechanical pump. From left to right, speeds are 0, 1, and 2.5 l/min.

suppression of time information so that averaged, summated, or end state (rather than continuous variables) will be used. *3*) Aggregate groups of component models into comprehensive simple models that encompass the details of component behavior and component interaction in an approximate expression of lumped subsystem behavior. This will usually require that behavior be further compressed and be expressed in yet a still slower time scale. *4*) Sequentially merge the various subsystem models by repeated aggregations into a global model of overall system behavior. In this, as in other aggregations, special attention needs to be paid to the nature of the interaction between components, as it is the interaction as much as the component properties that determine the appropriate form of an aggregate model. *5*) Experiment with the construct to predict system behavior in the presence of changes in system properties. *6*) Use the integrated model construct to solve several kinds of problems. Solving problems requires that the model hierarchy be systematically decomposed in a top-down fashion. Top-down decomposition follows an intellectual path through the hierarchy in a direction opposite to that taken in its construction. The recognition of the difference between the intellectual methods used in the rational construction of a hierarchy of abstract representations of a dynamic system and the methods that are followed in the use of that hierarchy to solve system problems is critical to the understanding of knowledge and its use.

These general steps constitute a prescription for teaching integrative physiology. They and their formal and theoretical foundations are not properly part of the didactic content of a course in physiology. However, we would claim that an appreciation of these steps can be made part of the tacit understanding of students by proper experiences with physiological knowledge. The major objective of the cardiovascular systems and dynamics program is to make possible these experiences. A description of how the program may be used to teach integrative cardiovascular physiology follows.

Step 1. Develop a mental model at the atomistic component level. Choice of an atomistic level is arbitrary. We chose the isolated LV and equivalent level component representations to be the lowest level that was reasonable for beginning a synthesis of knowledge about cardiovascular mechanics. The student begins by observing and experimenting with the isolated left heart section of the program. In this section, the student constructs and observes the Wiggers diagram of the heart cycle and the LV pressure-volume (PV) loop in dynamic form. These are the kinds of raw information from which mental models of LV pump function at its lowest level may be formed. The mental model is formed by observing a graphic image of instantaneous hemodynamic events. It is inconsequential that the image may have been generated from data from a numeric model in a computer. The image need only emulate the one generated from the real system in ways pertinent to the learning goals. The student need not be concerned with the abstract formalism of the time-varying elastance-resistance numeric model used by the program to generate the graphical images. Unlike the figures in a textbook, the program provides these images in a dynamic form and provides the opportunity for their manipulation and observation in a variety of formats. The means and procedures by which the program is used to generate such images have been described in detail elsewhere (10).

Step 2. Develop a mental model that emphasizes the interaction of the component with its environment. The important elements of the left heart environment in regard to its mechanical interactions with the rest of the cardiovascular system are its preloading and afterloading conditions. Left heart behavior in response to changes in preload and afterload is made observable to the student by allowing experiments on the isolated left heart in which *i*) incremental changes are made in filling pressure, P(f), while LV external performance as measured by stroke volume, SV, is observed, and separately, *ii*) incremental changes are made in end-systolic pressure, P(es), while the SV response is again observed. The resulting relationships between SV and P(f) in one case and SV and P(es) in the other are in fact a reduction of the multiple features of the cardiac cycle diagram and PV loop to the two loci of points that describe each of these relationships (Figures 5 and 6). This model reduction has involved a jump in the scale of perception, from continuous time in the cardiac cycle and PV loop to discrete states at the end of select periods within the cardiac cycle. Furthermore, the perception has changed from making simple temporal associations to relating one variable to another in a causal fashion through what are basically input-output characterizations. In the manual that accompanies the program, these two characterizations are referred to respectively as the left heart preload response and left heart afterload response curve.

The two input-output characterizations of left heart performances are not independent but are tightly coupled. The nature of this coupling can be demonstrated by having the student perform the experiments that generate one of these relationships, e.g., SV vs. P(f), at several values of the third variable, e.g., P(es).

At this point, the student possesses a two-level hierarchical set of models to describe the pumping LV: *i*) a detailed model of instantaneous internal events and *ii*) a higher level model that relates the LV to its mechanical environment, i.e., the environment through which it interacts with the rest of the cardiovascular system. It is important for the student to realize that these two models are consistent with one another. Thus, facility is provided in the program for the student to observe PV loops at each preload and afterload state that may be achieved and to examine the PV relationships that describe the end-diastolic and end-systolic states. The end-

state PV relationships are the mechanistic basis for relating the higher level model of the pumping LV to the lower level models. Thus, proper use of the program demonstrates that it is intellectually consistent to conceptualize LV pumping in terms of two alternative methods at the same time. Each model level will prove to have different utility.

Step 3. Aggregate groups of component models into a comprehensive simple model. Once the reduced model of the LV has been formed, the student can then begin to consider LV behavior in conjunction with a selected few other cardiovascular components with which it interacts. We have chosen the heart-lung blood pump as the next level of cardiovascular hierarchy to examine. The atomistic behaviors of the pulmonary circulation and right heart components of the heart-lung blood pump are not explicitly made available to the student for detailed examination. However, it is readily apparent from the various data displays provided by the program that the right heart, while quantitatively different, is phenomenologically equivalent to the left heart, and that the pulmonary circulation, while qualitatively different, is phenomenologically equivalent to the systemic circulation. Data to support reduced models of these components are presented. The intellectual task is to aggregate the three individual component models into a single simple comprehensive model.

The form of the aggregate model depends on the nature of the interactions among components. The interactions take place at the interface between components. Therefore, the program provides a visual representation of the behavior of the variables at the interface between each component. Thus, the student can observe pulmonary arterial pressure, Ppa, and RV SV at the interface between the right heart and pulmonary circulation and observe return to the left heart and left atrial pressure, Pla, at the interface between pulmonary circulation and left heart. Apparatus that can be used to vary the preload and afterload on the heart-lung unit are identical to that used with the isolated left heart and can now be used to perform similar kinds of experiments on the heart-lung blood pump unit. As with the left heart, the resulting input-output characterizations of the heart-lung pump are referred to as the heart-lung preload response curve and heart-lung afterload response curve.

As the right heart filling pressure or the left heart afterload resistance is changed, the student not only observes the changes in pumping output from the heart-lung unit but also observes the changes in variables at the interfaces between components within this system. From these observations the student learns that elevation of arterial pressure is transmitted back through the LV into the rest of the heart-lung unit poorly, whereas elevation of right atrial pressure is transmitted forward very readily through the right heart into the rest of the system. These mechanisms are responsible for the right heart being largely decoupled from changes in left heart afterload (especially at low Pla) while the left heart is driven very strongly by changes in right heart preload. Thus, the heart-lung unit as a pump is very much less sensitive to its afterload than the isolated left heart, while the heart-lung unit is nearly as sensitive as the right heart to the preload. Understanding the differences between the isolated right and left heart pumps and the aggregate heart-lung pump requires an understanding of the mechanisms of interaction within the heart-lung unit. The program provides the student the opportunity to learn these mechanisms through experimental means. The accompanying manual is used to guide the student through this reasonably difficult exercise.

In the preceding, behavior of the heart-lung unit was examined on the same time scale as that of the isolated left heart. This was done so that comparisons could be made between the heart-lung pump and the left heart pump. However, looking ahead to the merger of the heart-lung unit with the systemic circulation, there is a need to transform the time scale of description of heart-lung pumping behavior from end-state values to average values, i.e., from SV to cardiac output, CO, and from P(es) to average arterial pressure Psa. Because Pra is both end-state and average value, there is no need to transform this variable. At constant heart rate, the transformation from SV to CO is straightforward. The transformation from P(es) to Psa is conceptually more difficult. [See Sunagawa et al. (14) for a more rigorous approach to this transformation.] In the program, empirical means are employed to assist the student. P(es) and Psa are both presented simultaneously by the program in tabular form during the afterload experiment. From this table of values the student will be able to confirm that there is virtual equivalence between these two variables. Thus, CO, Pra, and Psa can be used to describe the heart-lung pumping properties just as well as SV, Pra, and P(es), and there will be no significant change in the behavioral pattern.

The conceptual hierarchy is now three-tiered. It includes *i*) the detailed atomistic model of a single component, *ii*) the reduced model of that component that relates it to its environment, and at the same level, the reduced models of two other components, and *iii*) an aggregate model for all three components (see Figures 5 and 6). It can be demonstrated by proper use of the program that these models are all consistent with one another even though the higher level models are only approximations of the net behavior of models at the lower levels.

Parallel with the development of a conceptual hierarchy for the heart-lung unit would be the equivalent level model development for the systemic circulation. At this time, the program does not contain atomistic behavioral components of the systemic circulation at the same level as provided for the left heart. For instance, the relationship between driving pressure and blood flow and between transmural pressure and blood vessel diameter in isolated blood vessel segments of different size, wall thickness, and wall stiffness would be a reasonable atomistic level from which to begin in the systemic circulation. A reduced model of a blood vessel segment could emphasize total segment properties of resistance and compliance. An aggregate model would represent properties of blood vessel subsystems in terms of lumped resistance and compliance. Finally, a further aggregation would be required to represent an entire blood vessel system composed of subsystems arranged together in-series and in-parallel with each subsystem possessing markedly different lumped capacitance and resistance properties. This would be the final step in achieving a global view of the systemic circulation. These sections could be added to the program. They can also be demonstrated in a wet laboratory.

At present, the program offers only the overall systemic circulatory system for student investigation. For

the purposes of demonstrating a sequential integrative process, a mental model of this lumped systemic circulatory component is all that is needed. The student develops this model by performing simulated experiments that are analogs to those described by Guyton and coworkers (4). The graphical icon in Figure 8 is of an isolated systemic circulation receiving blood from and delivering blood to a pump. The student controls the speed of the pump and observes the pressures at the arterial and venous ends of the circulation. The mercury manometers at each location provide an immediate visual reference for these pressures. The student can systematically raise and/or lower the pump speed and observe the changes in both pressures. Figure 9 shows the resulting change in each pressure from several stepwise changes in pump speed. The results are then translated into a graphical format that relates both venous and arterial pressure to the flow through the system (Figure 8). These representations can be examined over a broad spectrum of changes in total peripheral resistance, venous compliance, resistance to venous return, and blood volume. Thus, the mental model of the systemic circulation that will be used in merging it with the heart-lung unit is the relationship of venous and arterial pressures to flow through the system.

Step 4. Merger of subsystem models into a global model of overall system behavior. The final step in the integration comes from considering the interactions between the heart-lung unit as a pumping system and the systemic circulation as a loading system. The program facilitates the student's vision of this interaction by providing the graphs shown in Figure 10. The two graphs show values of the variables at the two interfaces between these interacting systems. Different from the linearly propagating component interactions encountered in the heart-lung unit, the interactions depicted in Figure 10 are of a causally circular form (see Ref. 15 for greater discussion of the meaning of circular causality). This circularity has great behavioral consequences for the merged system. A mechanistic explanation of how these consequences arise comes from examining the intersecting lines in each graph. At the interface between the veins and the right heart, an increase in right atrial or central venous pressure will cause the heart-lung unit to pump more blood (*line A*). However, that blood must be supplied by the venous return. If pumping is increased it will cause right atrial pressure to go down (*line B*). These competing effects cause the system to establish behavior at the unique point given by the intersection of the two lines describing the behavior of each subsystem. Simultaneously, a similar competition is occurring at the arterial-left heart junction. An increase in flow into the arteries will drive arterial pressures up (*line b*), while an elevation of arterial pressure will tend to interfere with the ability of the heart-lung unit to pump blood (*line a*). Again, an equilibrium point which satisfies both tendencies is established at the intersection of the two lines that describe the behavior of each subsystem.

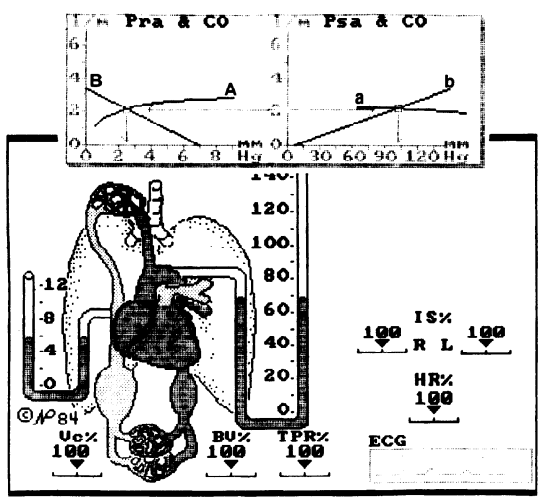

Figure 10

Overall: view of the complete cardiovascular system laboratory, showing student controlled variables: right and left inotropic state (ISr%, ISl%), heart rate (HR%), total active blood volume (BV%), a total peripheral resistance (TPR%), and central venous compliance (Vc%). *Right inset*: equilibrium condition for left heart-artery interaction (*box*). Line with positive slope was imported from Figure 8, the other line from Figure 6. *Left inset*: equilibrium condition for vein-right heart interaction (*box*). Line with negative slope was imported from Figure 8, the other curve from Figure 5. Only data represented by the two boxes may be displayed from the calculations in this laboratory. Lines, representing behavior of isolated components, must be created in their respective laboratories and imported. Conservation of volume requires cardiac output indicated by these equilibria to be the same, indicated at 2.2 l/min.

A third interaction comes about because the coupled cardiovascular system is closed and volume within the system must be conserved. Therefore, the venous return, on the average, must equal the cardiac output. The equilibrium point in the left panel of Figure 10 must be at the same level of flow as the equilbrium point in the right panel. The causal mechanisms that bring these equilibrium points to one level of flow can be traced to the coupling between the two input-output relationships that describe each subsystem. Earlier, the student observed that the location, but not the slope, of the afterload response curve of the heart-lung unit was very much affected by the right atrial pressure. This came about because of the very effective forward transmission of pressure through the heart-lung unit. The arterial pressure, because of the relatively poor backward transmission of pressure through this subsystem, had very much less of an effect on the location of the curve that related right atrial pressure to cardiac output. Additionally, volume shifts between the heart-lung unit and systemic circulation will shift both the venous pressure line (major effect) and the arterial pressure line (minor effect). It is these interdependencies between the locations of these curves that allow the equilibrium points on each interface between these two subsystems to settle at the same level of flow. The student can observe these actions by changing the blood volume in the system and noting that the new operating level is achieved far from the original afterload response and venous pressure lines but not far from the original preload response and arterial pressure lines.

The mental model of the integrated cardiovascular system recognizes forces that bring about three simultaneous equilibria in the interaction between heart-lung blood pump and systemic circulatory load. That these equilibria exist is a consequence of interaction within the system. However, the location of the equilibria points is determined by the properties of the system components.

Through appropriate use of the program the student will be able to appreciate the fact that both component

properties and component interaction participate in determining overall system behavior. The character of interaction can be of the kind in which events propagate linearly through the system, as in the heart-lung unit, or of the kind in which events have a circular relationship to one another, as in the intact cardiovascular system. These distinctions are important to the process of integrating the knowledge about the bits and pieces of the system. Such concepts are very difficult to convey through lecture, textbooks, or the animal laboratory. The simulated computer laboratory seems to be ideally suited for teaching these general principles. Since the concepts are critical to the integration of knowledge about dynamic systems, the simulated computer laboratory becomes the best, if not the only, tool available for teaching knowledge integration in these systems.

Step 5. Experiment to predict global system behavior in the presence of system changes. An appreciation of the degree of dependence of every system variable on every system property is critical to a predictive understanding of system behavior. Thus, the questions are asked "How much change is expected in CO, Psa, and Pra from a 50% increase in total peripheral resistance? How much from a 50% decrease in left ventricle inotropic state?" The model developed in *step 4* provides the kind of tool that can be used to make such predictions. The program, by giving the student the opportunity to change cardiovascular system properties and observe the consequences, provides the means by which the student may test these predictions and refine his understanding of system behavior. Multiple property changes that simulate physiological states such as exercise, shock, and congestive heart failure are also possible to achieve, and these may also be investigated in the integrated model construct shown in Figure 10.

Earlier, we presented a description of a laboratory exercise that addressed these issues using a computer model of the cardiovascular system on a minicomputer system (3). The current program on the microcomputer provides all the features of the earlier program plus the many additional features described here.

Step 6. Practice in top-down decomposition of the model hierarchy. The first four steps represented a process in constructing a hierarchy of mental representations of the cardiovascular system by working from the bottom elements in the hierarchy to the top. They provided a rational basis for the existence of such mental constructs. However, the value of these constructs lies in their utility. The prime utility will be in their usefulness in solving problems. Effective problem solving is a top-down procedure, beginning with a global vision of the problem setting.

One section of the program introduces faults into the cardiovascular system by changing one of the parameters to an abnormal value. The student is presented with a global vision of the system as in Figure 10. She observes that cardiac output, arterial pressure, and central venous pressure all exhibit abnormal values. Her task is to identify the parametric abnormality that caused the behavioral abnormality. This is done by deciding which one of two major components of the global system model contains the fault. The program allows the student to then isolate the suspected faulty component, examine it experimentally, and compare the experimental findings with normal results to see if one of the component properties is indeed abnormal. If further decomposition is needed, then the program allows the system to be further decomposed to its atomistic component level and each component to be examined experimentally until final verification of the fault has been achieved. Such practice inculcates top-down problem-solving skills. These skills can be the progenitor of medical diagnostic acumen.

A Classroom Experience

We used this program as part of a veterinary physiology class. For most of the 80 professinal and graduate students enrolled, this class was their first experience with both computers and cardiovascular physiology. The class was divided into 2 groups for laboratory sessions. In the wet laboratory students worked in 8 groups of 5, and for the computer laboratories they divided themselves into 12 groups of approximately 3 students. Each group had an IBM PC at its station in the university's microcomputer laboratory. Laboratory sessions lasted for 2 hours.

The students' response to the program and simulated laboratory was very positive. Perhaps the best example of this is that they did not want to leave at the end of their 2-hour sessions, and a number of students voluntarily came back to use the program evenings and weekends. As instructors, we found the experience rewarding. The students were very intent on the material and, judging from their questions, understood it better than they do when the same material is presented in our traditional wet laboratory and lecture format.

The first session was devoted to the cardiac cycle, the second to the left heart as a pump. The third focused on integrating the left and right heart models, using the heart-lung laboratory. The fourth worked with the systemic circulatory system and merged ideas from it with heart-lung data to explain behaviors of the complete system. If an extra session or two had been available, it could have profitably been used to further explore heart-lung and whole system integrations.

Unintentionally, the first laboratory session was scheduled before the students had received any cardiovascular physiology in the lecture portion of the class. We found that both we and they were very satisfied with the laboratory session as a primary introduction to the material. This freed the lecturer to relate the mechanical events that had been observed in the laboratory to a broader base of information, including nervous control, the electrocardiogram, and isolated muscle mechanics.

Conclusion

We have described the development of a hierarchical set of laboratories that allow for study of integrative behavior within the cardiovascular system. These laboratories may be used to perform aggregations, as illustrated, to build an explanation of cardiovascular mechanical self-regulation. Alternatively, the program's ability to decompose the complete cardiovascular system into subsystems may be used to analyze the cause of a disturbed state which has been created in the whole system. Software integration that permits sharing of model topology, data, and parameters makes these hierarchical transitions possible.

Our program attempts to teach the student a hierarchical viewpoint and how to use it for aggregating several functional elements into a more advanced, but

Table 3
Abbreviations

Major System Components

LV	Left ventricle
PC	Pulmonary circulation
RV	Right ventricle
SC	Systemic circulation

Model Variables and Parameters

C*xx*	Compliance in component *xx*
P*xx*	Pressure in component *xx*
Q*xx*	Flow through component *xx*
R*xx*	Resistance of component *xx*
V*xx*	Volume in component *xx*
	cv central veins
	(es) systemic artery pressure at end systole
	la left atrial
	lv left ventricle
	pa pulmonary artery
	pc pulmonary capillaries
	pr pulmonary return
	pv pulmonary veins
	ra right atrium
	rv right ventricle
	sa systemic artery
	tp total peripheral
	vr venous return
E(*t*)	Time-varying systolic ventricle elastance
HR	Heart Rate
Pa	Instantaneous pressure due to active properties
Pe	Instantaneous pressure due to both active and passive properties
Pp	Instantaneous pressure due to passive properties
VD	Ventricular dead space volume

still simple, system model. Rather than using formal mathematics of aggregation, we have relied on laboratory discovery, because we feel that its experiental and intuitive approach is better suited to the backgrounds of medical students.

The program runs on an IBM personal computer and will be distributed. Please contact the authors for details.

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Announcement

Leukemia Society Grants

The Leukemia Society of America is now accepting applications for 1986 grants to encourage research at both the basic science and clinical levels in the fields of leukemia and related diseases. The awards are a primary source of salary support for individuals whose work is concentrated on seeking the causes and eventual cures for leukemia, the lymphomas, Hodgkin's disease, and multiple myeloma. They include *1*) five-year Scholar grants for a total of $150,000 to researchers who have demonstrated over a period of not less than 5 years their abilities to conduct original investigations in the specified fields; *2*) three-year Special Fellow grants for a total of $63,000 for those investigators in the intermediate stages of career development; and *3*) two-year Fellow grants for a total of $34,000 for promising investigators with no or minimal prior experience assisting and training with scientists and physicians in the related fields. In all categories, candidates should hold a doctoral degree but may not have attained tenure status.

Deadline for filing applications: September 1, 1985. *For application forms and additional information*: Research Grant Coordinator, Leukemia Society of America, 733 Third Avenue, New York, NY 10017.

Physiology Laboratories Quantifying Gas Exchange in Health and Disease

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As eloquently pointed out by Dr. Randall in his past president's address (4), physiology is a laboratory science and effective teaching should incorporate opportunities for the student to appreciate the reality of the discipline. Yet in professional schools, the "tyranny of facts" has overwhelmed the curricula, assisting in the elimination of the costly and time-consuming laboratory exercises which demonstrate fundamental processes. Furthermore, in my experience, in curricula organized by system rather than discipline, physiology is too often perceived by beginning students as an annoying hurdle standing in the way of learning "real medicine." Appreciation of physiology as an important component of medical science seems to arrive with professional maturity. The Department of Veterinary Physiology and Pharmacology is attempting to reverse the decline of laboratory exercises by incorporating labs in the Core Curriculum. The challenge of this attempt is to design a lab that is quantitative and informative, yet cost effective in terms of student and faculty time, equipment, and personnel and judicious in the use of animal resources. The following two laboratories were designed to meet these criteria and, additionally, to capture the students' attention and imagination by incorporating the diagnostic procedures of radiology and physical exam with objective measurements of pulmonary function. The first laboratory quantifies gas exchange in normal lungs and demonstrates the effects of acute alterations in ventilation on arterial blood gases. The second lab quantifies gas exchange in four representative lung pathologies to emphasize the face that although there are many ways for the lung to fail, the end result of failure is inadequate gas exchange. The challenge to the clinician is, therefore, to utilize his or her diagnostic skill to discern the pathology and understand which therapeutic measure would restore normal function. Gas exchange efficiency was quantified by calculating physiological dead space (V_D/V_T using the Enghoff modification of the Bohr technique and pulmonary shunt fraction ($\dot{Q}_S/\dot{Q}_T$) based in the Fick principle (see Appendix) (5).

These exercised were designed specifically for veterinary students to provide an opportunity to incorporate disciplines taught piecewise in the respiratory system course. All animal preparation was done prior to the arrival of the students by personnel experienced with the techniques of pleural puncture and catheter placement. As with any laboratory, not every animal responds in a textbook fashion. This emphasizes the need for judgment in interpreting each clinical case individually and the meaning of "standard error" in relation to "fact."

Specific laboratory objectives were *1*) to provide insight into the mechanisms of gas exchange (ventilation, perfusion, and diffusion) and how they are altered by anesthesia and pulmonary pathology; *2*) to illustrate the relationship of dissolved and combined O_2, hemoglobin saturation, and O_2 content; *3*) to demonstrate the relationships among rate and depth of breathing, arterial blood gases, pulmonary and systemic arterial blood pressure, and heart rate by causing hypoventilation, hyperventilation, rebreathing of expired gas or O_2 breathing; *4*) to provide an opportunity to correlate findings on physical examination with objective measures of gas exchange and radiographic signs in typical lung pathologies; *5*) to expose students to physiological research techniques and how "facts" are generated; and *6*) to be esthetically pleasing by being relatively noninvasive, humane, and "goof-proof."

Five laboratory stations were equipped to accommodate one group of three second-year veterinary students each. An equipment list is provided in Table 1. Alveolar gas and arterial blood samples were analyzed at central stations. Two technicians assisted in blood gas analysis and polygraph operation and four DVM graduate students and a lab coordinator assisted with data collection, monitoring of anesthetic depth, and the clinical interpretation of results. The high personnel-to-student ratio promoted individual attention, maximizing student benefit.

The 2-hour labs were given twice in succession on two separate days permitting 30 students to use five dogs.

Table 1
Laboratory station equipment

Major Equipment
CO_2 gas analyzer
Spirometer
Blood gas analyzer to determine P_{O_2}, P_{CO_2}, pH, % saturation, and hemoglobin concentration
Ventilator capable of delivering O_2
Individual Station
1 Polygraph with 2 pressure transducers 1 impedance pneumograph 1 ECG channel
1 Ice bucket
1 Nonrebreathing valve
1 Gas collection bag (~20 liters)
3 5-ml Heparinized syringes for arterial blood samples
2 Syringes for clearing catheters
Sterile heparinized saline and syringes for flushing catheters
1 Thermometer
1 Stethoscope

Dogs recovered after Lab I, were treated with 1×10^6 U of penicillin G procaine intramuscularly, and used for the second lab 2 weeks later. Although it is feasible to recover four of the dogs used in the second lab, euthanasia is recommended.

General Methods

Approximately 2 hours prior to the lab the dogs were premedicated with acepromazine (2.5 mg/10 kg iv) and anesthetized with pentobarbital sodium (15 mg/kg iv). The dogs were intubated, and catheters were placed in the pulmonary artery and femoral artery or aorta using sterile technique. Supplemental anesthetic was given as needed. Students were not present during the preparation and recovery of the animals.

Lab I. Gas Exchange in Normal Lungs and Control of Ventilation

Methods and Protocol

Part A. Each group recorded base-line measurements of pulmonary arterial and systemic arterial blood pressure, body temperature, and respiratory rate. The gas collection bag was affixed to the expiratory port of the nonbreathing valve, and a 5-min timed collection of expired gas begun. After 2 min simultaneous mixed venous and systemic arterial blood samples were drawn, placed on ice, and taken to the blood gas station for analysis. At the end of 5 min the bag was removed from the nonrebreathing valve, clamped, and taken to the alveolar gas station for determination of expired volume and mixed expired P_{CO_2}.

Part B. In the second part of the normal lab each group followed a different protocol to demonstrate the effects of alterations in inspired gas and respiratory rate on minute ventilation and arterial blood gases.

Group I: used an Ambu bag to hyperventilate the dog for 2 min (respiratory alkalosis).

Group II: ventilated the dog with 100% O_2 for 2 min by attaching a bag filled with O_2 to the inspiratory port of the nonrebreathing valve.

Group III: paralyzed the dog (0.1 ml succinylcholine chloride iv) and used a Harvard ventilator to hypoventilate the dog for 2 min (respiratory acidosis).

Group IV: ventilated the dog with 95% O_2-5% CO_2 for 2 min by attaching a bag filled with the mixture to the inspiratory port of the nonrebreathing valve.

Group V: attached a long hose to the endotracheal tube to simulate increased dead space.

Systemic arterial blood samples were then collected and analyzed for P_{O_2}, P_{CO_2}, and pH.

Lab II. Gas Exchange in Abnormal Lungs

Methods and Protocol

For the second lab the dogs were anesthetized and instrumented as before. Prior to the lab period, four different pathologies were induced and one dog left normal for comparison.

Group I: 300 ml of sterile saline were injected into the left pleural space to simulate pleural effusion.

Group II: 700 ml of air were injected into the left pleural space to simulate pneumothorax.

Group III: the left caudal bronchus was occluded with a balloon tipped catheter to cause lobar collapse by resorption atelectasis.

Group IV: 0.1 mg/kg oleic acid shaken in 10 ml saline was injected into a peripheral vein to cause pulmonary edema (nonrecovery).

In the second laboratory the students collected mixed expired gas and simultaneous systemic and pulmonary arterial blood samples and calculated V_D/V_T and $\dot{Q}_S/\dot{Q}_T$ as in Lab I. The results were posted next to the animal, and students were asked to auscultate and percuss the chest to determine which pathology the dog had. Students then rotated through the stations and compared the physical findings with gas exchange parameters for each dog. Typical radiographs of each pathology were provided so students could correlate the findings on physical exam and gas exchange parameters with radiographic signs of each pathology.

Results

Data sheets with spaces for data and calculations were provided. Measured and calculated variables are listed in Table 2. Expected results are shown in Table 3. Because the same animals were used in both labs, each dog served as its own control.

Student Preparation

Prior to the lab, students were asked to read the appropriate chapters in the West (5, 6) and Burrows (1) books. They had received lectures on auscultation (2, 3) and percussion techniques and interpretation of radiographs. Prior to entering the lab, students were instructed in how the dogs were prepared, lab protocol, arterial blood sampling technique, and polygraph operation. Students felt this to be adequate preparation.

Errors and Potential Problems

Aside from the possibility of unhealthy research dogs, the major potential difficulty is the variable response to oleic acid. Preliminary experiments using the oleic acid pulmonary edema model determined the preparation to be viable for 6–8 hours if circulatory and ventilatory support were provided as necessary. The necessity for careful monitoring, providing support if necessary, and examining the lungs at necropsy to observe the gross damage all contributed to the learning experience.

Table 2
Measured and calculated variables

Measured Variables	Calculated Variables
Barometric pressure (P_B)	Alveolar P_{O_2} ($P_{A_{O_2}}$)
Heart rate	Average tidal volume ($\bar{V}_T$)
Breathing frequency (f)	Alveolar-arterial oxygen difference (A-aD_{O_2})
Body temperature	O_2 content of arterial, mixed venous and pulmonary capillary blood (C)
Arterial P_{O_2}, P_{CO_2}, pH, and % saturation	Physiological dead space (V_D/V_T)
Mixed venous P_{O_2}, P_{CO_2}, pH, and % saturation	Pulmonary shunt fraction ($\dot{Q}_S/\dot{Q}_T$)
Hemoglobin concentration (Hb)	
Expired volume (V_E) (ATPS)	
Mixed expired P_{CO_2} ($P\bar{E}_{CO_2}$)	
Systemic arterial blood pressure	
Pulmonary arterial blood pressure	

See Appendix for calculations.

Table 3
Results

Pathology	Radiographic Signs	Percussion	Breath Sounds	Gas Exchange $\dot{V}_D/\dot{V}_T$	Gas Exchange $\dot{Q}_S/\dot{Q}_T$
None	Normal	Resonant	Normal	~0.30*	<0.05*
Pneumothorax	Large hyperlucent pleural space, heart elevated off sternum in lateral recumbency	Hyperresonant	Reduced	↑	↑↑
Pleural effusion	↑ Opacity of pleural space, lobar fissures visible, heart obscured	Very dull	Muffled	↑	↑↑
Lobar collapse	Reduced vascular markings in collapsed lobe	Dull (focal)	Increased	↑	↑↑
Pulmonary edema	Air bronchograms	Dull	Crackles	↑ or ←→ (depending on severity)	↑ or ←→

*Probably larger due to anesthesia.

Students were advised of the error introduced in determining minute volume with the spirometer after first determining mixed expired CO_2. Because duplicate measurements were made on each animal by two groups of students, errors introduced by poor technique did not result in data loss.

Student Response

Following the labs, data were compiled into a handout incorporating the results and physiological interpretation. Group discussion afterward emphasized the potential causes of hypoxemia, how they present clinically, and why. It was emphasized that determining $\dot{Q}_S/\dot{Q}_T$ while the animal was breathing 100% O_2 could have measured the fraction due solely to right-to-left shunting of blood.

Student response to the labs was overwhelmingly favorable, with only one student objecting to the use of live animals. The correlation of clinical findings with physiology and pathophysiology was especially well received by both the veterinary students and the department administration.

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Appendix: Calculations

Minute ventilation:

$$\dot{V}_E = V_E/\text{collection period}$$

where V_E is the expired volume.

Average tidal volume (ATPS):

$$\bar{V}_T = V_E/f$$

where f is the breathing frequency.

Inspired P_{O_2}:

$$P_{I_{O_2}} = (P_B - P_{H_2O})F_{I_{O_2}}$$

where P_B is the barometric pressure, p_{H_2O} is the water vapor pressure, and $F_{I_{O_2}}$ is the fractional concentration of O_2 in dry inspired gas.

Alveolar P_{O_2}:

$$P_{A_{O_2}} = P_{I_{O_2}} - Pa_{CO_2}/R$$

where Pa_{CO_2} is the arterial P_{CO_2} and R, the respiratory exchange ratio, is assumed to be 0.8.

Alveolar-arterial O_2 difference:

$$A\text{-}aD_{O_2} = P_{A_{O_2}} - Pa_{O_2}$$

where Pa_{O_2} is the arterial P_{O_2}.

Blood O_2 content:

$$\text{arterial: } Ca_{O_2} = \left(\frac{0.0031 \text{ ml } O_2}{100 \text{ ml} - \text{mmHg}}\right) Pa_{O_2} + \left(\frac{1.34 \text{ ml } O_2}{\text{g Hb}}\right)\left(\frac{\text{g Hb}}{100 \text{ ml}}\right)\left(\frac{\%Sa_{O_2}}{100}\right)$$

$$\text{mixed venous: } C\bar{v}_{O_2} = 0.0031\ P\bar{v}_{O_2} + 1.34\ (Hb)\ (\%S\bar{v}_{O_2}/100)$$

$$\text{capillary: } Cc_{O_2} = 0.0031\ P_{A_{O_2}} + 1.34\ (Hb)\ (1.0)$$

where $P\bar{v}_{O_2}$ is the mixed venous P_{O_2} and $\%Sa_{O_2}$ and $\%S\bar{v}_{O_2}$ are the percent arterial and mixed venous O_2 saturations, respectively.

Physiological dead space:

$$V_D/V_T = (Pa_{CO_2} - P\bar{E}_{CO_2})/Pa_{CO_2}$$

where $P\bar{E}_{CO_2}$ is the mixed expired P_{CO_2}.

Pulmonary shunt blood fraction:

$$\dot{Q}_S/\dot{Q}_T = (Cc_{O_2} - Ca_{O_2})/(Cc_{O_2} - C\bar{v}_{O_2})$$

Writing Computer Lessons

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This article is written for those who would like to design and write computer lessons for their courses but have not yet tried. It assumes that these teachers are well versed in general educational skills. Also, only a few of the most essential issues having to do with computer hardware or software are addressed and then only in general terms. These factors are important, but they are not the intended scope of this discussion. This article deals with the design and communication issues that must be confronted by everyone who tries to write a computer lesson. It describes some of the limitations that courseware writers face; it prescribes some solutions and gives some examples that have enabled teachers to prepare educationally effective computer lessons.

Definitions

It is important first to define what is meant by a "computer lesson" and to justify the efforts that are required to prepare them.

A computer lesson, sometimes called a tutorial, is an interactive program that attempts to teach something, usually in a relatively small, circumscribed knowledge area. It is interactive because there is bidirectional communication between the student-user and the teacher by way of the program. However, the teacher is not physically present when the interchange actually takes place. Therefore, many things must be anticipated when the lesson is designed and written (2, 9).

I feel that computer lessons should not be primary teaching devices. That is, they should not attempt to be textbooks or lectures. Instead, lessons should presuppose that students have already acquired certain information and skills through other formal teaching activities (lectures, discussions, and laboratories) and through reading. The lessons should help students to integrate this information into useful schemata. They should pose quantitative and qualitative (relational) problems that may be solved through application of facts, relationships, and concepts. They should thereby improve students' problem solving skills. It is especially because computer-based educational (CBE) lessons may help students to integrate and apply information that they become exciting teaching tools.

Computer lessons may also help students and teachers to evaluate how well the course objectives have been realized. This is done for students on an individual basis and may be done for the teacher on both an individual and a classwide basis.

Preparing a Lesson

A computer lesson consists of a set of questions. Each answer that the student gives triggers a programmed response. The answers also control the sequence of events within the lesson, thus individualizing the lesson to the student's educational needs. For the student, it is a private lesson, and this anonymity allows even the most reticent, who would hardly participate in a small group discussion, to openly reveal the state of his or her knowledge. Further, this revelation may take place while a course is in progress and need not wait for a culminating final examination. Hence, needed corrective actions may be taken to enable the student to meet the course objectives on time.

Before actually starting to design and write a lesson one needs to choose a subject area and outline it. One needs to have a set of objectives to be accomplished by the lesson; ultimately the lesson should verify whether the student has met the objectives, and it should contribute toward this goal.

Unlike an annotated collection of questions, a lesson needs internal continuity. One can achieve continuity by using text or illustrations to tie parts of the lesson together. However, continuity can also be achieved through a logical progression of questions that reflects the structure and order of the subject. The lesson outline may be used as an index in organizing questions. All of the examples in this paper are taken from the lesson *Pressure/Flow Relations* (7). Figure 1 is the index of that lesson.

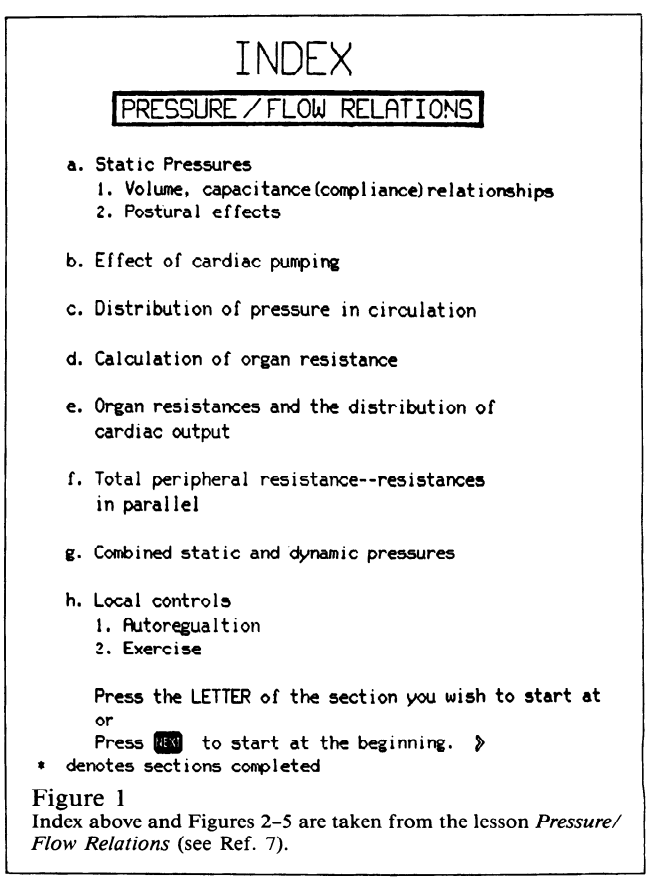

Figure 1
Index above and Figures 2–5 are taken from the lesson *Pressure/Flow Relations* (see Ref. 7).

Modified from a lecture presented at the American Physiological Society Workshop on Computer Based Education, 1 April 1984, Washington University, School of Medicine, St. Louis, MO.

Question Formats

Either multiple choice or "natural" language questions may be used in lessons. All multiple choice questions have a stem, which states the question and answers from which students must choose. The answers may be presented as a list or as a figure in which the student may indicate certain identified elements. When natural language is used, answers may be restricted to a single word, number, or phrase, or students may be permitted to use conversational language.

The form of questioning that an author may employ is determined by the computer programs that are available to him. Programs that facilitate the writing and evaluation of multiple choice questions are readily available (5, 6), so this format is the most widely used. Multiple choice questions may be written in many different styles (see Figures 2 and 3). Doull and Walaszek (5) identify nine types in their partial list. Thus lessons that employ only multiple choice questions may be varied in format to sustain the user's interest.

Judging the correctness of a numerical answer is no more difficult than judging a multiple choice reply if the answer is exact, like the product of two definite numbers (Figure 4). However, if the student must supply the values to be used in a calculation, and if one or more of these is indefinite (like normal arterial blood pressure), the answer judging process is more complex. The program must be able to accept a range of correct answers and may also have to be able to distinguish between marginally correct and clearly wrong ones.

Dealing with answers given in natural language are, not surprisingly, much more difficult. To judge single word or very short phrase answers one needs to develop a dictionary of correct answers that must contain all of the synonyms that students are likely to use. Since the dictionary usually does not have all of the correct answers that might be given, it is useful to collect the unanticipated responses for possible later addition. If a list of incorrect answers is also constructed, one may personalize responses to wrong answers by making them relate to the student's input. This allows more accurate correction of the specific student errors. Many of the authoring systems that are used for writing multiple choice questions also have routines for judging the correctness of short answers (6).

When short answer and other natural language format questions are used, it is useful to be able to judge the correctness of the answer while ignoring typing and spelling errors. Also some approach to dealing with unexpected replies is needed like: "I don't recognize your answer," "please check you spelling," or "use another term." It is exasperating for a student to know the correct answer to a question but be unable to find a way to get it accepted by the program.

There are programs for judging student answers in conversational language (2), and much is being done today in the area of language representation and analysis with computers (10). However, most authors do not have access to natural language analysis systems or have the time or expertise to develop one. Hence, the free use of natural language is usually not an option.

Responding to Student Answers

The way in which one responds to students' answers is most important. It may determine whether the lesson is an effective teaching device or not. Responses should

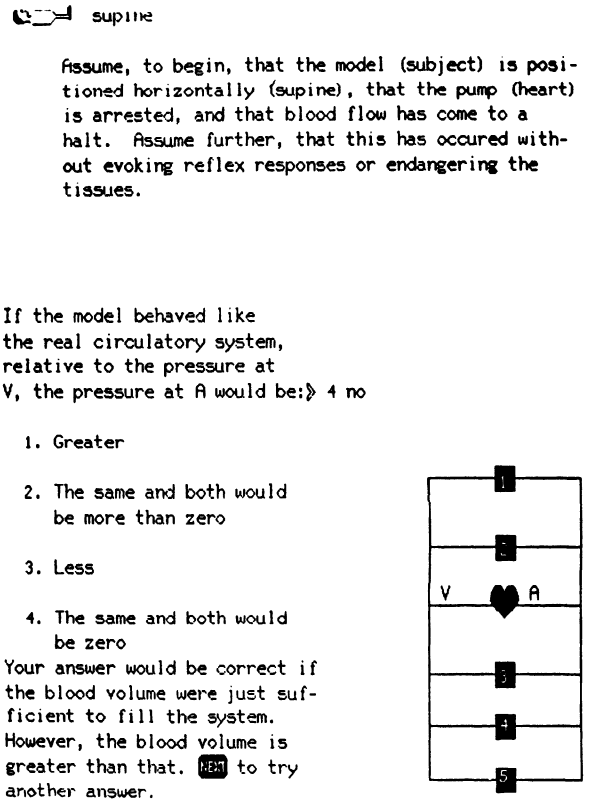

Figure 2
A multiple choice question is illustrated. A hint has been given in response to a student's first incorrect answer.

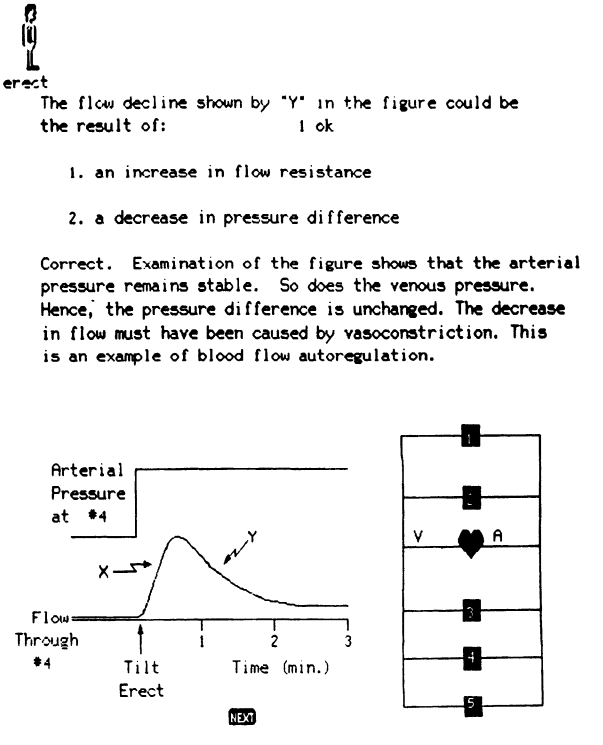

Figure 3
This is an example of a multiple choice question based on a figure. "Subject" has been passively tilted into an erect position. Arterial pressure and the flow in circuit #4 are shown. (The problem assumes that no reflexes are present.) The question is exploring the phenomenon at X.

appear to come from a helpful and knowledgable teacher and should try to establish a bond between the student and the program. They should also make the lesson a worthwhile learning experience, something that gives students a good return for the time spent. To do this responses should ideally *1*) state whether the student's answer is right or wrong, *2*) indicate what is right or wrong, and *3*) contain an additional message or information to reinforce correct answers or to correct wrong ones. Although inclusion of all three elements is the ideal way to formulate responses, not all questions warrant such expansive replies.

It is important to emphasize that one of the greatest benefits of computer-based lessons is that they provide immediate feedback. Thus, they can rapidly correct the students' knowledge and thinking processes when they are wrong and reinforce correctness. Therefore, it is essential that the program's replies be as unambiguous and effective as possible.

Individualization of Lessons

Computer lessons are individualized to each student's knowledge and skill because *1*) each student can complete a lesson at his own pace, *2*) the responses that are given depend on a student's input, and *3*) the direction of steps within the lesson is governed by the correctness of the students' answers.

Consider how one might react to an incorrect answer. The simplest response is to state the correct answer. For example, it is pointless to try to extract a specific fact or a numerical value from a student who does not know it. However, when a question deals with an important issue, a hint may be given, the underlying relationship or the governing equation may be stated, or some other form of guidance may be provided to jog the student's memory or to help the student to reason to a correct answer (Figure 2). Then the student should be given another chance to answer the question. Now if the answer is correct, the response to a correct answer should follow.

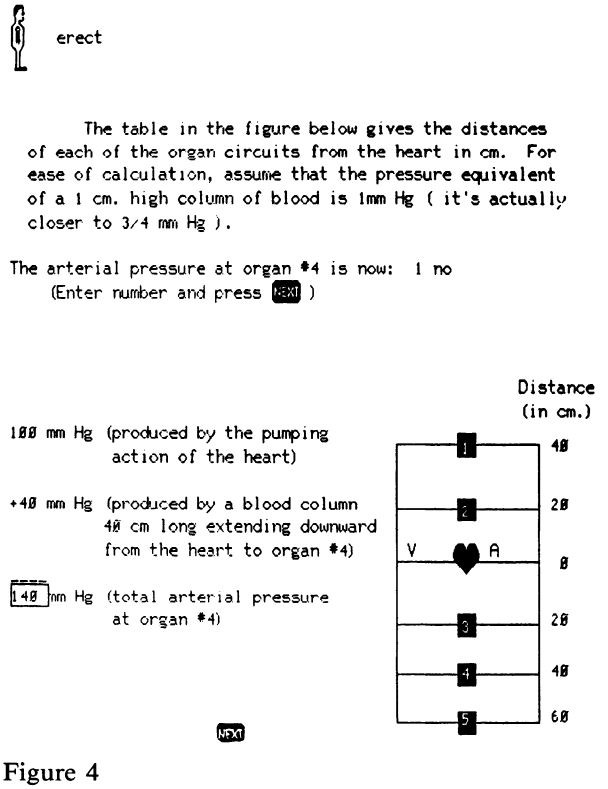

Figure 4
A question requiring a definite numerical answer to be calculated using values in the graphic circulation model is illustrated. Student previously answered incorrectly and had been given a hint. This second incorrect answer has elicited a response which shows the student how to do the required calculation.

However, if the answer is still wrong there are several possible directions that the lesson may take: *1*) state the correct answer or, in case of a numerical question, show how to do the calculation (Fig. 4); *2*) branch to a remedial lesson; or *3*) have the student stop doing the lesson. Which option is selected depends on the circumstances. If the question deals with material that is central to the lesson, the student's deficiency may prevent him from successfully completing the lesson or at the least will frustrate him if he tries to proceed. This is not likely to be a positive educational experience. It would be better to advise him what to study and then have him try the lesson again. If it seems that the student's difficulties can be corrected by a remedial lesson, suggest that the student try one before returning to the main lesson. In any case, the student should be given the correct answer or shown how to do the required calculation after he has made no more than two unsuccessful attempts at answering; it is unproductive and discouraging to ask more than that.

However, after the correct answer has been given one still has options: *1*) the student may be allowed to continue the lesson; *2*) another equivalent question may be posed, and the student should now be able to answer correctly. If he can, one may be confident that he has overcome his original difficulty. If he cannot, one must again decide what to do. This decision-making scheme is illustrated in Figure 5.

What does one do for the student who answers correctly? He will of course be told that his answer is correct. This, in itself, is positively reinforcing, should build the student's confidence, and probably will please him. Often that is sufficient. However, if some additional information is added to the response, it may help this student *1*) increase his knowledge, *2*) to correlate the lesson's subject with a larger base of information, and *3*) to further improve his problem-solving skill.

Graphics

Computer graphics can add greatly to the effectiveness of a lesson. Graphics enliven the presentation and provide an alternative to text as a means of providing information. For example, there are several postural changes in the lesson that has been used to illustrate this discussion (7). The little logo-type man at the top of Figures 2–4 helps the students to keep track of what posture applies in each question.

Graphics increase the flexibility of questioning and responding. They may provide the substrate for asking a question. In Figure 4 the circulatory model provides the basis for calculating the answers. In Figure 3 the "strip-chart recording" is the source of a question. Graphics also provide a way to illustrate an effect, supplement a response, summarize a part of a lesson, or emphasize a relationship.

Screen Design

In what form and where are things to be put on the screen? Generally, questions are centrally placed and prompts are put on the bottom. This is not a hard and

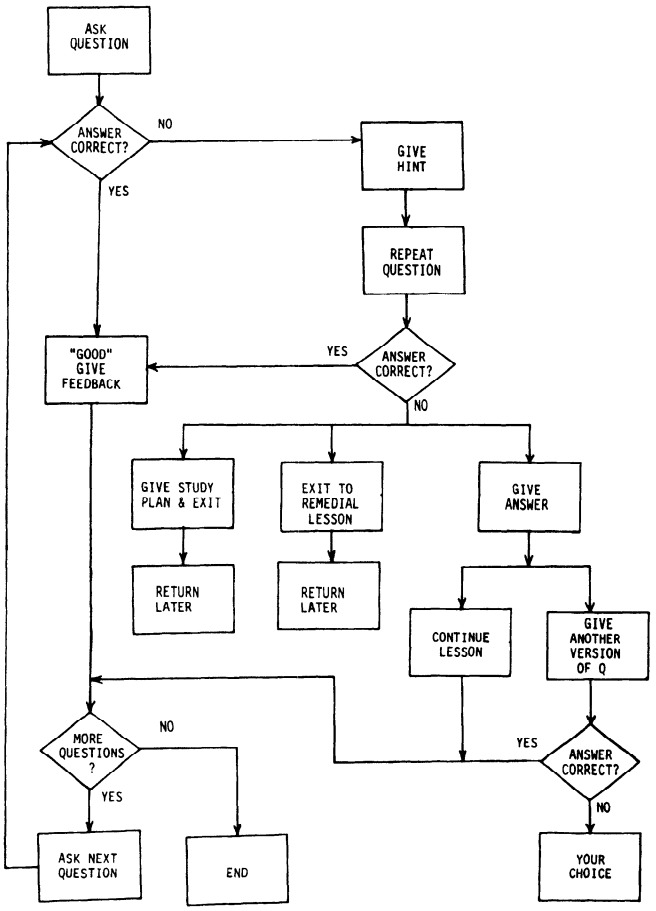

Figure 5
A schematic representation of a question-response algorithm.

fast rule; but where one puts things may be important. If some type of material appears in a particular location at one time it is useful to try to put it there throughout the lesson. There is no reason why discovering where to look should be part of the objectives of the lesson.

Not only will the screen contain a question and prompts, but the student's answer will appear, as will the response to that answer. Having a lot of things on the screen at one time can create confusion. One way to avoid screen clutter is to erase some things before entering others. However, one does not want to erase something that the student may find necessary or useful, such as the question itself or a value which may be needed in a chained sequence of questions.

Long waits for making erasures or entries can break the student's concentration, create boredom, and produce disinterest. Also, during computer processing, which is invisible to the user, it is important that the student knows that something is happening. Put a message on the screen during these periods.

Flow of the Lesson

Although the general flow of a lesson is from start to end, there are often reasons to change direction or to stop. Suppose a student cannot finish a lesson at one sitting. When he returns to complete it at another time, he should be able to skip what he has already done. The simplest way to do this is to allow students to select any point in the lesson index as a starting point (bottom of Figure 1). One may also allow the user to return to the index at the end of each section of the lesson. This would permit a student to review something he feels unsure of. If the sequences of the lesson are tightly connected and interdependent, a student may also benefit from being able to go back a step or two to review.

In areas that are particularly difficult for students, it is useful to provide a HELP routine. This is an extra part of the program, a loop, which the student may enter by pressing a designated key. It may provide explanations, examples, or other experiences to assist the student who is having trouble. When completed, the routine should return the student to the main lesson.

Conclusion

Writing lessons is not hard. It is like being alone with a student in a one-on-one tutorial. The computer lesson is your substitute. It must ask what you would ask, when you would ask it; and it must reply what and when you would. You can use this teaching system to encourage, stimulate, and challenge your students.

I do not want to put a damper on the desire to produce computer lessons, but it is important to add this final note. It takes time to write and polish a computer lesson. According to a report to the US Congress (4), it takes between 40 and 150 hours to prepare a 1-hour lesson (not counting the programming). So do not get into it if you are not willing to make the commitment. A bad computer lesson is worth no more than a bad lecture. Computer lessons, good or bad, demand student attention. It behooves the writer to make it worth the student's time and effort. The payoff, however, is that the lesson may be used by many students in many classes for several years.

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Computer-Based Educational Materials in Physiology

During the past 2 years, the Education Committee has attempted to establish a database catalog of computer-based educational (CBE) materials in Physiology. This effort has been delayed due to a number of unforeseen factors. The project was reviewed at the last meeting of the Committee, and it was apparent that, to best serve the APS membership and facilitate communication among APS members interested in CBE materials, more information is necessary concerning authors and users. The accompanying questionnaire is presented to readers of *The Physiologist* in an attempt to gather the necessary information. If you are an author of or use CBE materials in your teaching or if you are interested in using the computer as an instructional tool, please complete and return the questionnaire.

Questionnaire
Computer Software for Teaching Physiology
APS Education Committee, 1985

Return to: Harold Modell, Ph.D.
Virginia Mason Research Center
1000 Seneca St.
Seattle, WA 98101

Name: _____

Address: _____

_____ State _____ Zip _____

Please fill in appropriate blanks:

Are you an author ☐, user ☐, vendor ☐ of CBE material, or interested only ☐?

How long have you used CBE material? _____ years

		Auth.	Used		Auth.	Used
Type of programs authored or used:	Lessons	☐	☐	Lecture/demo	☐	☐
	Simulation	☐	☐	Other _____	☐	☐

Does documentation exist? ☐ Yes ☐ No ☐ Not necessary

Specialties covered by programs that you have authored.

- ☐ Cardiovascular
- ☐ Cell & Gen. Physiol.
- ☐ Comparative Physiol.
- ☐ Endocrine & Metab.
- ☐ Environ. Therm. Exercise
- ☐ Epithelial Transport
- ☐ Gastrointestinal
- ☐ Muscle
- ☐ Nervous System
- ☐ Control & ANS
- ☐ Respiratory
- ☐ Renal
- ☐ Water & Electrolyte
- ☐ Other _____

Student population served by programs you are using:

Level	No. of Students
☐ Undergraduate	_____
☐ Graduate	_____
☐ Medical	_____
☐ Allied Health/Dental	_____
☐ Other _____	_____

Equipment used:

	Manufacturer/model
☐ Mainframe/mini	_____
☐ Microcomputer	_____

Are you willing to:

- ☐ Sell program(s)
- ☐ Share (at cost of reproduction)
- ☐ Review CBE products

Comments: _____

_____

_____

Hormonal and Local Regulation of Bone Formation

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Bone formation is a process regulated by hormones, systemic growth factors, and local bone growth factors. These agents have complex, direct and indirect, effects on bone, and our understanding of bone formation is still incomplete. This is due to discrepancies between the in vitro or direct effects of hormones and their in vivo effects, which may be mediated by indirect mechanisms, and to difficulties in developing models to study bone formation in vivo and in vitro. Although bone formation is difficult to quantitate in vitro, a series of models has been developed to study the effects of agents on this process. Methods have been developed to study the synthesis of DNA and collagen in cultured bones in order to examine effects on bone cell replication and matrix formation. These methods have allowed the study of the direct effects of hormones on these two important parameters of bone growth. The synthesis of bone collagen, a major component of bone matrix, appears to be the initial and probably the most important step in the synthesis of bone matrix, and like DNA synthesis, it is regulated by various hormones and growth factors. In addition to collagen, bone contains a series of noncollagenous proteins that may be involved in the process of bone formation and bone mineralization, but this has not as yet been determined.

To study the direct effects of hormones and growth factors on bone DNA and collagen synthesis, a series of in vitro models has been developed. The goal of most investigators has been to obtain methods to examine effects on osteoblastic function, since the osteoblast is the cell responsible for bone matrix synthesis. Ideally, this would be accomplished by studying cultures of pure osteoblastic normal cell lines. While some investigators have used osteosarcoma cell lines with osteoblastic properties, nobody has as yet obtained a pure normal osteoblastic cell line. The advantage of using osteosarcoma cell lines is the use of a single cell population; but the disadvantage is that this model uses malignant as opposed to normal cells. Investigators using normal bones have developed methods to study either cultures of intact bone or cultures of isolated enriched osteoblastic bone cell populations. The organ culture model is appealing because the bone anatomy is not disrupted, but inasmuch as intact bones contain a mixed cell population, a tested agent may affect the osteoblast as well as other cells. To circumvent this problem, methods have been developed to analyze functions attributed to the osteoblast such as the synthesis of type I collagen and alkaline phosphatase. Osteoblasts are believed to synthesize exclusively type I collagen, whereas fibroblasts, the other collagen-synthesizing cells in intact bone, manufacture a mixture of type III and type I collagen. Cultured calvariae synthesize almost exclusively type I collagen, indicating that this is an appropriate model to study the effects of various hormones and growth factors on osteoblastic function. To study effects on the osteoblast, other investigators remove the periosteum and enrich the nonperiosteal osteoblastic cell population by a series of enzymatic digestions. Although many investigators favor the study of pure osteoblastic lines, it is possible that nonosteoblastic periosteal cells have an important role in the regulation of bone formation. This could be related to the presence of preosteoblastic cells present in the periosteum or related to some function of fibroblasts present in this cellular layer.

The agents known to affect bone formation can be classified as hormones, systemic growth factors, and local growth factors. Although the regulation of bone formation depends on the concerted action of multiple hormones and factors, only insulin and the somatomedins have been found to stimulate bone collagen synthesis, indicating that they are among the most impor-

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CME Category I Credits

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tant regulators of bone formation. The systemic growth factors have primarily mitogenic activity, but, in essence, they have not been found to stimulate bone collagen synthesis. Finally, there is now evidence indicating the existence of important local growth factors which are released and probably synthesized by bone and which regulate bone collagen and DNA synthesis. These factors may also be important to couple bone formation to bone resorption and might mediate the effect of systemic agents.

This article reviews our current knowledge on the effects of hormones as well as systemic and local growth factors on bone formation with emphasis on their direct or in vitro effects on bone collagen and DNA synthesis.

Effect of Hormones on Bone Formation

The hormones known to have an effect on bone formation are parathyroid hormone, vitamin D metabolites, glucocorticoids, sex steroids, thyroid hormones, insulin, growth hormone, and somatomedin.

Parathyroid Hormone

The effects of parathyroid hormone on bone formation are complex and poorly defined. Parathyroid hormone has a direct inhibitory effect on bone formation, but in vivo studies have indicated a stimulatory effect. This effect is probably indirect, and it might be in response to the stimulatory effect of parathyroid hormone on bone resorption, since parathyroid hormone enhances the release of growth factors that presumably couple bone formation to bone resorption. Since in vivo studies have indicated a stimulatory effect of parathyroid hormone on bone formation, some investigators have used it to treat patients with osteoporosis. However, patients with hyperparathyroidism develop osteoporosis, and the use of parathyroid hormone in osteoporosis may not be prudent. It is possible that the stimulatory effect of parathyroid hormone on bone resorption predominates, and this would result in decreased bone mass in hyperparathyroid patients.

In vitro, parathyroid hormone has been demonstrated to inhibit bone collagen synthesis in cultured rat and mouse calvariae. The effect of parathyroid hormone is specific for bone collagen, since it does not affect noncollagen protein synthesis. Parathyroid hormone probably inhibits osteoblastic bone collagen synthesis, since the osteoblast has specific receptors for parathyroid hormone, the collagen inhibited is type I, and the effect on bone collagen is primarily observed in the nonperiosteal osteoblastic-rich bone. The direct effect of parathyroid hormone on alkaline phosphatase activity is controversial, but we have found an inhibitory effect that correlates with the inhibition of bone collagen synthesis. In addition to the inhibitory effect on bone collagen synthesis, parathyroid hormone has a small stimulatory effect on bone DNA synthesis. This effect is observed primarily in the periosteum, which is rich in fibroblasts and precursor cells, and it is probably not an osteoblastic effect. The mechanism of action of the effects of parathyroid hormone on bone formation has not been established but could be mediated by adenosine 3',5'-cyclic monophosphate. Although parathyroid hormone inhibits bone formation in vitro, it has a direct stimulatory effect on cartilage formation that may alter the in vivo effects of parathyroid hormone in bone.

The role of parathyroid hormone in bone mineralization is uncertain. Parathyroid hormone may have a positive effect on bone mineralization by increasing the intestinal absorption of calcium, an effect mediated by 1,25-dihydroxyvitamin D_3. In addition, the effect of parathyroid hormone on bone resorption results in the release of calcium from bone, making it available for new bone mineralization. Parathyroid hormone and vitamin D also have direct synergistic effects on bone mineralization.

In contrast to the effect of parathyroid hormone on bone formation, calcitonin does not have direct or indirect effects on this process, and its main effect on bone is an inhibition of bone resorption. In addition, at high doses this hormone has been found to block intestinal absorption of calcium and phosphorus and this may affect bone mineralization. However, these effects were observed only at high hormonal doses.

Vitamin D

Vitamin D_3 is a hormone with known effects on bone and mineral metabolism that requires a series of changes to become biologically active. Vitamin D_3 is first transported to the liver where it is hydroxylated at the 25 position and is converted into 25-hydroxyvitamin D_3, which is transported to the kidney where it is hydroxylated at the 1 or at the 24 position, forming either 1, 25-dihydroxyvitamin D_3 or 24, 25-dihydroxyvitamin D_3. Although vitamin D is converted to other metabolites, 1,25- and 24,25-dihydroxyvitamin D_3 appear to be the most important regulators of bone formation. In addition, recent investigations have shown that bone can metabolize 25-hydroxyvitamin D_3 to either 1,25- or 24,25-dihydroxyvitamin D_3, suggesting that there may be local bone regulatory mechanisms for the metabolism and activation of vitamin D.

1,25-Dihydroxyvitamin D_3 is the most active metabolite of vitamin D, and although it may seem paradoxical, its effects are quite similar to the effects of parathyroid hormone on bone. In vivo, 1,25-dihydroxyvitamin D_3 is important to maintain normal serum calcium and to mineralize bone. This is accomplished by its effects on intestinal calcium absorption, an effect mediated by a calcium binding protein. In addition, 1,25-dihydroxyvitamin D_3 stimulates bone resorption, making calcium available to the serum and to the bone for mineralization. Therefore, patients who lack 1,25-dihydroxyvitamin D_3 may develop hypocalcemia and osteomalacia. 24,25-Dihydroxyvitamin D_3 has been considered essential for normal bone formation and mineralization by some investigators, but these studies are controversial. In contrast with their in vivo effects on bone formation, vitamin D metabolites do not stimulate bone formation in vitro, suggesting that if they stimulate bone formation in vivo, this is an indirect effect. 1,25-Dihydroxyvitamin D_3 binds to bone cytosol, and it inhibits bone collagen synthesis. This effect appears to be osteoblastic, since the collagen inhibited is type I and the effect is primarily observed in the nonperiosteal osteoblastic-rich bone. The direct effect of 1,25-dihydroxyvitamin D_3 on bone alkaline phosphatase is controversial, and this vitamin D metabolite appears to have a dual, stimulatory and inhibitory, effect on alkaline phosphatase activity, related to the time of exposure or dose of 1,25-dihydroxyvitamin D_3 used. Results from our laboratory, using fetal rat calvariae, have demonstrated that 1,25-dihydroxyvitamin

D_3 inhibits both type I collagen synthesis and alkaline phosphatase activity, and the two effects correlated well.

Additional effects of vitamin D are of unclear physiological importance at the present time. Vitamin D has been found to stimulate the synthesis of bone GLA protein or osteocalcin, which is a noncollagenous protein that may be important in bone mineralization.

Glucocorticoids

Glucocorticoids have marked in vivo effects on bone and mineral metabolism, and patients with glucocorticoid excess are known to develop osteoporosis. This has been attributed to increased bone resorption and decreased bone formation. The stimulatory effect on bone resorption is indirect and is probably the result of increased parathyroid hormone release, which is secondary to a decrease in the gastrointestinal absorption of calcium. This results in decreased serum calcium with a subsequent increase in parathyroid hormone release. The glucocorticoid-induced bone resorption could also be mediated by vitamin D_3, since glucocorticoids preserve the bone cytosol binding of 1,25-dihydroxyvitamin D_3 to bone. In contrast to this in vivo effect, the direct effect of glucocorticoids on bone resorption is inhibitory, and this effect has formed the basis for the use of glucocorticoids in the treatment of hypercalcemia.

While in vivo glucocorticoids decrease bone formation, their direct in vitro effects are quite complex. After short-term treatment they stimulate bone collagen synthesis and alkaline phosphatase activity, whereas after long-term exposure the effect of glucocorticoids is inhibitory. The short-term stimulator effect is observed at physiological concentrations, and it is an effect on osteoblastic differentiation. This effect is not limited to bone tissue, since glucocorticoids have a permissive effect on various aspects of tissue growth in a variety of nonskeletal tissues. The glucocorticoid stimulatory effect of bone collagen synthesis may be mediated by a bone-derived growth factor with somatomedin-like properties, since glucocorticoids enhance the effect of bone-derived factors and of the somatomedins on collagen synthesis. It is possible that glucocorticoids act by increasing the number of bone receptors for bone-derived growth factors, an effect recently demonstrated for somatomedin, or by other unknown mechanisms. In addition to this interaction with somatomedin at the bone level, glucocorticoids are necessary for the release of somatomedin by the liver, suggesting that, in vivo, the somatomedin-glucocorticoid interactions are important at a multitude of levels.

In contrast to the short-term stimulatory effects of glucocorticoids, the long-term direct effects on bone formation are inhibitory. After 48–96 h of exposure to glucocorticoids, bone collagen synthesis and alkaline phosphatase activity in bone are both decreased. These effects are secondary to a marked decrease in cell replication, which is an effect primarily observed in the periosteal preosteoblastic cells. Therefore, the long-term inhibitory effect of glucocorticoids is secondary to a depletion of osteoblastic cells due to an inhibition of preosteoblastic cell replication.

Sex Steroids

Estrogens and androgens are considered important in the skeletal maturation of growing individuals and in the prevention of the bone loss associated with aging. Bone does not have receptors for sex steroids; therefore, their effects are indirect and mediated by other hormones or mechanisms. There are a number of studies indicating that sex steroids prevent bone loss in vivo by decreasing bone resorption. However, they have not been shown to have a direct inhibitory effect on bone resorption in vitro. Although in vivo sex steroids inhibit bone resorption and prevent bone loss, their effects on bone formation are controversial and most studies indicate that they do not stimulate this process. In addition, in vitro studies have shown that neither estrogens nor androgens affect bone collagen synthesis. Recently, estrogens have been found to increase serum parathyroid hormone and 1,25-dihydroxyvitamin D_3 concentrations, suggesting that they may be important in bone mineralization. In summary, sex steroids prevent bone loss and may have an affect on bone mineralization. However, they do not have a stimulatory effect on bone formation either in vivo or in vitro, and one should not expect restoration of the bone mass lost in osteoporotic patients treated with sex steroids.

Thyroid Hormones

Thyroid hormones are necessary for normal growth and development. However, their effects on bone formation are not well established and appear to be indirect. Thyroid hormones are required for the synthesis of somatomedin by the liver, stimulate cartilage growth, and are synergistic with the stimulatory effect of somatomedin on cartilage growth. This suggests that their in vivo effects on bone and cartilage growth are in part mediated by somatomedin. In vitro, thyroid hormones have not been found to stimulate either bone collagen or noncollagen protein synthesis or cell replication, confirming that their in vivo effects are indirect.

Patients with hyperthyroidism occasionally develop hypercalcemia or osteoporosis. These effects are secondary to a direct stimulatory effect of thyroid hormones on bone resorption. It is possible that thyroid hormones stimulate bone formation in response to their effects on bone resorption, but this mechanism has not been demonstrated.

Insulin

Among the hormones, insulin and the somatomedins are the major stimulators of bone matrix synthesis. Insulin stimulates bone and cartilage growth. These effects are observed in vitro and in vivo and they are both direct and indirect. Patients with untreated diabetes mellitus have impaired growth and probably have a higher incidence of osteoporosis. Further, animals with experimental diabetes also have impaired bone and cartilage growth and decreased bone mineralization.

Some of the in vivo effects of insulin on bone formation are mediated by somatomedin, since insulin is important in the regulation of somatomedin release by the liver. In addition, insulin has direct stimulatory effects on cartilage and bone growth. The insulin receptor has not been studied in bone, but work in cartilage tissue has shown that part of the insulin effect is mediated by a somatomedin receptor, although cartilage also has specific insulin receptors. In bone, insulin stimulates amino acid transport, RNA, collagen, and noncollagen protein synthesis. The effect on collagen synthesis is a direct effect on the osteoblast, since the collagen synthe-

sized is type I; the effect is observed in nonperiosteal osteoblastic-rich bone; and it correlates with an effect on alkaline phosphatase activity. The effect of insulin on bone collagen is similar to the effect of somatomedin, but somatomedin also stimulates DNA synthesis, an effect observed only at high insulin doses suggesting that it is mediated by the somatomedin receptor.

In addition to its stimulatory effect on bone matrix synthesis, insulin may be required for normal bone mineralization. This effect has been observed primarily in experimental animals and not in humans. Since insulin is necessary for the synthesis of 1,25-dihydroxyvitamin D_3, its effect on bone mineralization is probably mediated by this vitamin D metabolite.

Growth Hormone and Somatomedin

Growth hormone, one of the major regulators of growth, has no direct effects on either bone or cartilage formation, and its effects on growth are mediated by somatomedin. In vivo, growth hormone stimulates bone formation, the intestinal absorption of calcium, and bone mineralization, causing an increase in skeletal mass; however, in vitro, it has no stimulatory effect on bone matrix synthesis.

The active core of growth hormone, a peptide with molecular weight of 21,000, is unknown, although structural modifications of the hormone may be necessary to achieve full biological activity. Proteolytic cleavage of the hormone has been shown to increase its in vivo effects, suggesting the need for structural changes to activate the hormone. In addition, cleaved growth hormone and fragments obtained from the parent molecule have been found to have direct growth-promoting activity on cartilage cultures. This would suggest that modified growth hormone and its fragments may be direct regulators of cartilage growth that do not require the synthesis of somatomedin to express their biological activity. Contrary to their effects on cartilage, neither intact nor modified growth hormone stimulated calvarial collagen synthesis, confirming that the stimulatory effect of growth hormone on bone matrix is mediated by indirect mechanisms, most likely somatomedin.

Prolactin has also been implicated in the regulation of growth, but it does not have a direct effect on bone collagen or noncollagen protein synthesis in cultured bones. Prolactin has been found to stimulate the transport of calcium in the intestine, indicating that it may have a role in bone mineralization. Patients with prolactin-producing tumors develop osteopenia, but this is probably related to inhibition of gonadotropins resulting in estrogen deficiency in these patients.

The somatomedins, a family of insulin-like peptides, have growth-promoting activity on a variety of tissues and are believed to mediate the effects of growth hormone on skeletal growth. They are known to have direct growth-promoting activity on bone and cartilage and are essential to establish normal linear growth. Since the available amount of the various somatomedins has been quite limited, most of the studies performed have investigated their in vitro but not their in vivo effects. Although there is considerable confusion about the classification of somatomedins, the two most important ones appear to be insulin-like growth factor I, which is identical to somatomedin C, and insulin-like growth factor II, which is closely related to multiplication stimulating activity. Insulin-like growth factor I is a single-chain peptide, with a molecular weight of 7,600, that is clearly growth hormone dependent and is the most important somatomedin in postnatal life. Multiplication stimulating activity is a peptide obtained from cultures of liver cell lines and of fibroblasts, which is probably the most important somatomedin in fetal life and its synthesis is regulated by placental lactogen.

In vitro studies have shown that insulin-like growth factors I and II are potent stimulators of collagen, noncollagen protein synthesis, and cell replication in cultured bones. These effects were observed at similar concentrations to those required to stimulate cell proliferation and proteoglycan synthesis in cartilage. The stimulatory effect of insulin-like growth factor I on bone DNA synthesis is observed in both the periosteal and nonperiosteal cell population, suggesting effects on fibroblasts, progenitor cells, and osteoblasts. In contrast, the effect on collagen synthesis is selective to the nonperiosteal osteoblastic-rich cell population. This indicates that collagen synthesis is specific for the osteoblast, although this could be secondary to an increased number of cells.

Although insulin primarily stimulates collagen synthesis and not DNA synthesis, the effects of insulin and the somatomedins are similar. This is, in part, due to similarities in the chemical structure of the hormones and in their tissue receptors.

While the somatomedins are important stimulators of bone formation, they have not as yet been found to have an effect on bone resorption or bone mineralization.

Effect of Systemic Growth Factors on Bone Formation

Recently, a number of growth factors has been isolated from serum as well as from a variety of tissues. Some of these factors are somatomedins and are probable regulators of growth, whereas others have primarily mitogenic activity and their physiological role has not been established. Three of these factors, with primarily mitogenic activity, have been studied for their effects on bone formation in vitro. These factors are fibroblast growth factor, epidermal growth factor, and platelet-derived growth factor. The effect of these factors on bone formation in vivo has not as yet been examined.

Fibroblast growth factor is a peptide isolated from bovine pituitary glands that stimulates cell replication in a number of mesodermal tissues including cartilage and bone. The effects of fibroblast growth factor in bone and cartilage cultures are similar. Fibroblast growth factor stimulates cell replication in these tissues, but it inhibits collagen synthesis in bone and proteoglycan synthesis in cartilage. Fibroblast growth factor also has a small stimulatory effect on bone resorption, but it has not been reported to have an effect on bone mineralization.

Epidermal growth factor is a single-chain peptide, with an approximate molecular weight of 6,000, that has been isolated from mouse submaxillary glands. Epidermal growth factor is probably identical to urogastrone. Epidermal growth factor has growth stimulatory activity on various ectoderm-, endoderm-, and mesoderm-derived tissues including cartilage and bone. The effects of epidermal growth factor on bone tissue are similar to the effects of fibroblast growth factor. However, epidermal growth factor is about 100 times more

potent in its stimulatory effect of bone cell replication and its inhibitory effect of bone collagen synthesis. The effect of epidermal growth factor on bone cell replication is primarily observed in the periosteal layers rich in progenitor preosteoblastic cells and fibroblasts. The inhibitory effect of epidermal and fibroblast growth factor on bone collagen synthesis is probably an effect on the osteoblast, since both factors inhibit type I collagen synthesis and alkaline phosphatase activity. The inhibition of collagen synthesis might be related to the concomitant stimulatory effect of these factors on cell replication, since cells, during periods of active replication, may not synthesize collagen. However, the inhibitory effect of epidermal growth factor on bone collagen synthesis was observed in the presence of DNA synthesis blockers. This would suggest that the inhibition of bone collagen synthesis by these growth factors is independent of their stimulatory effect on bone cell replication. In addition to its effects on bone formation, epidermal growth factor has a direct stimulatory effect on bone resorption that appears to be mediated by an increase in prostaglandin synthesis. In contrast, the effect on bone formation does not appear to be related to prostaglandin synthesis. It is unknown whether or not epidermal growth factor has a role in bone mineralization.

Platelet-derived growth factor is a peptide isolated from human platelets that stimulates DNA synthesis in a variety of tissues and cell systems and stimulates collagen and noncollagen protein synthesis in arterial smooth muscle cells. Platelet-derived growth factor was recently studied for its effects on bone formation in vitro, and it was found to stimulate cell replication. In addition, platelet-derived growth factor stimulated noncollagen protein synthesis but had only a small stimulatory effect on collagen synthesis. The stimulatory effect of platelet-derived growth factor on bone DNA synthesis was generalized and affected periosteal as well as nonperiosteal cells. The effects of platelet-derived growth factor are somewhat different from those of fibroblast growth factor and epidermal growth factor, since platelet-derived growth factor stimulates DNA synthesis but also has a nonspecific stimulatory effect on protein synthesis. Platelet-derived growth factor is released by platelets, and it may have a role in the acute healing of bone fractures. Cortisol enhances the stimulatory effect of platelet-derived growth factor on bone DNA synthesis and the effect of insulin-like growth factor on bone collagen synthesis. Thus the cortisol released during periods of stress, platelet-derived growth factor, and insulin-like growth factor may be important in the initiation of the bone healing process after a fracture. Platelet-derived growth factor also stimulates bone resorption, and as with epidermal growth factor, this effect is mediated by prostaglandins. The effect of platelet-derived growth factor on bone mineralization is unknown.

Although these systemic growth factors have powerful mitogenic activity for bone in vitro, their in vivo effects and their physiological role have not been determined. It is possible that they are important in the pathogenesis of bone disease, but this has not been determined.

Other systemic hormones and growth factors may have effects on growth and calcium metabolism, but their effects on bone formation have not been elucidated. Vasopressin and catecholamines are examples of these hormones. Relaxin, an insulin-related factor, was recently tested for its direct effects on bone formation but was found to have no effect. Osteoclast-activating factor, has been shown to be released by T-lymphocytes, myeloma, and other malignant cells and found to be responsible for the increased bone resorption observed in patients with tumors. Although osteoclast-activating factor stimulates bone resorption, it inhibits bone collagen synthesis. Therefore, it may be responsible not only for the hypercalcemia of some types of malignancy but also for the osteoporosis seen in these patients. It is unknown whether osteoclast-activating factor has a role in the physiological regulation of bone remodeling.

Local Regulators of Bone Formation

For the purpose of this review, local regulators of tissue growth are factors that stimulate the growth of the tissue where they are synthesized. These factors have been found both in skeletal and nonskeletal tissues and may be linked to another group of factors closely related to epidermal growth factor and have been isolated from neoplastic and normal tissues. These factors, also known as transforming growth factors, are powerful stimulators of cell growth and are believed to be important in the regulation of normal and tumor growth.

Skeletal tissue has been shown to release a number of growth factors. Fetal rat calvariae, embryonic chick bones, and human bone contain and release growth factors and cartilage contains a somatomedin-like peptide. These recently discovered factors may have a role in the local regulation of bone growth and may be important in linking bone resorption to bone formation during skeletal remodeling. Fetal rat calvariae, as well as embryonic chick bones, have been found to contain and release stimulators and inhibitors of bone growth. Embryonic chick bones were shown to contain two peptides, one of small molecular weight, which inhibits bone DNA synthesis, and another of higher molecular weight, which stimulates bone DNA and collagen synthesis. The release of the factor with stimulatory activity was enhanced by parathyroid hormone, and this led the investigators to suggest that it may be important in the coupling of bone formation to bone resorption. A similar growth factor isolated from human bone was found to stimulate the proliferation of bone cells in culture and was named skeletal growth factor.

Studies performed in our laboratory have shown that cultured fetal rat calvariae release, to the culture medium, factors which stimulate bone DNA, collagen, and noncollagen protein synthesis. This culture medium, conditioned by the calvariae, was dialyzed, lyophilized, and purified by gel filtration chromatography. We found two growth factors, one with an apparent molecular weight of about 10,000, which showed maximal stimulatory activity on bone collagen synthesis, and another, with apparent molecular weight of 25,000 to 30,000, which showed maximal stimulatory activity of bone DNA synthesis. The material, with molecular weight of 10,000, contains significant somatomedin by bioassay, radioreceptor, and radioimmunoassay, suggesting a close relationship to the somatomedins. Similar to the somatomedins, the effect of this factor on bone collagen synthesis was greatly enhanced in the presence of cortisol. The factor, with a molecular weight of 25,000–30,000, stimulated mostly bone DNA synthesis and was less effective on bone protein synthesis, resembling the

effects of platelet-derived growth factor. In addition, human osteosarcoma cell lines also release a peptide, with a molecular weight of 30,000, that is closely related to platelet-derived growth factor. Thus it appears that cultured fetal rat calvariae released somatomedin-like as well as platelet-derived growth factor-like materials. These factors appear to have important effects on the local regulation of collagen and DNA synthesis in fetal rat calvariae, but their role in adult and human bone growth and their role in disease remain to be established. Recent purification schemes carried out in our laboratory have suggested the presence of additional factors released by fetal rat calvariae. It therefore appears that bone releases several factors capable of stimulating bone formation in vitro.

Cartilage is also known to contain and release a peptide with somatomedin-like properties. This peptide has been named cartilage-derived factor and had been isolated from either cartilage tissue or conditioned medium of cultured chondrocytes. The molecular weight of this peptide is ~10,000. Cartilage-derived factor appears to be a local regulator of cartilage growth, since it stimulates cell replication and proteoglycan synthesis in cartilage cultures. In addition, cartilage-derived factor was recently found to stimulate bone DNA, collagen, and noncollagen protein synthesis in cultured bones. These studies indicate that cartilage-derived factor is a local regulator of skeletal growth and that it may be important in the control of bone formation. Cartilage-derived factor may also be closely related to one of the bone-derived growth factors isolated from fetal rat calvariae, but this has not as yet been determined.

A number of bone specific noncollagenous proteins has been isolated from fetal calf bone, but their role in the process of bone formation is still not known. One of these proteins, osteonectin, has a molecular weight of 32,000 and has been found to bind to bone collagen, and the resulting complex binds to hydroxyapatite crystals. Therefore, it has been proposed that osteonectin is important to initiate mineral deposition on the bone matrix. In preliminary experiments, we have found that osteonectin stimulates bone collagen synthesis and alkaline phosphatase activity in cultured bones. Osteonectin did not have an effect on bone DNA synthesis. Bone also synthesizes a smaller noncollagenous protein that contains the vitamin K-dependent amino acid, carboxyglutamic acid. This protein has been named bone GLA protein or osteocalcin, and its appearance in the developing bone depends on the prior deposition of mineral. Osteocalcin binds to hydroxyapatite and inhibits crystallization, also indicating a possible role in mineralization. The effects of osteocalcin on bone formation have not been fully studied. However, preliminary experiments from our laboratory have shown that osteocalcin does not have a clear stimulatory or inhibitory effect on bone formation. The effects of osteonectin and osteocalcin on crystallization may suggest that they may be important in the local regulation of bone mineralization.

Chemotactic factors may also affect bone remodeling, but their physiological role in the regulation of bone formation has not been explored. Recent studies have indicated that collagen and collagen-derived peptides are chemotactic for fibroblasts. Further, material released from bone, possibly related to collagen fragments, was found to be chemotactic for tumor cells. The effect of these substances on bone formation has not been studied.

Cultured bones and osteosarcoma cell lines release protaglandins, indicating that they may be important as local regulators of bone formation. Prostaglandins are potent stimulators of bone resorption, and tumor extracts have been shown to stimulate prostaglandin synthesis by bone. While prostaglandins mediate bone resorption and the resulting hypercalcemia observed in some patients with malignant tumors, their role in the regulation of bone formation has not been fully established. At high concentration, they inhibit bone collagen and noncollagen protein synthesis, but at low doses they appear to be stimulatory.

In addition to local regulators of bone formation, studies from several laboratories have demonstrated that subcutaneous injections of demineralized bone matrix result in new endochondral bone formation. This effect has been attributed to a bone-morphogenetic protein. It is possible that this bone-morphogenetic protein is related to local regulators of bone growth. However, bone-morphogenetic protein has not been examined for its effect on bone formation in vitro or compared with these factors.

In conclusion, bone formation is a complex process regulated by a series of hormonal, systemic, and local growth factors that have direct and indirect effects on bone formation. Their effects on bone matrix synthesis and cell replication appear to be vital to the control of bone formation. Although many hormones have been studied for their direct effects on bone, only insulin and the somatomedins have been found to stimulate bone collagen synthesis. The main calcium regulatory hormones, parathyroid hormone and 1,25-dihydroxyvitamin D_3, inhibit bone formation in vitro. Glucocorticoids have dual, stimulatory and inhibitory, effects that are dose and time dependent, and thyroid hormones and sex steroids do not have direct effects on bone formation. The three systemic growth factors studied, fibroblast, epidermal, and platelet-derived growth factor, are mostly stimulators of bone cell replication, and their physiological role has not been established. Finally, recent investigations, aimed at the study of local regulators of bone, have shown that bone releases stimulators and probably also releases inhibitors of bone growth. These factors may be mediators of systemic hormones and factors and may couple bone formation to bone resorption. The role of these factors in health and disease is suspected to be important, but it has not been as yet established.

Future studies on the mechanism of action of hormones and growth factors as well as further research on local regulators of bone growth are needed to increase our understanding of bone formation.

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Regulation of Bone Formation
Multiple Choice Questions

1. Bone formation is regulated by
   a. hormones
   b. systemic growth factors
   c. local growth factors
   d. all of the above
   e. none of the above

2. Calcitonin
   a. stimulates bone resorption
   b. stimulates bone formation
   c. inhibits bone formation
   d. is part of the routine treatment of osteoporosis
   e. does not have a major effect on bone formation

3. Vitamin D
   a. in vivo, it is necessary for normal bone mineralization
   b. the active metabolite [1,25 $(OH)_2$ D_3] of vitamin D inhibits bone collagen synthesis in vitro
   c. its direct effects on bone are similar to those of parathyroid hormone
   d. all of the above

4. The long-term inhibitory effect of glucocorticoids on bone matrix formation is secondary to
   a. a stimulation of bone resorption
   b. a depletion or inhibition of the bone cell population
   c. an inhibition of the expression of osteoblastic function
   d. a stimulation of 1,25-dihydroxyvitamin D_3 synthesis

5. Estrogens
   a. prevent bone loss in vivo
   b. bind to receptors in the osteoblast
   c. bind to receptors in the osteoclast
   d. stimulate bone resorption in vitro
   e. stimulate bone matrix synthesis in vitro

6. The major hormones known to stimulate bone formation (collagen synthesis) in vitro are
   a. estrogens and androgens
   b. parathyroid hormone and vitamin D
   c. insulin and somatomedin
   d. cortisol and thyroxine
   e. triiodothyronine and calcitonin

7. Untreated diabetic patients probably have decreased bone mass. The main effects of insulin on bone metabolism are
   a. it stimulates bone formation and mineralization
   b. it inhibits bone resorption
   c. it stimulates bone resorption
   d. it has direct effects on intestinal calcium transport
   e. all of the above

8. The somatomedins
   a. are growth hormone-dependent peptides that stimulate bone and cartilage growth
   b. are called insulin-like growth factor because they are powerful hypoglycemic agents
   c. stimulate bone collagen but inhibit bone cell replication
   d. stimulate bone resorption and mineralization
   e. none of the above

9. Epidermal and fibroblast growth factors
   a. are specific stimulators of bone growth
   b. stimulate bone cell replication but inhibit bone collagen synthesis
   c. inhibit bone resorption
   d. stimulate bone collagen synthesis but inhibit bone cell replication

10. Bone is known to synthesize factors which
    a. stimulate bone growth
    b. inhibit bone growth
    c. might mediate the effects of hormones on bone
    d. they are not fully characterized but some of them resemble the somatomedins
    e. all of the above

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Regulation of Energy Balance

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This article on the control of energy balance will deal with the relationships between energy intake and energy expenditure. It will also include a description of the processes involved in storage, mobilization, and utilization of metabolic fuels. Clinical interest in energy balance arises from the clinical disturbances that manifest themselves as obesity, bulimia, anorexia nervosa, and malnutrition. Psychological interest in obesity focuses on the cellular and chemical mechanisms involved in regulation of energy balance. This discussion will deal principally with this latter focus. For other perspectives, the reader is referred to several recent monographs and articles (1–9).

A scheme for approaching the problem of energy balance is shown in Figure 1. Energy-containing compounds enter the body as food or infused nutrients. These food stuffs supply energy from carbohydrates, proteins, and fats. The energy derived from these nutrients is used for resting metabolic functions such as protein synthesis and maintenance of ionic gradients, and this accounts for nearly two-thirds of total daily energy expenditure. The energy required for do physical work accounts for about one-third of total energy expenditure. The heat lost due to the thermic effects of food is small and variable. Below we will trace the flow of nutrient energy into the body and through the processes of digestion and absorption. We will then follow the flow of energy to its storage forms in fat, glycogen, or protein or as it is used for energy needs. Finally we will examine the nervous and endocrine systems, which integrate the components of this system. A number of physiological and mathematical models have been developed to facilitate the process of integrating the known facts.

Gastrointestinal Tract and Regulation of Feeding

The gastrointestinal tract plays a pivotal role in monitoring food intake. The left-hand side of Figure 1 depicts the processes of food intake, including digestion and assimilation of nutrients. The taste and smell of appetizing foods activates the parasympathetic side of the autonomic nervous system to prepare the intestine and circulation for the anticipated arrival of nutrients. Among these changes are an increase in insulin secretion as well as alterations in intestinal motility.

Entry of food into the stomach or intestine may control further food intake by at least two mechanisms. The first is distension of the stomach. The size of the stomach is determined by the rate at which food and gastric juices enter it minus the rate at which gastric contents exit through the pylorus into the intestine. More than 50 years ago a gastromechanical theory of hunger was proposed. Hunger was thought to be related to gastric contractions that were in turn triggered by changes in blood sugar. The weaknesses of this theory were that hunger was poorly related to blood sugar levels and that subjects with no stomach at all still experienced hunger. Nonetheless distension of the stomach by any means will temporarily reduce or eliminate food intake.

However, gastric distension is not essential to terminate feeding. For sham-feeding animals in which food exits through an esophageal or gastric fistula, introduction of nutrients into the intestine will terminate eating. The work of Smith and his colleagues has focused on the role of chemical messages, particularly gastrointestinal peptides, in this process of intestinal satiety. Entergastrone was the first peptide to be identified that could inhibit feeding, but cholecystokinin has received the most study. Cholecystokinin produces a dose-related decrease in food intake. This effect is abolished by vagotomy and does not work on an empty stomach. Thus cholecystokinin may slow gastric emptying with subsequent distension of the stomach and a reflex inhibition of eating involving the vagus nerve. Recent data have shown that obese subjects, particularly males, have more rapid gastric emptying than normal subjects.

The concentration of calories in food also plays an important role in the quantity of food ingested. In classic studies, Adolph demonstrated that the addition of indigestible substances to food would increase the quantity of food ingested in order to maintain a constant intake of calories. However, during the first meal or so after the dilution or concentration of calories there is an inappropriate caloric intake, indicating that some component of the ingested calories must be measured physiologically to provide a relation between intake and need. Recent data of McHugh and Moran et al. showed that in the monkey there is a highly responsive "caloric meter" in the upper intestine. When glucose is put into the stomach of monkeys, the rate of "caloric emptying" is constant at 0.4 kcal/min. A failure of this or other adaptive mechanisms to compensate appropriately for changes in caloric intake could produce obesity.

The regulation of food intake by distension of the stomach is modified by the subsequent nutrient value of the meal, providing that time is allowed for adaptation. When food is put into the stomach prior to ingestion of a meal, the subsequent intake of food may be reduced, although not necessarily by an amount sufficient to completely offset what was put into the stomach. The temporal relationships between putting food into the stomach and the inhibitory effects on the further intake has been examined. Food intake was reduced to the greatest degree when the preload was given 15 min before the meal. When it was introduced into the stomach either 1 or 60 min before the meal the effect was less

apparent. In some studies humans seem to be able to adapt to an intragastric load, but this is often incomplete and may require a considerable amount of time.

Taste is a confounding variable in the gastrointestinal signals that regulate caloric intake. When sweet solutions are available animals and humans will drink them. Over the pleasant range of sweet tastes, animals will ingest a relatively constant amount of mono- or disaccharide, regardless of concentration. There is an adaptive reduction in the intake of other foods, including protein, to maintain caloric intake at near balance. In some strains of rats and possibly in humans, however, the compensation is inadequate and obesity will slowly develop. If monkeys are given aspartame, a substance 200 times sweeter than sucrose and having few calories, they do not reduce caloric intake indicating that the monkeys can tell the presence of calories from mono- or disaccharide enriched solutions from absence of calories in solutions sweetened with aspartame. Although rats will maintain energy balance when bar pressing for food, they will overeat when given an intragastric feeding and ad libitum oral intake of food. These data indicate the potential overriding importance of taste, particularly sweet tastes. The sweetness of many beverages with aspartame may be analogous to the type of obesity that results when animals ingest sugar containing solutions in addition to their regular diet. The cafeteria is a common eating place for most of us. When the choices of food are numerous and tempting, cafeteria obesity may result in human beings as it does in animals.

The intestines may provide a second site for regulation of food intake. Intestinal distension may produce feelings of nausea and decrease food intake. In addition, intestinal hormones are known to modulate the rate of gastric emptying and may produce satiety by this mechanism (see above). Motilin, a recently identified and characterized intestinal hormone, is involved in the periodic surges of gastrointestinal peristalsis which might signal hunger.

Absorption of nutrients may also serve as signals for caloric ingestion that can suppress further feeding in a negative-feedback loop. Whether such signals operate directly through peripheral concentrations of hormones and/or nutrients or through effects on the liver and, in turn, the vagus nerve is at present uncertain.

Absorption and Storage of Nutrient Energy

Since food intake is periodic, the storage of nutrients must be periodic. For purposes of discussion it is convenient to separate the events following ingestion of food into absorptive and postabsorptive phases. The absorptive phase is the time from initiation of food intake through the principal digestive, absorptive, and storage period. This lasts 3 h or so and is considerably longer than the ingestive phase. During the absorptive phase, insulin is secreted and acts as the principal anabolic hormone for fat synthesis and storage as well as glycogen storage. The postabsorptive phase begins roughly at the time that the storage or anabolic phase is complete and ends at the onset of the next ingestive event. During the postabsorptive or catabolic phase, nutrients that were processed and stored during the absorptive phase are mobilized for energy and other nutrient needs.

Most of the absorbed nutrients enter the portal vein and are transported to the liver. Glucoreceptors located in the liver monitor portal glucose levels and transduce this information into afferent vagal signals that may be relayed to the brain. The lacteals provide an alternate route by which chylomicrons containing dietary fatty acids can enter the circulation without passing through the liver. Triglycerides composed of long-chain fatty acids enter the venous circulation packaged in chylomicrons. The fact that diets containing large quantities of fat are frequently associated with the development of massive obesity in experimental animals suggests that short circuiting of energy around the liver to the general circulation may diminish the "sensing" of these calories that would occur if they flowed through the liver.

In addition to experimental dietary obesity in animals fed a high-fat diet ad libitum, there are two other types of dietary obesity. The first is produced by offering a sucrose solution in addition to a normal diet (see above). The second occurs in animals fed a variety of snack foods in addition to their regular diet: the so-called supermarket or cafeteria diet. In each instance the animal fails to compensate for the novel foods or change in fat content by lowering caloric intake to maintain energy balance. These types of dietary obesity have obvious human implications. The current diet in most affluent western countries contains up to 40% or more of calories as fat. In susceptible strains of animals this level will produce obesity, and the same may be true of humans. At least two epidemiologic studies are consistent with this interpretation. The first is the study of Japanese and their descendents living in Japan, Hawaii, and San Francisco. The relatives eating the western diet and living in San Francisco and Hawaii were as a group heavier and fatter than the relatives remaining in Japan. A similar conclusion can be reached from an analysis of 1,994 middle-aged men, including 500 pairs of Irish brothers, one residing in Boston and one in Ireland. The brothers living in the US ate less than did those living in Ireland but were nonetheless fatter.

Adipose Tissue

Over 90% of the body energy is stored as triglyceride in adipose tissue. This tissue has two principal functions: *1*) the synthesis and storage of fatty acids and *2*) mobilization of fatty acids as a source of fuel. The synthesis of fatty acids by adipose tissue is increased in the presence of insulin and is enhanced by eating a high-carbohydrate diet or one with an excess number of calories. Small adipocytes are more responsive to insulin than large adipocytes. In some animals, fat tissue is the main site for synthesis of fatty acids, but in human beings, the liver appears to be more important. The fatty acids reach their storage site as lipoproteins, where the fatty acids are released by lipoprotein lipase and then enter the fat cell. These fatty acids are then stored in the triglyceride droplet.

The rate of release of free fatty acids from the triglyceride stores in adipocytes is related to the size of the fat cell. Larger fat cells release more glycerol and fatty acids than small fat cells, but adipose cells of similar size obtained from lean or formerly obese individuals have similar rates of lipolysis.

In the early years of life fat cells increase in both size and number. The multiplication of fat cells continues

throughout the growing years. After puberty, fat is stored primarily by increasing the size of adipocytes that already exist, although the total number may also increase under some circumstances. Thus, when obesity develops in the early years of life, it is almost always "hypercellular" in type with an increased number of fat cells. Obesity developing in adult life, however, occurs by an increase in size rather than in the number of adipocytes. Adult-onset obesity is thus primarily "hypertrophic" in type, but recent evidence indicates that this distinction is not absolute.

The anatomic difference between hypertrophic and hypercellular obesity is important because fat cells survive a long time. Fat cells develop from stem cells of mesenchymal origin and do not contain fat. Once differentiated, a fat cell does not appear to divide to form new fat cells. Thus, with acute changes in body fat, the size of the individual adipocyte varies, but there is little or no change in the total number of fat cells. However, with prolonged weight loss or gain there may be a corresponding change in the number of fat cells. In individuals increase in weight the total number of adipocytes may rise. Conversely, a decrease in the number of fat cells may occur prolonged weight loss.

Energy Expenditure

Energy expenditure is depicted in the two lower boxes of Figure 1. One box shows brown fat, which produces heat, primarily in the form of uncoupled oxidation, and all other metabolic tissues whose energy output is measured as both heat production and/or mechanical work. Energy intake is influenced by age, sex, physical activity, ambient, temperature, and hormonal status. The peak levels of caloric intake occur in the first and second decades of life, with the peak intakes for males being 30–50% higher than the peak for females. Following the peak there is a gradual decline in energy intake over successive decades.

Despite the decrease in food intake with age, Americans over the past 50 years have become progressively heavier. The inductees in World War II were heavier than men of the same height and age inducted into World War I. Similarly, the inductees into the Korean conflict were heavier than those in World War II. The longitudinal prospective data from Framingham, MA, have shown a progressive increase in body weight for males. However, the females in these same cohorts showed a smaller rise except for those born in 1916–1921. The recent data obtained by the National Center of Health Statistics in its Health and Nutritional Examination Survey also showed that for most age categories there has been a rise in body weight. Life insurance statistics also show the same trend. Because this increase in weight almost certainly reflects a rise in body fat, there is concern that the increase in fat storage may be translated into added health problems.

Resting metabolism, defined as the total energy required by the body in a resting state, is higher than the minimum heat production during the sleeping hours but lower than the peaks achieved following meals or with activity during the daytime. Resting metabolism also increases as body weight increases; i.e., heavier individuals require more energy for their resting metabolic needs. When corrected for surface area, however, these differences disappear. The so-called basal metabolism of adult females is ~ 850 kcal/m^2 per day and of adult males ~ 900 kcal/m^2 per day. There is $\sim 20\%$ variation in energy requirements around the median figure even for individuals of the same surface area, same age, and same sex. This means that with a mean intake of 1,000 kcal/day two normal people could differ by 400 kcal/day, with one eating 1,200 kcal and the other 800 kcal/day and yet both maintain body weight.

The total energy requirement for resting metabolism is also related to nutritional status. In the classic study entitled the "Biology of human starvation," Keys and his colleagues noted a decline in energy expenditure that was greater than the decline in surface area. A similar decline in resting metabolism during reduced caloric intake has also been observed in obese subjects. When obese individuals ate a 3,500-kcal diet for 7 days followed by a 450-kcal diet, there was no change in body weight when they ate 3,500 kcal/day, but when they ate 450 kcal/day there was a decline in total metabolism that was greater than the changes in body weight.

Several mechanisms have been proposed for this metabolic adaptation to fasting. The first hypothesis suggests that this effect results from a decrease in the concentration of triiodothyronine (T_3). Within the first hours following food deprivation there is a drop in the serum concentration of this hormone. Conversely with overfeeding the concentration of T_3 increases. This normal nutritional effect appears to result from reduced formation of T_3 from its precursor circulating pool of thyroxine rather than an increased rate of peripheral removal of T_3. However, the reduction in the concentration of T_3 might play a role in the reduced metabolic expenditure with starvation.

A second mechanism that might explain the fall in metabolic expenditure is the reduced activity of the sympathetic nervous system which occurs during fasting. When individuals are starved, the activity of the sympathetic nervous system, as measured by the turnover of catecholamines in peripheral tissues, is sharply reduced. This reduction in sympathetic activity might be reflected in a decrease in activity of the metabolic tissues dependent on tonic stimulation from the sympathetic nervous system for their activity. Conversely overfeeding increases the activity of the sympathetic nervous system.

Futile cycles are another possible mechanism for metabolic adaptations to nutrition. These cycles are of importance in insect and mammalian biochemistry. A futile cycle is defined as a cycle in which ATP is used to form a phosphorylated product that is then dephosphorylated with the loss of the energy in the ATP molecule. Formation of glucose 6-phosphate from glucose and the subsequent breakdown of glucose 6-phosphate to form glucose with the release of inorganic phosphate would be one such cycle. The glycerophosphate cycle, another example, has attracted particular attention because of its dependence on thyroid hormone. The activity of this cycle is reduced in adipose tissue from obese subjects compared with lean ones. The activity of this cycle is increased by thyroid hormone. The quantitative importance of the glycerophosphate cycle in the energetic efficiency of obesity however remains to be established. A similar statement applies to other so-called futile cycles.

Another mechanism that might modulate metabolic efficiency is the rate of protein turnover. This might also be termed, loosely, a futile cycle. In an analysis of nitro-

gen loss during fasting, Forbes and Drenick have argued that the obese individual loses nitrogen at a slower rate than the nonobese individual. Such a finding, if corroborated, would point to the possibility that turnover rates for stores of body protein might be slower in obese subjects and thus provide a mechanism for reducing energy expenditure. This would allow extra energy for fat storage, since protein synthesis is costly in terms of metabolic fuels. Studies with obese experimental animals have also suggested that turnover rates for protein may be lower, again supporting the possibility of an important role for protein metabolism in energy efficiency.

Alterations in the sodium pump provide still another mechanism to modulate energy efficiency. This hypothesis was formulated when animals with one form of genetic obesity were shown to have a reduction in the activity of sodium-pumping enzyme in liver and skeletal muscle. This reduction was accompanied by increased concentrations of intracellular sodium. This metabolic derangement was proposed as one mechanism for the metabolic efficiency and enhanced fat storage of these genetically obese animals.

Recent investigations have examined the sodium pump in human beings. Studies on the activity of the Na^+-K^+-ATPase (sodium pump) in erythrocytes from obese humans have provided conflicting data. In one study, using ouabain binding to measure the activity of the sodium-pumping enzyme, it was reduced in erythrocytes from obese subjects. Other studies, however, have found no difference when lean and obese subjects were compared. In human liver, on the other hand, there was a positive correlation between the sodium-pumping enzyme (Na^+-K^+-ATPase) and body fat. Thus, the role of the sodium-pumping enzyme in the development of human obesity is unclear and awaits further studies.

Alterations in metabolism of brown adipose tissue is the final mechanism that has been proposed for regulating energy efficiency. Brown adipose tissue is named for its vascularity and increased concentration of cytochrome and other oxidative pigments. It is distributed anatomically in the interscapular region as well as in the thorax around the pericardium and sinoatrial node, along the aorta, and around the adrenal gland and sympathetic chains in the abdomen. It represents $<1\%$ of body weight and functions primarily as a tissue with high respiratory capacity, which is important in maintaining body temperature in early postnatal life and during adaptation to cold. Recently, Rothwell and Stock and other investigators have demonstrated that the mass of brown fat could be increased by dietary means, suggesting that this tissue might play a role in metabolic efficiency.

In contrast to these intriguing and fascinating studies from experimental animals, data from human beings are scanty. Daniels and his colleagues and Welle and Campbell have documented that the response to norepinephrine, a sensitive measure of brown adipose tissue metabolism in experimental animals, is not different between obese and lean subjects nor is it altered by dietary-induced overeating in normal human beings. In contrast, Jung et al. have reported that formerly obese subjects as well as those who are currently obese have a reduced calorigenic response when norepinephrine is infused. These differing data comparing the response to norepinephrine emphasize the need for additional studies in an effort to resolve the important issues of the role of brown adipose tissue as a system for metabolic efficiency in humans. Although several mechanisms exist by which metabolic deficiency can be altered, clear documentation indicating that these mechanisms play an important role in the development of human obesity have not yet been provided.

Several studies have examined the efficiency of exercising muscle in obese subjects in the laboratory. Åstrand and Stunkard, using a bicycle ergometer, claimed that the efficiencies between obese and lean subjects differed, but they did not correct for the work associated with moving the legs per se. We have reinvestigated this question in both lean subjects before and after weight gain and in markedly obese subjects who exercised on a bicycle ergometer. The resting level of energy expenditure in massively obese subjects weighing in excess of 140 kg is twice that of the lean subjects. In each group of individuals the efficiency of coupling energy production to muscular contraction was 30%, when the work associated with moving the legs was considered. Similarly, the efficiency of coupling metabolism to muscle contraction remains the same following acute weight gain in normal subjects. In a study comparing big and small eaters who maintained comparable weight Rose and Williams also could find no differences in the metabolic efficiency of coupling energy production to muscular contraction. We thus conclude that there is no evidence to indicate an abnormality in the metabolic coupling of substrate metabolism to the contraction of muscular tissue in moderately or massively obese subjects.

A second approach to studying energy expenditure is that of naturalistic observation. The use of time-lapse motion pictures to study obese adolescents showed reduced activity with volleyball, tennis, or swimming. Three other studies, found little differences between obese and control. Among adults the amount of spontaneous activity in obese subjects is also reduced whether measured with pedometers or by more direct observation of the frequency with which the obese climb stairs as opposed to taking the escalator. A lower level of spontaneous movement, however, does not necessarily imply reduced energy expenditure, since the overweight individuals use more energy for any given movement. In one approach to this problem, Waxman and Stunkard related movement to energy expenditure and found that obese boys expended more energy on the playground and similar amounts inside the home compared with lean siblings. It is thus not possible to conclude that the apparent lowering of physical activity results in a reduction in energy expenditure.

Integration of Feeding

The overall control of energy intake is integrated by the nervous system with an assist from the endocrine system shown in the center of Figure 1. External information provided by the sense of smell and sight play an important role in identifying the presence and quality of food during food seeking activities. When the hungry human being or animal searches for food it uses information provided by these senses as well as the sense of taste in choosing its food. The hypothalamus provides an important integrating and relay station in this process.

The anatomic basis for control of food intake appears to be similar in all homeothermic species. Destruction of the ventromedial hypothalamus produces hyperphagia in mice, rats, dogs, cats, monkeys, chickens, and human

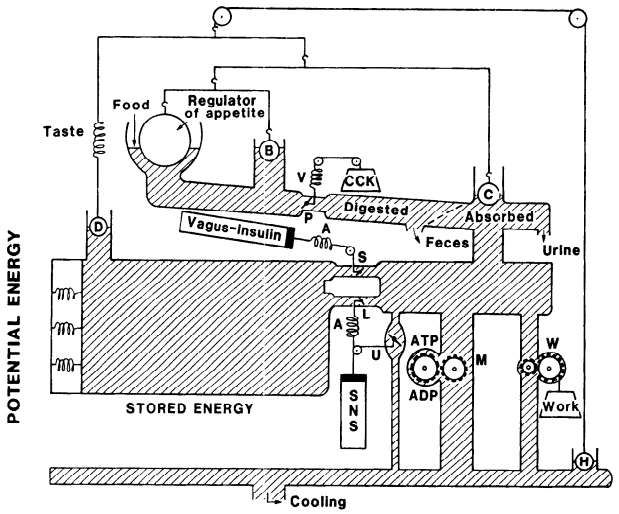

Figure 1

A thermomechanical model for control of energy balance. *Ordinate* shows potential energy of food entering the body, all of which has been dissipated at the end of the metabolic cycles. There are 5 feedbacks that can control ingestion of food. First regulator is distension of the stomach (valve B), which will respond to entry of food into the stomach. Rate of exit of food through the pylorus is modulated by the vagus and cholecystokinin. Absorbed calories (valve C) are a second possible site for feedback on food intake. Size of storage depot may also modify energy intake by raising reservoir D. Finally, rate of energy production through an increase of heat in cooling compartment may also feedback on food intake through reservoir E. Thermostatic or heat capacity model depicted by reservoir E may well be the most important controller. Autonomic nervous system controls flow of energy through regulation of storage (S) and mobilization (L) of nutrients as well as by regulating flow of energy through valve U (uncoupled), which does not generate ATP. Corticosteroid may modify the function of this model by modifying tension on springs labeled A.

beings. The hyperphagic part of the syndrome of hypothalamic obesity involves destruction of fiber tracts that run lateral to the ventromedial nucleus of the hypothalamus and may originate in the paraventricular nucleus. Destruction of the ventromedial nucleus itself is associated with hyperinsulinemia and hypertriglyceridemia but not necessarily with hyperphagia. Destruction of either the ventromedial nucleus or the adjacent fiber tracts is also associated with changes in the autonomic nervous system. This constellation of events has lead to the development of the autonomic hypothesis which proposes that ventromedial hypothalamic injury produces its peripheral manifestations primarily through modulation of the autonomic nervous system. This is depicted in Figure 2. The vagus nerve appears to become hyperactive after damage to the ventromedial nucleus. Vagotomy will reverse the obesity of animals with ventromedial hypothalamic lesions and will prevent the development of obesity during controlled experiments with constant intragastric feeding in animals with hypothalamic injury. Vagotomy will also acutely reverse the hyperinsulinemia induced when glucose is infused into ventromedial hypothalamus-lesioned animals, however, treatment with scopolamine or vagotomy before hypothalamic injury will attenuate but not completely block the hyperphagia and weight gain.

The sympathetic nervous system may also be affected by ventromedial hypothalamic lesions. The mobilization of free fatty acids and depletion of fat stores during starvation or during other "stressful" situations is reduced after damage to the ventromedial hypothalamus. Damage to the ventromedial hypothalamus also slows the turnover of norepinephrine in peripheral tissues from weanling rats. In mature animals damage to the ventromedial hypothalamus does not slow the turnover of norepinephrine in peripheral tissues. However, animals with ventromedial hypothalamic lesions do not show the expected slowing of norepinephrine turnover with starvation and show less acceleration after exposure to the cold.

In contrast to the hyperphagia and obesity that characterize destruction of the ventromedial hypothalamus, destruction of the lateral hypothalamus produces graded hypophagia, which is related to the size of the lesion. A small lesion will reduce food intake and body weight will decline and then recover, but not to the normal level. Large lesions on the other hand can even produce complete aphagia. Recovery, although with a number of residual neurological and behavioral deficits, will occur in animals that are tube fed during the early period after large lateral hypothalamic lesions. Electrical stimulation of the lateral hypothalamus has the opposite effect to that of lesions. During the period of stimulation of the lateral hypothalamus, food intake increases. If the stimulation is continued long enough, body weight and body fat increase. When the electrical stimulation is stopped, however, food intake drops and body weight returns to normal. In the first 18 h after a lateral hypothalamic lesion, the lesioned rat loses more weight than the control animal and shows an increase in metabolic rate. The rat with a lateral hypothalamic lesion also has an increased peripheral norepinephrine turnover. These findings suggest that the sympathetic nervous system has an important role in regulation of metabolism and in the long-term maintenance of energy balance.

The biochemical messages involved in neural transmission within the feeding system include monoamines, amino acids, and peptides. Serotonin, dopamine, norepinephrine, acetylcholine, and γ-aminobutyric acid may

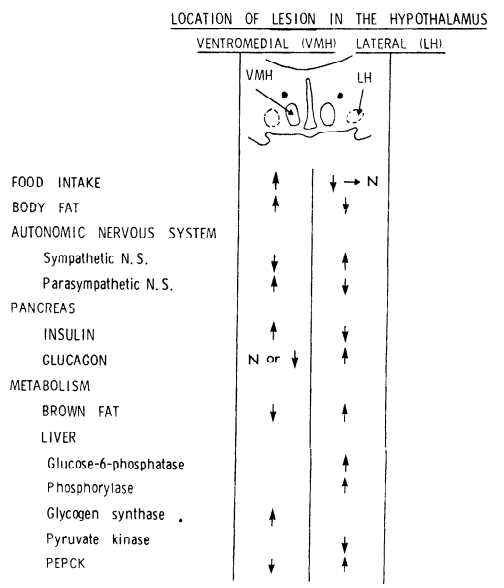

Figure 2

Comparison of physiological and metabolic changes which accompany destructive lesions in ventromedial or lateral hypothalamus.

all be involved in this control process. Destructive lesions in the lateral hypothalamus, which impair feeding, also destroy significant components of the dopaminergic fiber tracts that pass through this region of the brain. Injections of norepinephrine into the paraventricular region of the brain can initiate feeding in the satiated animal, and similar injections can inhibit feeding if administered into the lateral hypothalamus.

In addition to the effects of feeding on monoamine-containing neurons, there is also evidence for involvement of several peptides in the feeding system. Injection of cholecystokinin into the cerebral ventricle reduces food intake in sheep and in rats. Bombesin, another peptide originally isolated from frog skin but also found in brain and gut, will also lower food intake when injected into the cerebral ventricles. In contrast to cholecystokinin, however, the effect of bombesin is not reduced by adrenalectomy or vagotomy. Other peptides including thyroid-releasing hormone, calcitonin, substance P, pancreatic polypeptide, and somatostatin have also been implicated as inhibitors of food intake. The precise mechanism and interrelations between these peptides, however, still seem to be unravelled.

Although most of the peptides studied inhibit feeding, β-endorphin has been shown to stimulate feeding. Experiments with injections of endorphin into the cerebral ventricles suggest that its acute effects may be mediated through intermediary neurons, since the stimulation of feeding can be inhibited with bicuccline, a drug which blocks the action of γ-aminobutyric acid. Thus γ-aminobutyric acid represents a potentially important transmitter in the feeding system that may mediate the effects of endogenous opioid-like peptides.

Injections of naloxone, a drug which blocks opioid receptors, have been used to study the role of endorphins in the control of feeding. Acute injections of naloxone reduced food intake in obese and lean mice as well as in rats and human beings. This effect is dose dependent, competitively modified by morphine, and does not interact with the suppression of food intake seen with *d*-amphetamine. The possibility that naloxone or one of its derivatives might be a potential therapeutic agent in controlling food intake deserves further detailed study.

In addition to the peptide hormones located in the brain and gut that appear to play important intermediary role of regulation of feeding and satiety, there are a group of classical hormones that appear to be involved in monitoring body fat. Growth hormone, produced by the pituitary gland, is associated with changes in body fat. In hypopituitary animals and humans treated with growth hormone there is a reduction in body fat and an increase in lean body mass. This change in body composition in the presence of growth hormone is associated with an increase in metabolic rate in both humans and animals. Indeed one hypothesis for regulation of lean and fat mass is related to the quantity of growth hormones secreted. The problem with this hypothesis is that the secretion of growth hormone in response to many metabolic stimuli is impaired with overeating and in people who have spontaneous obesity, suggesting however that it is under important nutritional influences.

Thyroid hormones, secreted from the thyroid gland as thyroxine and converted to the biologically potent T_3 in peripheral tissues, play an important role in overall regulation of energy balance. Hypothyroidism is associated with reduced metabolic rate and an increase in body fatness. Hyperthyroidism, on the other hand, is associated with an increase in metabolic rate, a loss of body fat and increased metabolism.

Adrenal hormones also play an important role of regulation of body fat. Low levels of adrenal corticosteroids are associated with a wasting of body fat and a loss of body weight. Conversely, hyperadrenocorticolism (Cushing's disease) is associated with increased fat storage primarily in the abdomen and facial regions and a shift in metabolism from protein storage to fat storage. A critical role for glucocorticoid has been identified in all three forms of genetically transmitted obesity. In the obese mouse, the diabetic mouse, and the fatty rat adrenalectomy is associated with a return toward normal for most of the abnormalities in these animals. In the obese mouse where the most extensive studies are available, adrenalectomy lowers food intake to normal, increases energy expenditure, increases catecholamine turnover in brown adipose tissue and heart to normal, and leads to an increase in the weight of the brain, spleen, muscle, and bone tissues. There is also an associated reduction in insulin and disappearance of the insulin resistance in muscle. Similar although less complete studies on the diabetic mouse and fatty rat show that glucocorticoid plays a similarly critical role.

Gonadal steroids also play a role in the modulation of energy balance. In the rodent there is an association between estrus cycle and the intake of food and physical activity. When estrogen rises during the estrus cycle running activity increases and food intake decreases significantly. During diestrus on the other hand estrogen is low, running activity is decreased, food intake increases and body weight rises. Castration in the female rat abolishes this cycle pattern and administration of the estrogen will restore it. Androgens likewise influence the distribution of body fat. Testosterone, one of the most potent androgens, increases lean tissue and decreases total body fat. The important roles of hormones in regulating body fat suggests that the integration of food intake by the brain must be modulated by the levels of these hormones.

In this review we have explored a number of facets of energy balance. Although food intake is a periodic event it is this periodic ingestion of energy which must be integrated over time to provide the regulation of scored energy. The redundancy of mechanisms seems apparent. Gastric distension, gastric emptying, and associated hormonal and neural signals provide one level of modulation. Circulating and stored nutrients provide a second level for modulation. The neural and hormonal signals provide still another line of integration. And finally there is the potential escape valve of dietary thermogenesis and exercise.

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Regulation of Energy Balance

1. Food intake can be inhibited by increased:
   a. distension of the stomach
   b. entergastrone
   c. cholecystokinin
   d. "concentration" of calories
   e. all of the above
2. Obesity in experimental animals is frequently associated with a diet in which a large fraction of the calories are present in the form of:
   a. fats
   b. glucose
   c. carbohydrates
   d. proteins
3. Adipose tissue has as its principal function(s):
   a. synthesis and storage of fatty acids
   b. mobilization of fatty acids as a fuel source
   c. gluconeogenesis
   d. *a* and *b*
   e. *a*, *b*, and *c*
4. Adult-onset obesity is usually associated with an increase in the:
   a. number of adipocytes
   b. size of adipocytes
   c. number and size of adipocytes
5. Resting metabolism decreases during starvation or fasting because:
   a. ATP production from each molecule of carbohydrate increases
   b. sympathetic stimulation of metabolically active tissues decreases
   c. the concentration of triiodothyronine (T_3) increases
   d. the turnover rate of proteins increases
   e. activity of the glycerophosphate cycle is increased
6. Brown adipose tissue:
   a. functions primarily to generate heat for thermoregulation
   b. is less vascular than normal adipose tissue
   c. represents only 1% of body weight
   d. is found in the intercapular region and in the thorax
   e. all but *b*
7. The hyperphagia that accompanies hypothalamic obesity results from:
   a. decreased activity in the vagus nerve
   b. increased sympathetic activity
   c. destruction of the ventromedial nucleus
   d. lateral hypothalamic lesions
   e. all of the above
8. Neuronal transmission in the hypothalamic feeding system utilizes as transmitter(s):
   a. monoamines only
   b. amino acids only
   c. peptides only
   d. all of the above
   e. none of the above
9. High levels of glucocorticoids, as may be present in genetically obese mice, seem to cause:
   a. increased food intake
   b. decreased energy expenditure
   c. increased insulin release
   d. all of the above
   e. none of the above
10. Obesity will result *only* if:
    a. energy intake exceeds energy expenditure
    b. intake is up *and* expenditure is down
    c. the organism is metabolically inefficient
    d. neural regulatory reflexes malfunction
    e. none of the above

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