# 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,* Walter C. Randall, Loyola University, Maywood, IL; *President-Elect,* Alfred P. Fishman, University of Pennsylvania Hospital, Philadelphia, PA; *Past President,* Francis J. Haddy, Uniformed Services University of the Health Sciences, Bethesda, MD ; *Council,* Walter C. Randall, Alfred P. Fishman, Francis J. Haddy, Leon E. Farhi, Franklyn G. Knox, Jack L. Kostyo, John B. West; *Executive Secretary-Treasurer,* Orr E. Reynolds, 9650 Rockville Pike, Bethesda, MD 20814.

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## The Physiology Teacher



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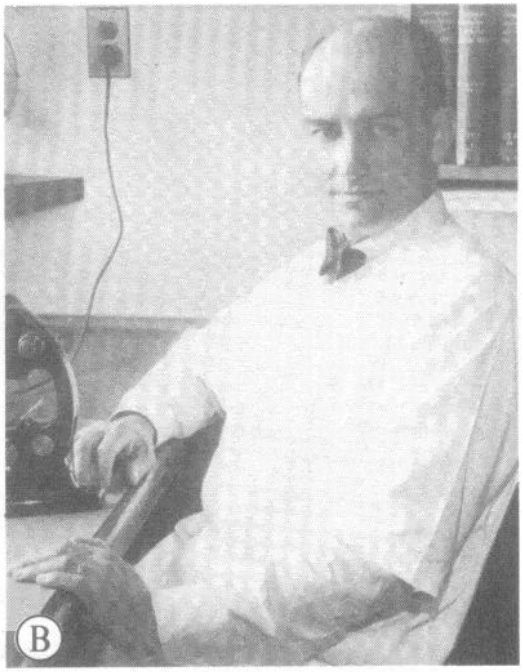
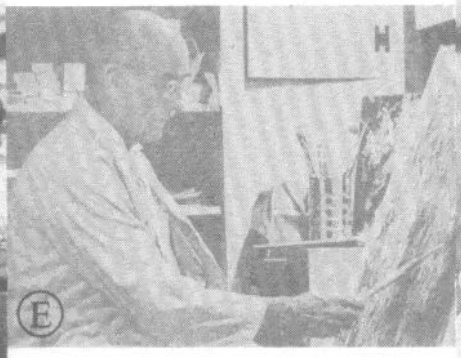
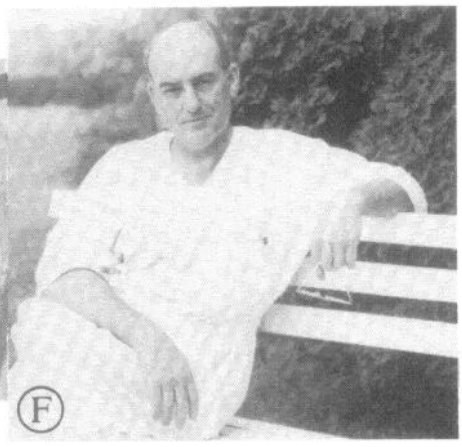
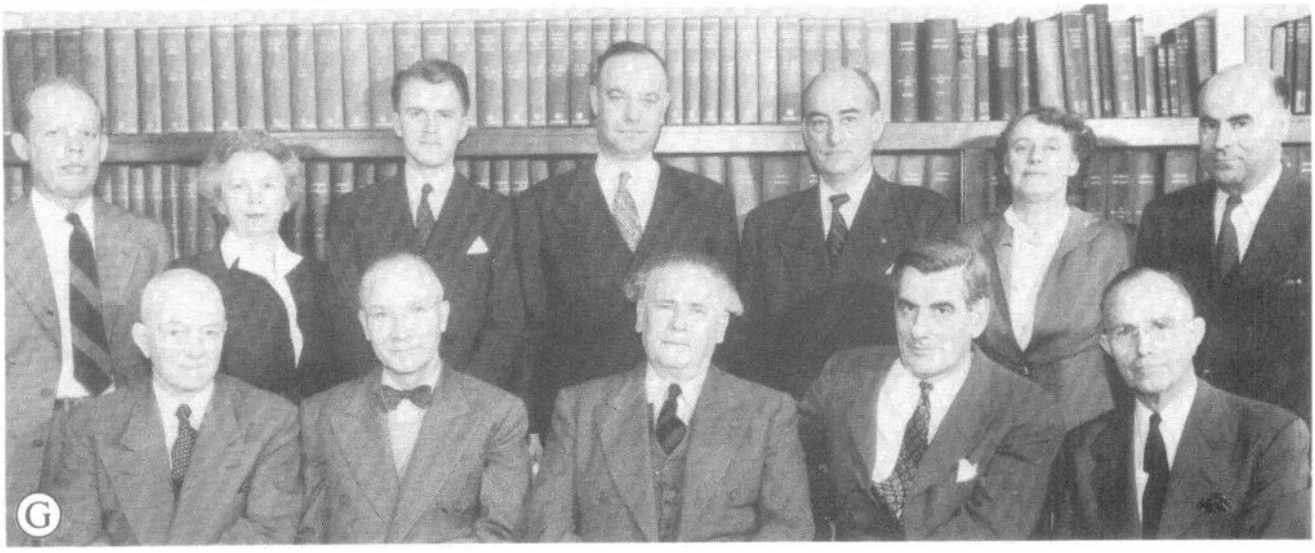
*Cover:* See Hiram Eli Essex, 27th APS President, p. 1.









*A*: Drs. **H. Essex** and C. J. Wiggers, Institute of Experimental Medicine, Rochester, MN, ca. 1952

*B*: Dr. **Essex,** Institute of Experimental Medicine, 1936.

*C*: Drs. W. Hamilton, L. N. Katz, and **Essex,** September 1963.

*D*: Drs. **Essex** and Katz, September 1963.

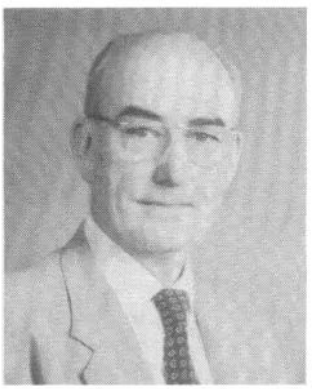
*E*: Dr. **Essex** painting at his home.

*F*: Dr. **Essex,** Institute of Experimental Medicine, 1952.

*G*: Staff, Institute of Experimental Medicine, ca. 1952. *Back row*: Drs. J. Grindley, J. Herrick, W. Anderson, A. Karlson, **H. Essex,** E. Flock, K. Wakim. *Front row*: Drs. W. Feldman, C. Schlottlauer, F. C. Mann, j. L. Bollman, G. Higgins.

# Hiram Eli Essex
# 27th APS President

Hiram Eli Essex, humanist, scientist, farmer, and painter. Born 1893; died 1978. Married with three surviving children. Member of the American Physiological Society, in the affairs of which he played a conspicuous role. Professor of Experimental Physiology in the Mayo Clinic Graduate School of Medicine and author or coauthor of more than 200 scientific papers. This brief statistic suggests an individual with varied interests but fails to delineate the diverse talents and wide-ranging activities of a man who could well serve as a model for Tinbergen's "Curious Naturalist."



Dr. Essex was born in Glasford, Illinois, the son of Reverend Hiram Essex and Sarah Catherine Waters Essex. After graduating from high school he taught for three years in the country schools of Knox County, Illinois. These early experiences were the seed beds of his love of nature and matters rural and his later distinction as a teacher and educator.

During World War I, Dr. Essex served for 19 months as second lieutenant of infantry at Camp Custer, Michigan.

In contrast to present times when early specialization is the rule rather than the exception, Dr. Essex did not immediately pursue his final and major field of interest, the cardiovascular system. Following graduation as Bachelor of Science, cum laude, from Knox College, Galesburg, Illinois, in 1919, he was for two years the sales representative of the Rowe Manufacturing Company in Kansas and Oklahoma; during 1922 and 1923 he was principal of Ellisville Community High School, Illinois. He then returned to academic life in the Graduate School of the University of Illinois, Champaign-Urbana, receiving the degree of Master of Science in 1924 and of Doctor of Philosophy in Zoology in 1927. He remained at the University until 1928 doing graduate courses, research in marine biology at Friday Harbor, Washington, and zoological field studies in tapeworm infestation of channel catfish, bowfin, and walleyed pike in the northwestern regions of the United States.

Dr. Essex came to the Mayo Graduate School of Medicine, Rochester, Minnesota, in July 1928 and began his now widely recognized career in experimental biology. He was successively instructor (1928), assistant (1932), associate (1936), and full professor in experimental physiology (1942). From 1932 to 1952 he directed the laboratory of physiology at the Institute of Experimental Medicine (Dr. F. C. Mann, Chairman). When the animal research laboratories moved to the Medical Sciences Building in Rochester in 1952, he became cochairman, with Dr. C. F. Code, of the Section of Physiology of the Mayo Clinic and Mayo Graduate School of Medicine, an association that lasted until Dr. Essex retired in April 1958. In regard to the formation of the Department of Physiology at Mayo, Dr. C. F. Code comments, "On proposing cochairman leadership of the department we were immediately called to task by a member of the Board of Governors, a man with years of experience in the military and who was convinced of the importance of a stratified administrative structure, and the vital requirement of a commanding officer. He told us, 'you are creating a double headed monster that will devour itself and surely fail.' After a few moments of reflection Dr. Essex stood up and said with all the firmness and conviction that his nature provided, 'anything is possible between men of goodwill and honesty. Charlie and I are such men and we can make this arrangement work.' With that he walked from the room. I followed with admiration and pride in him. We were 'commissioned' and built the department together."

Dr. Essex's interest in teaching and investigation did not terminate with his retirement, and in 1959 and 1960 he was director of undergraduate research for a program in experimental biology at Saint Mary's College in Winona, Minnesota.

Initially on coming to Rochester, Dr. Essex pursued his interest in the life cycle of various parasites afflicting man and animals. Together with Dr. T. B. Magath he conducted studies to demonstrate that the dog was an unnatural host to the broadfish tapeworm, *Diphyllobothrium latum*, and that man was the most important factor in the spread and maintenance of tapeworm infestation on this continent.

The leadership of Dr. Mann and the stimulating association of colleagues concerned with problems relating to basic physiology and medicine incited Dr. Essex to expand his interests, and he began a series of studies in experimental physiology and pharmacology having particular reference to the cardiovascular system. In this regard his association with Dr. J. Markowitz had considerable influence in directing the attention of Dr. Essex to the use of experimental surgical techniques in studies of the circulation.

Alone and with colleagues he studied the effects on the circulation of snake and bee venoms, extracts of parasitic worms, histamine, and the endotoxins of bacteria. He was particularly concerned with the genesis and mechanism of anaphylactic shock and its relations to and differences from hemorrhagic and cardiac shock. He summarized his early work in the *Encyclopedia Britannica* in 1955 and more fully in the 1965 *Handbook of Physiology* (sect. 2: *Circulation,* vol. III).

A feature of Dr. Essex's approach to a biological problem was to engage the interest of colleagues in disciplines other than his own and so permit a multifaceted investigation. His collaboration with biophysicists, C. P. Sheard, A. J. Baldes, and J. F. Herrick, allowed early studies on circulation time using an ionization technique, and of regional blood flow with a

modification of the thermostromuhr of Rein, and are typical of many such collaborative efforts. Dr. Essex refined the thermostromuhr to permit its use in trained conscious dogs and described the changes in regional blood flow (muscle, kidney, intestine, and heart) during exercise, digestion of food, anesthesia, and exposure to various drugs and hormones. The technique of measuring regional blood flow allowed collaboration with biochemical colleagues (S. Soskin, E. Flock, and J. L. Bollman) in metabolic studies of the liver, skeletal muscle, and the myocardium. These pioneering studies by Dr. Essex on regional blood flow in anesthetized and conscious dogs opened a new field of circulatory physiology and stimulated later work by others using different and more refined techniques of measurement and analysis.

Cardiac function was another area of interest. Dr. Essex made important observations on coronary blood flow in resting and exercising normal dogs and, after extrinsic cardiac denervation, on the spread of the excitatory impulse in the atria and ventricles, particularly in the ventricular septum and on the effect on cardiac rhythm and function of exposure to cardenolides and to alteration in the ionic content of the perfusion medium. He described the physiological effects of creating and closing atrial and ventricular septal defects and studied pulmonary arteriovenous fistulas and arteriolar embolism. In 1949 he produced a motion film of the action of the heart valves and correlated cardiac motion with cardiac sounds. This film has been used extensively in medical schools here and abroad. Later researches in intact dogs and isolated perfused hearts examined the role of the cardiac sympathetic and vagal nerves in the regulation of cardiac frequency and force of contraction.

The tolerance that certain animals develop to massive doses of epinephrine was of considerable interest to Dr. Essex. He showed this was nonspecific, varied in degree between species, and not due to the development of an antihormone or interference with the blood pressure raising effect of the hormone. These studies would be worth repeating in view of newer information on the nature of pre- and postjunctional receptors on the sympathetic nerve terminals.

Dr. Essex's studies on the hypophyseal gland illustrate the wide range of his interests. He standarized a transbuccal technique of hypophysectomy in the dog and showed in dogs and rats that pituitary secretions had a role in the compensatory hypertrophy of the kidney after unilateral nephrectomy but not in the regeneration of the liver after partial hepatectomy. He also examined the effects of extracts of the posterior pituitary on the contractile properties of visceral and vascular smooth muscle.

Much concerned with the humane care and treatment of experimental animals, Dr. Essex was chairman of the APS Committee on Animal Care and Experimentation when that committee developed the "Guiding Principles in the Care and Use of Animals," which in slightly modified form is still supported by the Society and has been adopted by the Federation of American Societies of Experimental Biology.

Dr. Essex's interest in teaching persisted throughout his professional career and was an integral part of his research program. It took a very personal form, involving an active part in the planning and execution of the work and frequent, critical, and stimulating discussions as the investigation proceeded. He supervised the preparation of theses of 10 candidates for the doctorate and 17 candidates for the master of science degree in the graduate school of the University of Minnesota, under the Mayo Graduate School of Medicine.

In 1941 Dr. Essex was elected to the Council of the American Physiological Society on which he served almost continuously until 1956. Among his duties was that of a member of the Board of Publication Trustees, which managed the journals and other publications of the Society. During his tenure of office he became convinced, as did Milton Lee, that the Federation of American Societies for Experimental Biology would not prosper unless a headquarters for the central organization and constituent societies could be developed. Property in the form of a private residence with 38 acres of land was available in Bethesda, Maryland. Dr. Essex as a member of an ad hoc Committee on a Society Headquarters represented the committee to the Federation Board and advised its purchase, proposing that the Board of Publication Trustees of the American Physiological Society would provide temporary financing. Wallace Fenn was skeptical—the stakes were high and there were risks. Dr. Essex's arguments convinced Dr. Fenn and with him, the Board of Publication Trustees. The purchase was consummated, and Beaumont House came into being. Within a year the property in excess of that needed for the headquarters was sold, and the borrowed dollars were returned to the Board of Publication Trustees. It was an extraordinarily successful venture, realized in no small part through the foresightedness, financial acumen, and drive of Dr. Essex, characteristics he continued to display when he acted as the 27th elected President of the Society in 1954 and 1955.

Dr. Essex also held membership in the American Society for Pharmacology and Experimental Therapeutics, the Society for Experimental Biology and Medicine, and American Society of Parasitologists, the American Microscopical Society, the American Society for the Advancement of Science, the American Association of University Professors, and the Minnesota Academy of Science of which he was president in 1949 and 1950. Dr. Essex was secretary-treasurer of the Mayo Foundation chapter of Sigma Xi and served as its President in 1944. He was a member of the Board of Directors of the Hormel Institute, Austin, Minnesota, until his retirement in 1958. Dr. Essex served for 5 years as a member of the Cardiovascular Study Section of the National Institute of Health. During his tenure he conducted a national survey to determine the financial needs of medical schools to conduct research on problems relating to the cardiovascular system. He was President of the National Society for Medical Research from 1961 through 1965.

Dr. Essex has been the recipient of numerous awards and honors recognizing his researches. He delivered the Joseph Graham Mayo Lecture at the State University of Iowa College of Medicine in 1954 and the Hatfield Lecture at the College of Physicians and Surgeons in Philadelphia in 1958. Also in that year he received the Alumni Achievement Award of Knox College. In 1953 he was made a distinguished member of the Section of Circulation of the American Physiological Society.

Dr. Essex took an active part in the civic and social life of the Rochester, Minnesota, community. He was a founder-member and served on the Board of Directors of the Rochester Art Center. He was president of the Rochester Music Club, the Rochester Parent-Teachers Association Council, and the Rochester Kiwanis Club. He chaired a fund-raising campaign that secured $500,000 for a camp facility for the River Trails Girl Scouts.

A single career in Physiology did not provide sufficient outlet for Dr. Essex's abundant energy, and he sought further satisfaction in farming and painting. Temporarily restricted by a knee injury in 1935 he began to work in crayon and oil, somewhat in the manner of the American Primitives, but after several years he became dissatisfied with his efforts to reproduce nature directly and his work became increasingly abstract. In his attempts to use subconscious intuition to guide in the creative process he was influenced by the work of Pollock, while his use of color shows his empathy with the impressionists, especially van Gogh, Kandinsky, and Renoir. Dr. Essex's use of free-floating forms and fluid sinuous lines are reminiscent of the theatrical art of Marc Chagall. As a scientist so as an artist Dr. Essex remained an experimenter, using a wide range of media. In his later works he employed an individually derived combination of wax and acrylic paint to obtain novel and brillant effects.

In conversation with friends Dr. Essex frequently admitted to being a farmer at heart. This ambition was realized in 1940 when he and Mrs. Essex purchased a farm a few miles north of Rochester. Starting virtually from scratch and using scientific agricultural practices they built up a herd of Holstein cattle that gained local and statewide recognition. Typical of Dr. Essex's character was his comment that theirs was a working farm, not a hobby or a tax shelter. He was always ready to share his expertise and to help others realize their own goals. He was president of the Olmsted Holstein Breeders Association in 1950, vice-president of the Minnesota Holstein Association in 1957, and president in 1958.

The preceding is a list recognizing his scientific and civic contributions. What of the person behind these deeds? One could well echo Hamlet's requiem for his father-king. "He was a man, take him for all in all, I shall not look upon his like again." Of above average height, strongly built, bold featured, and prematurely bald, Dr. Essex enjoyed an immense vitality and appetite for life that were the admiration, envy and sometimes despair of his friends. "Slow down Hi" was a not uncommon request. An upright man incapable of deceit, his forthright and often brusque manner of speech left no doubt as to his meaning and sometimes masked his innate kindness and generosity of spirit. The numerous scientists from this country, Europe, India, and the Near East who date their scientific careers from their tutelage with Dr. Essex and who enjoyed the warm hospitality of the Essex home and the relaxation of their country cottage at Cedar Beach (outside of Rochester) attest to this aspect of his character. A final and fitting testimonial of this interest and concern for the present and future community was offered just before his death in 1978 in the munificent gift of 160 acres of woodland and stream-bordered meadow to the County Park System (north of Rochester). Dedicated as the Essex Park in 1981 it is a lasting memorial, the significance and value of which can only increase with time.

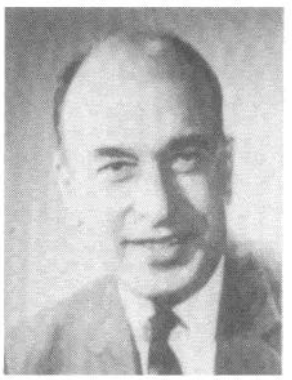
The section describing the role played by Dr. Essex in the purchase of Beaumont House was contributed by Dr. C. F. Code.

The writer wishes to thank Mrs. Marion Essex for informative discussion of Dr. Essex's many activities.

D. E. Donald
Mayo Foundation

## Robert W. Berliner Elected to AAAS Board of Directors

**Robert W. Berliner,** dean and professor of physiology and medicine, Yale University School of Medicine, has been selected to the Board of Directors of the American



Association for the Advancement of Science (AAAS). His four-year term will begin 1 June 1983, immediately following the Association's Annual Meeting in Detroit, Michigan (26-31 May). Prior to joining the faculty at the Yale University School of Medicine in 1973, Berliner served as deputy director for science at the National Institutes of Health. His earlier professional affiliations were with the Goldwater Memorial Hospital, New York University, Columbia University, George Washington University, and Georgetown University. Berliner earned a B.S. degree from Yale University and the M.D. degree from Columbia University. He holds honorary degrees from the Medical College of Wisconsin and Yale University. He received the US Department of Health, Education, and Welfare's Distinguished Service Award, 1962; the Homer W. Smith Award in Renal Physiology, 1965; Alumni Award for Distinguished Achievement, 1966; Bicentennial Medal, 1967; and Joseph Mather Smith Prize, 1978, Columbia University; *Modern Medicine's* Distinguished Achievement Award, 1969; American Heart Association's Research Achievement Award, 1970; A. Ross McIntyre Award, University of Nebraska Medical Center, 1974; and Ray G. Daggs Award, American Physiological Society, 1982. Berliner served as president, American Society for Clinical Investigation, 1959, American Physiological Society, 1967, American Society of Nephrology, 1968, and Society for Experimental Biology and Medicine, 1979-81. A member of the National Academy of Science and the Institute of Medicine, his Academy activities include serving on the Committee on Science and Public Policy, 1973-77; NAS Council, 1978-81; executive committee, Assembly of Life Science, 1973-78; and chair, Division of Medical Sciences, 1976-78. Long involved with the AAAS, Berliner has held a number of Association offices including chair of the Medical Sciences section in 1972 and 1977; Council member from 1971-72, 1974-75, and in 1978; and member of the Committee on Council Affairs from 1974-75.

# Animal Rights Groups Escalate Movement To Malicious Actions

The actions of the animal rights movement in the United States have been escalated in their intensity from passive public demonstrations protesting the use of animals for research purposes to malicious acts of breaking and entering, the destruction of private property, and the stealing of animals from research facilities.

The most recent actions of escalation were initiated by a militant group, calling itself the Animal Liberation Front, whose members conducted three raids on two Washington, DC, area research institutions. The first raid resulted in the theft of at least 28 cats from a Howard University Medical School research facility near downtown Washington. Two days later members of the Animal Liberation Front entered an animal-holding area at the National Naval Medical Center at Bethesda, MD, and stole a dog. Eighteen days later, they returned to the Navy facility and stole three more dogs.

Several months prior to these raids another animal rights group calling itself The Band of Mercy broke into a classroom-laboratory building at the University of Maryland and stole several dozen rabbits that were being used for instructional purposes. All of the raids were conducted after another animal rights group, called People for the Ethical Treatment of Animals, initiated a police raid on a Silver Spring, MD, behavioral research facility where 17 monkeys were confiscated.

Immediately after each of its raids the Animal Liberation Front held press conferences where spokeswomen said that raids were conducted to demonstrate publicly the abuses of animals by researchers. The organization also indicated that more raids would be forthcoming and that such raids can also now be anticipated elsewhere in the United States.

The Animal Liberation Front spokeswomen said that the Washington area targets were selected first to attract the attention of the Congress to the need for legislative reforms and to point up the need for stronger Federal laws to protect animals from abuses by researchers.

The first raid by the Animal Liberation Front took place on Christmas night, which was just two days after the 97th Congress had adjourned, killing several research animals reform bills pending before both the House and the Senate.

The Animal Liberation Front raiders broke the front-door glass to gain entry to the Howard University Medical School research facility and stole cats that were being used in a study of the effects of certain drugs on nervous disorders.

A spokeswoman for the Animal Liberation Front—who said she flew to Washington from Gainesville, FL, for this purpose but added that she did not take part in the break-in—claimed that 35 cats, including a dead feline, were taken in the raid. However, Howard University officials, who estimated the total damage and loss at approximately $3,000, reported that only 28 cats were missing.

Two days after the raid on Howard University two women put on white lab coats and during normal working hours walked into an animal-holding building at the Navy research facility, where they placed a dog in a satchel and then walked out.

At the press conference held in a church parking lot immediately after the animal was taken the spokeswomen displayed a black schnauzer-like dog with multiple scars and scabs. The Animal Liberation Front spokeswomen indicated that they believe the dog had once been someone's pet.

The Navy public information office issued a statement confirming that one of its dogs was missing from an animal-holding area but that the missing animal was an old dog that had been in a fight several weeks earlier and had not been used for research purposes.

Several days after stealing the dog from the Navy facility the Animal Liberation Front reported that a local veterinarian had examined the animal and had found it to be infested with scabies.

The second invasion of the Navy research facility took place at night when Animal Liberation Front members slipped past security to the laboratory to take three of the dogs that were being used for medical research. A Navy spokesman denied the animal rights group's charge that the dogs had been mistreated.

Both the Howard University and the Navy animal research facilities are accredited by the American Association for Accreditation of Laboratory Animal Care.

## Animal Research Bills to be Reintroduced

The sponsors of the "Humane Care and Development of Substitutes for Animals in Research Act" (HR 6928 and S 2948) are expected to reintroduce these bills early in the first session of the 98th Congress. Both bills had died when the 97th Congress adjourned on December 23.

During the interim between the two Congresses the American Physiological Society has been working with Rep. Doug Walgren (D-PA), author of the House version of the bill, and with the staff of Sen. Robert Dole (R-KS), the prime sponsor of the Senate version of the bill, concerning several proposed amendments.

A revision to the House version of the bill during the final days of the 97th Congress charged the Secretary of the US Department of Health and Human Services with establishing "standards for proper animal care, treatment, and use in experimental procedures, including appropriate and reasonable requirements with respect to handling, housing, feeding, watering, sanitation, ventilation, shelter from extremes of weather and temperature, and exercise...".

These standards would be in addition to the accreditation requirements, the National Institutes of Health "Guide for the Care and Use of Laboratory Animals,"

and the requirements for animal facility established by the US Department of Agriculture's Animal and Plant Health Inspection Service (APHIS).

In providing several suggested amendments to the House version of the bill the Society told Rep. Walgren that "One of our concerns is the possibility of conflicting standards arising between the Secretary of HHS, the accrediting entity, and the APHIS. It is our opinion that this possibility would be ameliorated by revising Section 202(b) to read: 'The Secretary, in consultation with the Director, Animal and Plant Health Inspection Service, shall by regulation establish standards...(and) the procedures specified in the "Guide for the Care and Use of Laboratory Animals" of the National Institutes of Health shall be established as interim standards pending formal regulations'."

Because of the concerns raised earlier by the Society and others regarding the costs to institutions of mandatory accreditation, the Senate version calls for a one-year study of the accreditation costs based on current standards but not the standards that would be required by the Secretary of Health and Human Services. This is the reason for the Society's recommendation that the NIH Guide be used as the Secretary's interim standards.

Inasmuch as the House Subcommittee on Science, Research, and Technology and on Health and the Environment have held hearings on HR 6928 during the last session of the Congress and the full Committee on Science and Technology has approved the measure, it is possible that these committees would waive their jurisdiction on a new bill and send it directly to the House floor for consideration. However, whether the new bill is to be placed on a fast track will not be determined until after it has been reintroduced.

The Senate version of the bill is expected by the Committee on Labor and Human Resources, which has jurisdiction on all legislation concerning research.

William M. Samuels, CAE

# Announcements

## Animal Stress Conference

The University of California, Davis, will hold an international conference on Animal Stress: New Directions in Defining and Evaluating the Effects of Stress in Animals on July 6-8, 1983, at the University of California, Davis. The main program will consist of invited papers from behaviorists, physiologists, nutritionists, veterinarians, and experts in animal welfare addressing the definition, study, and effects of stress in animals. In addition to the invited papers, there will be workshops and a poster session open to conference participants. *For information concerning registration contact*: Dr. Gary P. Moberg, Dean's Office A&ES, University of California, Davis, CA 95616.

## Thirty-Fourth Annual Session of American Association for Laboratory Animal Science

The 34th Annual Session of the American Association for Laboratory Animal Science will be held on November 6-11, 1983, at the Convention Center, San Antonio, TX. *For information contact:* Donald W. Keene, Executive Secretary, AALAS, 210 N. Hammes Ave., Suite 205, Joliet, IL 60435. *Deadline for receipt of abstracts of original papers:* April 1, 1983. Abstract forms may be obtained from the Program Committee Chairman, Dr. Steven P. Pakes, Div. of Comp. Med., Univ. of Texas Health Sci. Ctr., 5323 Harry Hines Blvd., Dallas, TX 75235. Telephone: (214)688-3340.

## Thirty-Seventh Annual Symposium of Society of General Physiologists

The 37th Annual Symposium of the Society of General Physiologists on "Regulation and Development of Membrane Transport Processes" will be held at the Marine Biological Laboratory, Woods Hole, MA, on September 11-14, 1983. *Sessions*: regulation of cell membrane transport; regulation of transepithelial ion transport; membrane transport during differentiation; development of alkali cation transport. *Workshops*: molecular biological approaches to membrane metabolism; electrophysiological techniques in developmental studies.

*Abstracts* for posters dealing with general physiology and the regulation or development of membrane components are invited by the Society; those from nonmembers must be sponsored by a member of the Society of General Physiologists. *Deadline*: June 1, 1983. A $20 check to cover the cost of publication (made payable to the Society of General Physiologists) must accompany each abstract. Submit two copies, double spaced, including title, author(s) (designate nonmembers by *), institution, 300-word text, and grant acknowledgment, if any, along with a self-addressed postcard to: Dr. James S. Graves, Dept. of Physiology, Medical University of South Carolina, Charleston, SC 29425.

*For forms and information on registration and housing contact:* Society of General Physiologists, Box 407, Woods Hole, MA 02543.

## Course in Design and Analysis of Scientific Experiments

Massachusetts Institute of Technology will offer a one-week elementary course in Design and Analysis of Scientific Experiments, 11-16 July 1983. Applications will be made to the physical, chemical, biological, medical, engineering, and industrial sciences and to experimentation in psychology and economics. The course will be taught by Professors Harold Freeman and Paul Berger. *Further particulars may be obtained by writing to*: Director of Summer Session, Room E19-356, Massachusetts Institute of Technology, Cambridge, MA 021389.

# SOCIETY NEWS

## New APS Lecture Series
### FASEB Spring Meeting
### April 13, 1983

### First APS Physiology in Perspective Lecture
### Wednesday, April 13, 1983
### Grand Ballroom, Conrad Hilton Hotel

9:00 A.M. Functional Significance of Neurotransmitter Diversity
**Floyd Bloom**, Director
Davis Center for Behavioral Neurobiology
The Salk Institute
San Diego, CA

9:45 A.M. APS Business Meeting
**Walter C. Randall**, President
American Physiological Society

10:30 A.M.–1:30 P.M.
Free Time to Visit the Exhibits
(APS Symposia and sessions will *not* be scheduled during this period)

A new series of lectures entitled *Physiology in Perspective* will begin with a presentation by Floyd Bloom of the Salk Institute. His topic will be "Functional Significance of Neurotransmitter Diversity." The lecture will be delivered at 9:00 A.M., Wednesday, April 13, in the Grand Ballroom of the Conrad Hilton Hotel. Immediately following the lecture, the American Physiological Society will hold its Business Meeting. It is anticipated that the attendance at the Business Meeting will increase greatly because of this shift in time. No scientific sessions other than Dr. Bloom's lecture will be scheduled for Wednesday morning. Following the Business Meeting, the remainder of the morning will be left free for visiting the exhibits at McCormack Place.

## Future Meetings

| | |
|---|---|
| 1983 | |
| FASEB Annual Meeting | Apr 10-15, Chicago |
| APS "Fall" Meeting | Aug 20-24, Honolulu |
| IUPS Congress | Aug 28-Sep 3, Sydney |
| 1984 | |
| FASEB Annual Meeting | Apr 1-6, St Louis |
| *APS "Fall" Meeting | Jul 29-Aug 7, Lexington |
| 1985 | |
| FASEB Annual Meeting | Apr 21-26, Anaheim |
| *APS "Fall" Meeting | Aug 4-9, Buffalo |

*Campus meeting

## APS and Guest Society Programs
## FASEB Spring Meeting
## April 10-15, 1983

### Monday, Apr 11, A.M.

Tutorial: Automatic literature search and retrieval. Chaired by H. M. Kissman

BMES Symposium: Bioengineering in exploration. Chaired by J. L. Katz and G. van B. Cochran

Theme Symposium: Neuroendocrine control of CRF-ACTH secretion. Chaired by M. F. Dallman

Theme Minisymposium: Influence of endogenous and exogenous opioids on neuroendocrine function. Chaired by T. Cicero

### Monday, Apr 11, P.M.

Theme Symposium: Neuroendocrinology and behavior. Chaired by D. Pfaff

Theme Minisymposium: Control of CRF and ACTH secretion. Chaired by S. Gann

BMES Symposium: Recent advances in arterial wall research (physiology and bioengineering aspects). Chaired by K. Fronek

Symposium: Cell to cell communications. Chaired by W. C. DeMello

### Tuesday, Apr 12, A.M.

Theme Symposium: Neuroendocrinology of aging. Chaired by J. Meites

Instrumentation Tutorial: Image enhancement and image analysis in biology. Session I. Chaired by M. J. Jaffe and N. S. Allen

BMES Symposium: Musculoskeletal mechanics. Chaired by A. B. Schultz

Symposium: Ion transport processes in apical membranes of epithelia. Chaired by D. G. Warnock

Theme Slide Session: Circadian rhythms of hormone secretion. Chaired by R. R. Gala

### Tuesday, Apr 12 P.M.

SEBM Symposium: Recent approaches in developmental physiology. Chaired by M. A. Hofer

Instrumentation Tutorial: Image enhancement and image analysis in biology. Session II: "Hands on" workshop. Chaired by M. J. Jaffe and N. S. Allen

BMES Symposium: Theoretical models of mass transport in the microcirculation. Chaired by J. Gross

Theme Symposium: GnRH regulation of the gonadotropins. Chaired by M. Conn

Symposium: Information retrievable from ventricular pressure volume relationships. Chaired by K. Sagawa

Symposium: Ion transport processes in basolateral membranes of epithelia. Chaired by L. Reuss

Theme Slide Session: Stress-induced hormone secretion. Chaired by R. P. Maickel

Theme Poster Session: Neuroendocrinology of aging

### Wednesday, Apr 13, A.M.

Theme Symposium: Neuroendocrinology of nutrients. Chaired by J. D. Fernstrom

BMES Symposium: Bioengineering aspects of noninvasive diagnosis of peripheral vascular disease. Chaired by A. Fronek

Minisymposium: Minority hypertension (Research Development Summer Program). Session I

Theme Minisymposium: Mechanisms of anterior pituitary hormone secretion. Chaired by R. MacLeod

AIN/APS Symposium: Transport and metabolism of water soluble vitamins in intestine and kidney (programmed by AIN). Organized by R. C. Rose and L. M. Henderson

APS Plenary Lecture and Business Meeting
Physiology in Perspective Lecture: Functional significance of neurotransmitter diversity. Speaker F. Bloom

### Wednesday, Apr 13, P.M.

Minisymposium: Minority hypertension (Research Development Summer Program). Session II

Clinical Symposium: Interaction of platelets with the vessel wall. Session I: Receptor function of platelets. Chaired by J. Hawiger

Theme Poster Session: Hypothalamic-pituitary regulation of reproduction

Theme Slide Session: Growth hormone, thyroid stimulating hormone. Chaired by S. M. McCann

Symposium: The cellular and subcellular basis of myocardial hypertrophy. Chaired by N. R. Alpert and B. B. Hamrell

Symposium: Control of glomerular function by intrinsic contractile elements. Chaired by B. M. Brenner

BMES Symposium: The interaction between the heart and vascular system. Chaired by F. C. P. Yin

4:30 P.M. Career Symposium: Career Opportunities in Physiology. Initiation of an academic career in a basic science or clinical department as a Ph.D. physiologist. Chaired by T. M. Saba

4:30 P.M. Computers in Physiology Teaching: How can APS help? Chaired by J. A. Michael, APS Education Committee

### Thursday, Apr 14, A.M.

Symposium: Body composition and exercise. Chaired by D. Robertshaw

Clinical Symposium: Interaction of platelets with the vessel wall. Session II: Mediation and regulation of the platelet response by metabolites of arachidonic acid. Chaired by J. A. Oates

Symposium: Neuroendocrine control of the pancreatic islet. Chaired by D. Porte, Jr.

AIN/APS Symposium: Nutritional and physiological factors influencing lactation. Chaired by M. C. Neville and D. Bauman

BMES Symposium: Mechanical behavior of vascular smooth muscle. Chaired by J. M. Price and P. B. Dobrin

### Thursday, Apr 14, P.M.

BMES Symposium: Transport mechanisms of high frequency ventilation. Chaired by J. S. Lee

Clinical Symposium: Interaction of platelets with the vessel wall. Session III: The action of platelets on the vessel wall. Chaired by R. Ross

Symposium: Area postrema. Session I: Structure, connections and chemistry. Chaired by K. R. Brizzee

Symposium: Electrophysiology of secretory cells. Chaired by C. S. Pace

Symposium: Regulation of vascular smooth muscle contraction (in honor of David F. Bohr). Chaired by H. V. Sparks, Jr.

Poster Discussion: Regulation of vascular smooth muscle (in honor of David F. Bohr)

4:30–6:30 P.M. Workshop: Methodologies in human lactation. Chaired by M. C. Neville

### Friday, Apr 15, A.M.

BMES Symposium: Single cell mechanics. Chaired by G. Schmid-Schoenbein and R. Skalak

Symposium: Aspects of contraction of gastrointestinal smooth muscle. Organized by N. W. Weisbrodt

Symposium: Autonomic control of cardiac electrophysiology. Chaired by D. P. Zipes

Symposium: Area postrema. Session II: Functions. Chaired by H. L. Borison

## APS Fall Meeting, Honolulu
## Aug. 20-24, 1983

## XXIX IUPS Congress, Sydney
## Aug. 28-Sep. 3, 1983

### Travel Plans

*Los Angeles/Honolulu*: Block seats reserved on American Airlines for $296.00 round trip (plus lowest fares from home city to Los Angeles).

*West Coast to Sydney, Australia*: Special low **guaranteed** air fares on Continental Airlines and Qantas Airways for $960.00 round trip.

This fare allows stopovers in Honolulu, Melbourne, Sydney, Auckland, and Fiji (on Continental) or Tahiti (on Qantas). In addition we have prepared for you a complete selection of pre- and post-Congress tours including the Outer Islands of Hawaii, tours of Australia (including Heron Island on the Great Barrier Reef), New Zealand, and China.

Please **note:** Regulations stipulate that, in order to qualify for the low fares to Sydney, you must purchase a land package through us at a minimum of $190.00.

*Hotel Accommodations:* For your convenience we have blocked hotel rooms in Sydney at special group rates: Hotel Hilton (deluxe category) and Hotel Koala Oxford Square (first class). Both are excellent and centrally located. If you wish to reserve rooms at either of these hotels, do **not** complete the Housing portion of your Registration Form when returning it to Sydney. Instead make your hotel reservations when completing the Chevy Chase Travel reservation form.

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## APS Fall Meeting, Honolulu Aug. 20-24, 1983

The 34th Annual Meeting of the American Physiological Society will be held August 20-24, 1983 in Honolulu, HI. *Symposia and Special Sessions*: $H^+$ Transport in Epithelia; Factors Influencing Vasopressin in Body Fluids; Prostaglandins, Leukotrienes, and Lung Fluid Balance; Sea Bird Energetics; Physiology of Water Immersion; Neurohumoral Regulation of Circulation; and Autonomic Control of Coronary Tone. *Refresher Course*: Physiology and Biochemistry of Receptors, Wed., August 24, 1983. Tutorial lectures and contributed slide and poster sessions will also be held at the Meeting. Call for abstracts and meeting information to be mailed March 1983. Deadline for receipt of contributed abstracts, May 13, 1983. Persons who are not APS members may receive the call for abstracts by contacting Membership Services, American Physiological Society, 9650 Rockville Pike, Bethesda, MD 20814. Telephone: (301) 530-7171.

## Comparative Physiology Section

The new officers for the Comparative Physiology Section elected at the Annual Meeting in San Diego are Fred N. White, Chairman; H. T. Hammel, Councillor; Steven C. Wood, Councillor; Donald C. Jackson, Program Advisory Committee; and M. Roger Fedde, Secretary.

The Regulatory, Integrative and Comparative Physiology Section of the *American Journal of Physiology* will appear monthly starting January 1983. The editorial board has been expanded, and editorial reviews and symposia can now be published in the Journal. A rapid communication section has been established in the Journal for short papers of special interest. Manuscripts should be directed to Dr. William Dantzler through the Bethesda office.

All members of the APS who would like to join the Comparative Physiology Section are encouraged to contact the secretary so their names can be placed on the mailing list.

Roger Fedde, Secretary

# FASEB Life Sciences Research Office

## New LSRO Studies Underway

The National Aeronautics and Space Administration (NASA) has awarded a contract to FASEB's Life Sciences Research Office (LSRO) to provide two evaluative reports concerning research progress and opportunities in regard to the NASA research programs on bone demineralization and muscle atrophy during spaceflight. The first study will consider such topics as mechanisms of bone loss incurred during periods of real and simulated weightlessness and/or immobilization; continued development and use of noninvasive methods for measuring skeletal status; examination of the roles of dietary and hormonal factors directly and indirectly affecting calcium metabolism; minimization of increased calcium loss including dietary, physical, and pharmacological approaches; and reversibility and long-term consequences of bone loss occurring during spaceflight. Subjects addressed in the second study will include mechanisms of altered skeletal muscle metabolism and protein turnover associated with real or simulated weightlessness; skeletal muscle atrophy including biochemical and structural changes and reversibility; other influences on muscle integrity such as neurologic, hormonal, circulatory, nutritional, and work-exercise; dynamic and static exercise and other potential countermeasures; and needed improvements in methodology, instrumentation, and equipment. To assist in these evaluations, the LSRO will appoint two ad hoc expert panels of knowledgeable scientists with expertise related to these study topics. Critical questions and suggested research to aid in solving these problems will be included in the deliberations of the expert panels, which will meet in April or May. Members of the Federated Societies with an interest in these subjects are invited to communicate with Dr. John Talbot or Dr. Sue Ann Anderson, Life Sciences Research Office, 9650 Rockville Pike, Bethesda, MD 20814. Telephone: (301)530-7030.

The Human Nutrition Information Service of the USDA Consumer Nutrition Center has awarded a grant to FASEB's Life Sciences Research Office to review and recommend changes for improvement of the Atwater System for measuring the energy content of foods. The study will focus on possible needs for updating experimental data on which present tables of energy values are based, advances in analytical methodology, treatment of the energy value of carbohydrates, and the applicability of the factors 4, 9, and 4 kcal/g, respectively, for calculating the energy values of protein, fat, and carbohydrate in various diets. The LSRO will appoint an ad hoc committee of knowledgeable scientists with expertise in areas related to food analysis and composition, calorimetry, energy metabolism, clinical nutrition,

and dietetics. Research opportunities to further validate or improve present techniques of food energy assessment will be included in a final report that summarizes the conclusions and recommendations from the study to be completed by September 1983. Members of the Federated Societies with an interest in this subject are invited to correspond with Dr. Richard G. Allison, Senior Staff Scientist, Life Sciences Research Office, 9650 Rockville Pike, Bethesda, MD 20814.

## LSRO Reports Available

The Life Sciences Research Office has completed reports entitled *Effects of Certain Vitamins and Minerals on Calcium and Phosphorus Homeostasis* and *An Evaluation of the Potential for Dietary Proteins to Contribute to Systemic Diseases.*

A limited number of copies of these reports are available to FASEB Society members from the Life Sciences Research Office, 9650 Rockville Pike, Bethesda, MD 20814.

## FASEB Announces Summer Conference Series for 1983

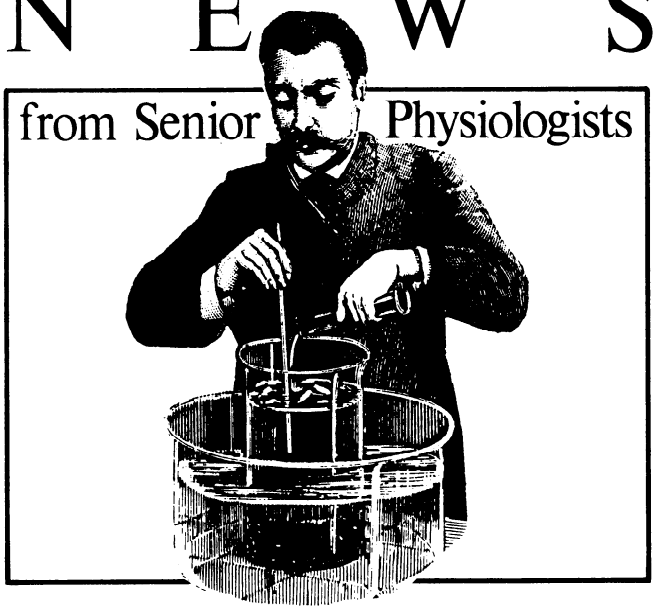
The Federation is pleased to announce that it will again sponsor a Summer Research Conference Series at the Vermont Academy in Saxton's River, VT.
*Topics and Chairmen*: Secretion (June 12–17), P. Rubin, Medical College of Virginia; Neural Control of Respiration (June 19–24), D. Frazier, University of Kentucky Medical Center; Neurotransmitters (June 26–July 1), S. Parsons, University of California, Santa Barbara; Micronutrients: Trace Metals (July 3–8), B. O'Dell, University of Missouri; Somatic Cell Genetics (July 10–15), R. L. Davidson, University of Illinois Medical Center; Developmental Neurobiology (July 17–22), P. Patterson, Harvard Medical School; Mechanisms of Carcinogenesis (July 24–29), D. Lowy, National Cancer Institute; Autoimmunity (July 31–August 5), C. G. Fathman, Stanford University Medical Center. *For Information*: Dr. Robert W. Krauss, Executive Director, FASEB, 9650 Rockville Pike, Bethesda, MD 20814.

## Are You Interested in Working in Space Biology?

NASA is offering several Research Associate Awards for scientists to work in laboratories capable of providing scientific advice and facilities relevant to Space Biology. The awards will vary from $14,000-$18,000 based on experience. They are planned for a 12-month period with the possibility of renewal. Proposals are due April 1 for July 1 funding and October 1 for January 1 funding. *Eligible* US citizens having Ph.D., D.Sc., M.D., D.D.S., or D.V.M. *For information/application forms contact* (specify award date applied for): Dr. X. J. Musacchia, Chairman NASA Award Committee, Graduate School, University of Louisville, Louisville, KY 40292 or Dr. Thora W. Halstead, Space Biology Research Associates' Program, Life Sciences Division, NASA Headquarters, Washington, DC 20546.

# N E W S

## from Senior Physiologists



### Reginald Bromily to Louise Marshall:

Although Reg Bromily wrote "I have nothing to say for publication," we believe this quotation is pertinent: "Words of wisdom from the wizen! At 18 or so I suspected all persons of 45 or so should be eliminated. I was 50-55 before I realized how near to wisdom I had approached at 18! Mankind seems to be forever destined to reinvention of the square wheel.

"Which I guess leads me to announce that last year I took up pottery. I now make bowls—just big bowls. I visit the studio 5-7 times a week. Justine and I are in fine health. Spend 3-5 months at our cabin on a lake and the rest of the time in Ottawa a city we love. She's busy with sculpting (soapstone, alabaster, cement) and bronze casting. All very amateurish but great fun."

It is worth adding that in addition to his scientific accomplishments in physiological psychology, Reg has the distinction of having rescued from oblivion the instruments that John B. Watson used in his studies of human sexual behavior. They were in a cigar box which was junked together with other discarded apparatus from the psychology department at Johns Hopkins. The records from those studies, the first such in America, were destroyed at the time of Watson's divorce and dismissal from Hopkins. The instruments, however, reside in the Canadian Psychological Association Archives.

216 Metcalf St., Apt. 7
Ottawa, Ontario

### Charles D. Kochakian to Louise:

On my retirement in 1979 from the Division of Endocrinology and Metabolism, University of Alabama, Birmingham, the Department of Biochemistry offered me a laboratory and the School of Dentistry an office. I disposed of much of my equipment but retained pertinent equipment and supplies to continue one phase of my research program. I have had no assistants except for a part-time work study student during the 1979-80 year. The research provided material for three manuscripts which were recently submitted for publication.

In the first year of retirement I also prepared and published a report in the *Alabama Journal of Medical Sciences* 17: 215-227, 1980 entitled "The Summer Student Program: a summary and evaluation." This program for Alabama high school senior students and college undergraduates was initiated by me shortly after arrival in Birmingham to provide opportunities for gifted young Alabamians and to stimulate enrollment to these students in the medical, dental, and graduate schools. The program was continued from 1960 to 1970 and provided opportunities for 235 young Alabamians. A reprint of this article and letters from the students have been bound and deposited in the Lister Hill Medical Library of the University of Alabama in Birmingham.

This past summer I compiled as a manual the laboratory experiments in endocrinology which I had developed from 1940-50 for the medical students when I was a member of the Department of Vital Economics at the University of Rochester. Many of these experiments were also used by me in the undergraduate course in physiology at the University of Rochester. I hoped that one of the publishers of biomedical books would publish this manual, but I fear laboratory exercises are not very often included in course work at this point in time. I have watched with great dismay the gradual reduction of laboratory exercises for medical students.

In December 1981, I was requested to vacate the laboratory space in the biochemistry department to provide space for the new chairman of the department. Fortunately, Dr. Buris R. Boshell, Director of the Diabetes Hospital, invited me to join him as a visiting professor. A new visiting professor's unit will be built in the hospital to accommodate my activities. The completion of the until will take several months. In the meantime I hope to complete the writing of my memoirs. I have been urged to do this by several colleagues to record the events, planning, and the personal aspects involved in my discovery of the anabolic action of androgens and my subsequent seminal pioneering reports. I also will serve as a consultant to a group at the Diabetes Hospital in the study of the use of the anabolic action of androgens as a supplement in the treatment of diabetic patients especially those prone to ulcers and gangrene.

3617 Oakdale Rd.
Birmingham, AL 35223

### W. B. Youmans to E. Brown:

Five years ago I became emeritus and we moved from Madison, WI, to a house on two acres on the outskirts of Port Angeles, WA, in the rain shadow of the Olympic Mountains. The Olympic Peninsula is invaded by tourists in the summer. Port Angeles is directly across the Strait of Juan de Fuca from Victoria, BC, which is located at the southern tip of Vancouver Island. There is much movement by ferry between these two cities and we go over several times per year.

One of my main hobbies is vegetable and landscape gardening. We made a list of 41 food items that I am growing. Douglas firs and rhododendrons surround us. We enjoy camping in a tent trailer at the sea coast or in the Cascades.

I have continued to do a little writing and have had a technical comment published in *Science* and a letter in the *New England Journal of Medicine.*

In reading recent textbooks of basic sciences and cardiology, I am surprised to find lapses into "backward failure" terminology to describe effects of cardiac failure. There is reference to "backpressure in the pulmonary system" or "damming back of blood in the venous system (so-called backward failure)". As pointed out by Isaac Starr (first?), the backward failure theory postulates that a decrease in cardiac output leads to a rise in end-diastolic pressure in the left ventricle before a rise in pressure in the left atrium, whereas in fact the reverse is true.

162 Benson Rd.
Port Angeles, WA 93862

## Bruno Balke to E. B.:

It is now nine years since I retired from the University of Wisconsin, where I had a double appointment with the Departments of Physiology and Physical Education. During the nine years in that position (after 14 years of research in Governmental Aerospace Laboratories), I was fortunate to have excellent graduate students enrolled in a newly established Ph.D. program in "Biodynamics" (exercise and environmental physiology). In addition, I became rather successful in instigating a cardiac prevention and rehabilitation program at a time when it was still frowned upon in many parts of the country.

Unfortunately, the cessation of experimental physiological research kept me from further participation in Meetings of the Physiological Society. Without active contributions to the scientific sessions I would have felt somewhat out of place. Instead I contributed more to the area of Sports Medicine by founding and editing a new journal, *Medicine and Science in Sports*, and by writing many articles and chapters for books.

After my "retirement" in 1973 I moved to Aspen, CO, with the idea of getting some experience on how moderate altitude would affect the cardiac rehabilitation process. The results with a few post-infarct and post-bypass patients were encouraging and could justify a more thorough study on a larger population. The combination of adequate exercise training and moderate altitude (between 8,000 to 11,000 feet) did not seem to increase the risk of incidents. In many hundreds or even thousands of hours spent in exercise testing and training I have encountered more serious incidents only twice. But both men recovered quickly with application of simple procedures of restoring and ensuring venous return to the heart. Possibly, this was one of the most important lessons I learned and emphasized in practice and teaching: especially cardiac patients are very susceptible to and critically affected by the pooling of blood in the lower extremities and in the splanchnic area. I firmly believe that reported fatal "heart attacks" of long-distance runners, after they shortly paused during exhausting runs, were caused by this pooling phenomenon.

Of course, one cannot live in the resort town of Aspen without getting involved in the winter season of cross-country and downhill skiing. Especially the latter is most enjoyable to me, because the modern ski-lift systems ensure painless uphill transport. After arthroplastic surgery of both hip joints my enthusiasm for physical activities has been damped somewhat, although not totally. With the aid of crutches I still manage long hikes in the mountains during Summer and Fall, with the exclusion of my former enthusiasm for more difficult climbs. Bicycling and skulling come easier to the hips and are useful preconditioners for skiing.

After you have read this brief account of my more recent life you certainly will agree that I have never been a pure physiologist, but I still try to apply essential physiological principles in my service to mankind.

P. O. Box 630
Aspen, CO 81612

## Richard L. Riley to E. B.:

In response to your letter of some time back, I am enclosing a picture of me, probably from the 1950's, using the Roughton-Scholander syringe. This foolish little instrument made my reputation as a respiratory physiologist, because we were able to measure arterial $Po_2$ and $Pco_2$ relatively quickly an easily more than 10 years before the electrodes came in. The method was developed in 1944 or 45 when I was working with Joseph L. Lilienthal, Jr., at the Naval School of Aviation Medicine in Pensacola, FL.

Right now I am about to take off for Sicily, where I will talk on "Historical review of hypoxia" at meeting of the European Society for Clinical Respiratory Physiology. Then, at the invitation of Carlo Giuntini, I will go to the University of Pisa to talk on "Corner stones of alveolar-capillary gas exchange: quantitative description of the alveolar gas composition of an ideal lung." I also want to talk on our current ideas concerning the peripheral circulation, including the postulated arteriolar-capillary "waterfall" and the control of blood flow.

Petersham, MA

## Curt P. Richter to Roy O. Greep:

It delighted me to hear from you again. Your letter brought back memories of the happy days of early Endocrinology, when we were all so much concerned with the whole animal or person. Now I get lost in trying to follow all the Endocrine related substances through the many intricacies of the brain. I still get to my lab every day. I am trying to catch up with a lot of unpublished material and also to work out some more general principles underlying my studies on behavior. If you ever come this way, please be sure to stop in to see me. With all best wishes.

The Henry Phipps Psychiatric Clinic
601 N. Broadway
Baltimore, MD 21205

## Jane Sands Robb Johnson to Roy:

I have your birthday card and its request at hand—but what to write! When I state that I have had similar requests from Edward Adolph, Maurice Visscher, Hal Davis, and Philip Dow, you will realize I am far beyond 80. It is years since I've done any medical work largely because of eye sight. At first there were bilateral cataracts, next edema followed by degeneration of both maculae, and finally a double ptosis. As I

write I can only try to keep lines from overlapping; my pen moves by memory.

There are still some ways of contributing. In this home I can answer some medical questions for other residents-(I do not take care of any), just listen, and answer queries. I can read large print to one who sees less than I do. Then I have many grandchildren to whom I can listen and sometimes help. Finally three great grandchildren to whom I can tell stories.

This is not much to record in a journal. Maybe we could say that at 89 I live comfortably and happily in a retirement home, an excellent one.

Clara Welch Thanksgiving Home
Cooperstown, NY 13326

## Horace W. Davenport to Charles F. Code:

You are correct about my age; I will be 70 in October and retire next June. That won't make any difference to what I am doing. I quit research two years ago for the reason that I had run out of ideas and techniques. I do miss the actual work of the laboratory, but I have no regrets otherwise. I was extremely fortunate to have you point me to a problem that my talents enabled me to tackle with some results.

I am working full time on history, and I will continue to do so as long as I have the ability. I am just in the early stages of a big project that will take at least two more years. My complaint about so much medical and university history is that it is little more than a list of names and dates. I am trying to discover who the persons were and what they actually did. It is a great deal of fun finding out who a person really was. Just last week I began to make the acquaintance of George Linius Streeter, who was Professor of Anatomy here for seven years. I now know something about him including the fact that he was an artist of great skill. I have recently learned about the man who was the first director of Roentgenology at the Mayo Clinic, for he ran the X-ray laboratory here until 1909. And so on. It's a lot of fun, and I hope that some others will appreciate the persons I have tried to bring back to life if my work is ever published. Perhaps I will simply circulate it in duplicate as I did my "Swan Song."

Department of Physiology
The University of Michigan
Ann Arbor, MI 48109

## Fred B. Benjamin to Charles:

I appreciate the opportunity to keep in contact with the rest of the physiological world through the pages of *The Physiologist.*

I retired from my job as Senior Research Physiologist with the Department of Transportation some two and a half years ago. For two years I continued working part time as a consultant for the Government. Now, being fully retired, I find myself busier than ever, and I believe that this is the key to a successful retirement. I am living in a retirement community, and there I am chairing the health committee, giving a series of lectures on "Health and Aging," and leading discussion groups in Nursing Homes. I am a docent at the National Air and Space Museum. In addition, I do a lot of traveling, hike, paint, and play chess, bridge, and pool.

I am on excellent terms with my children and grandchildren. But essentially we lead separate lives. Frequently I have dinner at their places or we go out together. Sometimes I do some baby sitting, and I can always count on their help if and when required.

I have one fear, which I share with many older people, the fear of being incapacitated, of becoming a burden to family, friends, and society. For the physiological and medical reseacher this means that extension of life is a poor goal, unless the additional time is meaningful, productive, and enjoyable.

15300 Beaverbrook Ct.
Silver Spring, MD 20906

## A. Baird Hastings to Arthur B. Otis

There has been no change since last year in my University position or role. Though I was 87 on November 20, the Regents have continued my annual appointment as Research Associate in Neurosciences, without remuneration. My Office continues in the Physiological Research Laboratory, Scripps Institution of Oceanography, UCSD, where I go Mondays through Fridays from 9 to 3. There I write, read, and consult with students and staff.

As to activities this year, I have published two items, one a paper with Dr. Colin Bloor in the *Journal of Applied Physiology* on responses to exercise by dogs and pigs. The other a note in *Geriatrics* on the start of the National Institute of Aging. In October I spent a week in Boston attending the Harvard Medical School's bicentennial celebration. It was full of nostalgia for me, seeing old students and colleagues, visiting the labs that I know so well for 23 years and marching in the academic procession on the last day as the official respresentation of UCSD Medical School. (Dean Petersdorf was unable to be present).

I stayed with the Jack Buchanan's, Professor of Biochemistry at MIT. Their home is in Lexington, where the fall coloring was at its height. It was altogether a strenuous but rewarding experience.

Scripps Institution of Oceanography
La Jolla, CA 92093

## J. H. Wills to Arthur:

When I retired, I was sufficiently fortunate to be accepted as a Visiting Professor of Pharmacology (without salary) at the Uniformed Services University of the Health Sciences. Here, I have been occupied in doing a minor amount of teaching, in analyzing data that have never been written up for publication, and in performing some new research supported by a small grant. I offer a 2-hour course on the Pharmacology of Voluntary Activity, which has been given once, in addition to taking part in other courses offered by the Department. I have had four papers published since retirement, have two other in the works, and am involved currently in producing a chapter for a book to be entitled *The Pharmacologic Basis for Treatment of Critically Ill Patients.* My chapter is on "Antipersonnel toxic agents and radiation." I have done some work also for the National Research Council; this will be published as an appendix

to one of their reports and relates to research on the central effects of anticholinergic compounds with which I, and many other people, were involved at Edgewood years ago.

At some time in the past, Wallace Fenn said to me: "Never give up on what you think is right." I have tried to follow that precept through my various shifts of activity. I do not know for how much longer I shall be able to continue to follow it, but I would like to be able to do as well temporally as WOF.

Uniformed Services University
of the Health Sciences
Bethesda, MD

## Hermann Rahn to Arthur:

Thank you for your best wishes on my 70th birthday, which I celebrated in a snowstorm at the North Polar Research Institute of Norway, at the 79th parallel, 700 miles from the North Pole, on the Island of Spitzbergen.

State University of New York
at Buffalo

## Edward D. Freis to Arthur:

This note is to let you know that I have not retired and am still very active in the same position as Senior Medical Investigator of the Veterans Administration. While most of my work at present is involved in the clinical evaluation of antihypertensive agents, I still carry out some physiological studies related to hypertension. These include the effects of weight reduction in blood pressure in spontaneously hypertensive rats and on the relationship between volume expansion on blood pressure. We have made an incidental observation of interest in one of our VA Cooperative Therapeutic Trials in that we have found a significantly lower potassium excretion in 24-hour urine collection in blacks compared to whites.

The only words of wisdom I would have to younger colleagues is to avoid administrative responsibilities as much as possible if you wish to remain productive in research.

Veterans Administration Medical Center
Washington, DC

## Francis O. Schmidt to Arthur:

The efforts of your Committee on Senior Physiologists are, I am sure, appreciated by the large number of elder physiologists, including me, but probably also by a yet larger number of their former students. Thanks for your birthday greetings and personal note.

Massachusetts Institute of Technology
Cambridge, MA 02139

## Hallowell Davis to Arthur:

I am a very lucky man. I am still active as a physiologist at the age of 86. My hearing is failing and cataracts are beginning to appear and I can no longer handle my extension ladder alone, but I am healthy and I think I still have most of my marbles. Here at Central Institute for the Deaf the administration is broadminded on the subject of geriatric retirement, and I still draw a nominal salary and have an office and secretarial service. I go to the Institute and to St. Louis Children's Hospital three days a week. I still have something to do, and I expect to complete my final project, which I began in earnest in 1960, before old age finally catches up with me. Physiology means more than ever to me now that I am living alone.

My project is to perfect a method for assessing the peripheral auditory system in children who are too young or otherwise difficult to test by conventional methods. We need such a method to identify and institute proper management of hearing-impaired children. We want to equip them with hearing aids and start teaching them speech, lip-reading, and language before they are six months old if possible. My method is an adaptation of EEG, which was one of my major interests in the 1930's. We use computer-averaged auditory evoked potentials of the brain stem. It has taken all these years to learn enough about evoked potentials and to take advantage of advancing computer technique to find a response that is sensitive enough and also robust enough to serve as an indicator, even when the child is tested under sedation. We have it at last and can estimate the peripheral thresholds at 500, 1,000, 2,000, and 4,000 Hz with an accuracy of $\pm 10$ db.

My advice to young physiologists (and others as well) is to stay healthy and keep busy. Of course to stay healthy beyond 80 you should have done a careful job of selecting your ancestors and not be stuck with genes that predispose to cancer, cardiovascular disease, metabolic disorders, or psychiatric aberrations. Then you must have a devoted wife to take care of you and encourage you. You should find a career in which you get paid for doing exactly the thing you most want to do. But in the future, life will be much more difficult than it was for me. You must avoid the final epidemic of nuclear warfare. You must grin and bear it with supply-side economics and Ronald-sized military budgets. You must contend with worldwide irrational religious fanaticism, and you will have to endure the squeeze between population pressures and finite resources. I realize full well how lucky I have been. It is too late for you young fellows. I had it during the best century, past or future. But perhaps you can help mankind achieve a steady state of interaction with one another and with the environment. I cherish a lingering hope for world government under law with justice. It is the only way. Otherwise *Homo sapiens* will go the way of the dinosaurs.

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# HUMAN
# A Comprehensive Physiological Model

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As important as the concept of homeostasis is to understanding physiology, the term may not convey the complexity of interactions which are actually involved in the many facets of regulation. Adolph (1) has recently reflected upon the integrative nature of the discipline by giving specific examples of the coordination involved in many body functions. Most of us acquire the integrative perspective from years of experience, but the concept is so central to physiology that it deserves special emphasis for students. This is particularly important during this era of exciting advances at the subcellular level.

Mammaliam animal experiments have been the traditional way for students to observe the organism as a whole. Tidball (10) has affirmed the need for conventional physiology laboratory exercises in spite of economic and other constraints. Experience with living material is an essential component in biomedical education, but there are practical limitations that detract from the desired integrated view. Much of the laboratory attention must be directed to techniques at the expense of global concepts. Even in the hands of skilled technicians there are limits to the number of variables that can be measured on-line. Some experiments of a chronic nature may take days of observation before the physiological actions are manifested. Furthermore, undergraduate courses in physiology may not be instrumented for dynamic mearsurements of more than the simplest of variables.

## Computer Simulation

The sudden arrival of microcomputer technology has sparked a new awareness of the potential of computer simulations in teaching, not only for insight of complex systems but also to follow the time-dependent nature of physiological variables. Computer simulations cannot replace animal experimentation, but they can overcome many of the practical constraints listed above. Standing and Tidball (9) have assessed the advantages and limitations of the use of computer simulations in the teaching of physiology, including large integrated models. Their paper has been reprinted, along with several other relevant ones, in *Frontiers in the Teaching of Physiology: Computer Literacy and Simulation*, edited by Drs. Tidball and Shelesnyak (11), and published by the American Physiological Society.

Many of the organ-system functions can be adequately represented by mathematical formulations based on physicochemical principles, such as conservation of mass and energy. In other cases the relationships may still be empirical correlations. But these representations are being used as teaching exercises, such as "MacPuf" (4) for respiration and microcomputer versions (7) of the Hodgkin and Huxley models for excitation in the squid axon. On the other hand, comprehensive models integrating the functions of several of the organ systems (5, 6) have largely been research oriented, in a continuing state of development, or not sufficiently interactive for the nonspecialist to either use or even appreciate.

The purpose of the present paper is to describe to physiology teachers the potential of a comprehensive model, called HUMAN. This model consists of the dynamic interactions of over 150 physiological variables and integrated approximations of cardiovascular, renal, lung, temperature regulation, and some hormone functions. This digital computer simulation has been used (as has MacPuf) for several years as part of the laboratory exercises in the medical course at the University of Mississippi and elsewhere. The model was written in FORTRAN for a time-shared mainframe computer accessed by video terminals. It has also been implemented for microcomputers supporting the popular operating system called CP/M-80 (8).

The model may be used to simulate physiological experiments or to simulate patient pathology. For experimental protocols the operator may manipulate any of up to 60 parameters in the model. Parameters represent values of a body property or environmental condition which remains constant during a simulation.

Examples might be respiratory dead space or the percentage of inspired carbon dioxide. The mathematical relationships then update all of the computed variables, simulating the dynamic homeostatic responses to the perturbations introduced in the teaching exercise.

Output of the simulation consists of tabulations of any eight of the computed variables displayed in tabular form on the video terminal or on a printer. Simulation may be stopped temporarily in order to view all of the variables on a number of charts organized according to the organ systems involved.

Some of the parameters mimic patient pathology, such as the extent of coronary disease or the rate of blood loss during hemorrhage. Such conditions may be saved to provide exercises in diagnosis and treatment.

Before presenting examples of simulated physiological exercises or patient encounters it will be helpful to describe the modular structure of the model and the nature of the operator interactions.

## Functional Modules

Conceptually one can think of the computer program as consisting of three functional units: the main program, the mathematical model as a subroutine, and the data array. The main program handles the interaction with the operator and with peripheral devices, such as the video screen, the printer, and the mass storage. Upon instructions from the operator the program calls the subroutine containing the mathematical model. Each pass through the subroutine updates all of the FORTRAN variables, using their interrelations as proposed in the model. These variables, collectively called the data array, express the state of the system at any instant.

Keep in mind a major limitation of present digital simulation methodology. Processes occurring simultaneously in the body must be approximated by sequential computations of each process in turn. The approximation is adequate only if the computation time increment is small compared with the time constants of changing variables.

This model is organized into 31 modules, each designed to approximate some body function. Such a program structure allows for ongoing improvements in the validity of individual units without reorganization of the whole model. The list of a few of the functional modules in Table 1 shows the breadth of the model. Some of these will be discussed to give an idea of the detail of each and their methods of interaction.

Several of these modules are concerned with mass or energy balance. The various gains and losses are summed and then integrated over the computation increment to give a new value of the variable. Regulation may involve the coordination of several of the modules.

### Temperature Regulation

As an example, temperature is calculated on the basis of heat content and specific heat. On each pass through the temperature regulation module, the contributions of heat production and of heat loss are summed and integrated to give a new heat content.

In the model, heat production has contributions from basal metabolic rate and muscular metabolism. The basic metabolic rate is influenced by a thyroid multiplier, sympathetic activity, and body temperature itself. Muscle metabolism is geared to level of exercise, a shivering induced at low body temperature, and the contribution of the respiratory muscles. This explicitly illustrates the interdependence of organ systems in that calculations of body temperature depend on values calculated in modules concerned with muscle metabolism and with ventilation.

The heat loss depends on ambient temperature and humidity parameters as well as a sweating level, which is a function of body temperature. Interaction occurs with the circulatory modules, since skin blood flow influences the conductance between core and ambient temperatures. In turn, skin vascular resistance influences total peripheral resistance. The sweat produced influences the water and sodium balance as calculated in their respective modules.

Table 1
Functional Modules in the Computer Model

| | |
|---|---|
| Pharmacology Section | 24-Hour Urine Collection |
| Cardiovascular Reflexes | Hemodialysis |
| Cardiac Function | Fluid Infusion and Loss |
| Heart-Reflex Interaction | Water Balance |
| General Circulation | Sodium Balance |
| Oxygen Balance | Acid-Base Balance |
| Carbon Dioxide | Urea Balance |
| Control of Ventilation | Potassium Balance |
| Gas Exchange | Protein Balance |
| Basic Renal Hormones | Volume Distribution |
| Status of Kidney | Blood Volume, RBC Mass |
| Renal Excretion | Temperature Regulation |

Computer model is organized into these modules, each dedicated to some specific body function. As an example, Water Balance module integrates net gains and losses of water as computed in other modules.

### Sodium Balance

Sodium mass is initially set according to a total extracellular space of 15 liters and a concentration of 145 meg/1. This is modified on each iteration according to the net balance of *1*) dietary intake (a fixed parameter), *2*) excreted sodium (set by kidney function), *3*) sodium lost by sweat (from temperature regulation), *4*) sodium changes by infusion of tranfusion (from fluids section), and *5*) sodium lost by dialysis (set by that section).

The same kinds of logic apply to water balance, potassium balance, oxygen balance, carbon dioxide balance, protein balance, and blood volume.

### Heart-Reflex Interaction

One of the more involved modules is concerned with distribution of cardiac output to the organ systems in such a way as to satisfy a number of constraints imposed by the function of the individual organs. Skin resistance is influenced by body temperature, coronary resistance by the work of the heart, and renal resistance by plasma renin activity to name the major factors considered in the model.

Furthermore, the resulting total peripheral resistance combines with total flow to determine arterial pressure. This is sensed by the baroreceptors to in turn influence peripheral resistance and cardiac output. Because the reflexes involved in these actions respond quickly compared with practical integrating intervals, the multiple interactions within the module must be satisfied before progressing to compute those in the next module.

### Pharmacology Section

At several points in the model multipliers mimic a pharmacodynamic action. As an example, the basic heart rate is influenced by a balance between sympathetic and vagal nerve activities. But vagal slowing of the heart is modulated by an atropine multiplier, so that heart rate increases with increase in atropine dose. The pharmacology section handles the pharmacokinetics for atropine and several other drugs. In most cases these are represented by first-order disappearances.

Other drugs include nitroglycerine (which influences vascular resistance), digitalis (which influences ventricular function), two kinds of diuretics, norepinephrine, and a converting enzyme inhibitor.

### Clamps

One of the indications of the complexity of interactions in both the model and the living organism is the difficulty in changing only one of the variables and having it stay fixed. In demonstrations to experienced physiologists, it has been amusing to explain that one cannot just set and hold the blood volume to some new value. On the next iteration it will be modified by a number of compensatory mechanisms.

There are several places in the model where it is possible to open specific feedback loops and force the system with selected parameters that remain constant. This is the case for an artificial respirator, where the operator sets tidal volume and frequency. Other points include an artificial heart (fixed stroke volume and heart rate), artificial kidney (selected dialysis concentrations), fixed sympathetic outflow, and a renal stenosis of fixed pressure drop.

### Symptom Messages

Throughout the model there are a number of variables that take on the value of either 0 or 1. Their states can be used to turn on messages of a subjective nature. Prolonged hypotension may activate "I feel dizzy"; low arterial oxygen, "Your patient is cyanotic"; fluid retention, "My feet swell." The state of the "alive-or-dead" variable is changed if any of the vital variables get out of range. This terminates further computations. Messages at autopsy may show fibrillation for elevated plasma potassium, distended left ventricle for high left atrial pressures, ventricular hypertrophy following prolonged cardiac loads, and fluid in the lungs along with others.

## Operator Interaction

Since most users of teaching simulations lack experience with computers, it is important to make the operating procedures as obvious as possible. This is particularly easy to do for the microcomputer version of HUMAN, because the hardware is compact and the program starts automatically when the power switch is turned on. Thereafter operation proceeds by making a selection from a menu.

Microcomputers having the capacity to run HUMAN typically cost about $3,000. These have the size and appearance of a small television set placed on an office typewriter. Programs are stored on a 5.25-inch magnetic disk that is placed into a slot in a drive mechanism. When the power switch is turned on, the cathode-ray tube (CRT) displays a menu of options, shown in Fig. 1. The prompting line, at the bottom of the screen, is waiting for the operator to enter one of the letters indicated in the display. This same prompt appears at other times when one of these commands is required from the operator. The response of "H" will then redisplay this menu as a reminder of the options available.

The choice of "I" allows setting the initial values of parameters and computed variables either for normal or for previously stored patient encounters using abnormal parameters. These conditions have previously been saved in a disk file and called into the common area of the FORTRAN program for the model. For example, an initial massive hemorrhage might be followed by a slower ongoing one representing internal bleeding. This state of the simulation may be saved after a simulated few hours, so that the student is presented with conditions of falling blood pressure, falling hematocrit, and tachycardia. If the cause of these symptoms is recognized soon enough, it may be reversed by appropriate transfusion.

The "T" option selects the titles of the columns containing the variables to be followed as tabular displays with increasing time. There are default selections in place for experiments or for patients (showing only clinically observable values); or selections may be made according to the items of interest.

The "C" and "P" both initiate simulation with tabular displays on the video screen (CRT), but "P" also sends a copy to the optional printer. The operator is asked to select the total duration of the simulation and the time increment between displays. Figure 2 shows the initialization and computation steps for five variables: systemic arterial pressure (mmHg), cardiac output (ml/min), muscle blood flow (ml/min), ventilation (l/min), and venous oxygen content (ml/ml).

Individual variables may be examined with the "V" option, unless these are "locked out," as for values which might not be routinely available clinically. Parameters, depending on whether it is a patient or not, can be both examined and changed. For example, a student could not peek at the parameter for hemorrhage but would be able to set the rate and duration for a transfusion.

Hidden commands, used by instructors, permit returning to the CP/M operating system or saving the current data. These are useful in establishing new patient simulations.

```
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          I = Initialize Parameters

          C = Continue Computations

          P = Print Computations

          V = Values of Variables

          T = Titles of Columns

          E = Exit to Run Charts

     NEXT (H For for HELP) > ■
```

Figure 1

Command options. This menu is displayed on video screen when power is turned on; or it may be recalled at any time by operator. Black rectangle is a cursor, indicating that computer is waiting for operator to make a selection. Options permit setting model to normal base-line conditions, doing a simulation, and other choices as explained in text.

```
NEXT (H for HELP) > C

Minutes till next stop = ? 10
Minutes between printouts = ? 5

DAY = 1 --- TIME = 12:00 AM
 TIME      AP        CO       MUSFLO       VENT        O2V
12:00    99.00     5439.       1113.      5.736       .147
12:05    99.00     5439.       1113.      5.735       .147
12:10    99.00     5442.       1113.      5.736       .147
```

Figure 2

Base-line values for five of computed variables as displayed on video screen or on printer. Operator chose command "C" (Compute) for 10 min of simulated time with values printed at 5-min intervals. Variables are AP, arterial pressure in mmHg; CO, cardiac output in ml/min; MUSFLO, skeletal muscle blood flow in ml/min; VENT, ventilation in l/min; and venous oxygen content in ml/ml. Operator may choose those variables to be displayed during a simulation.

Pressing the "E" exits from the computing program and activates a second program which shares the current set of values in the data array. This program organizes related computed values into charts selected from a menu shown in Fig. 3. This data format provides a quick glimpse of the status of all organ systems. Some of these chart displays will be illustrated later.

## Physiological Experiments

In its present state HUMAN contains over 20 experiments, which are described in a student's manual, stating the objective of each and asking leading questions to be answered by the simulation. Since there are at least 50 parameters, each of which may be set independently to a wide range of values, there is the potential for many, many more experiments. The organization is such that experiments can be designed either by instructors or by motivated students.

To keep the program size within memory limitations, the present version depends on printed instructions, protocols, and questions. Thus the design of new experiments does not depend on program modifications, only the writing of new printed material. Such documentation should contain the symbols depicting the parameters to be manipulated in a given experiment. The student manual does this in an alphabetized glossary of 67 entries; the individual experiments indicate just which few are to be changed. For example, in producing a hemorrhage, two parameters must be changed from the default value of 0: HEMVOL is the volume of the hemorrhage in ml; HEMMIN is the duration of the hemorrhage in minutes.

The student manual contains an alphabetized glossary of 150 physiological variables, many of which may change during a given experimental manipulation. Instructions for a given experiment must indicate which of these variables are to be presented to the CRT screen or to the printer in order to follow the dynamic responses. Alternatively, all variables are displayed in the form of charts when the "E" (exit) option is selected.

```
                .... HELP ....

The following charts are available:

          B:   Blood Chemistry
          C: * Circulation Summary
          D:   Drugs in Use
          G: * Blood Gases
          K: * Kidney Summary
          L: * Lungs & Vent. Summary
          M: * Muscle and O2 Debt
          P:   Pharmacy of Drugs
          S:   Urine Specimen
          U:   24-hour Urine Collection
          Y:   Your Patient's Chart

             *  Not available during
                diagnosis of patients

         XP:   Print Chart X
          E:   Exit to Continue Compute

CHARTS (H for HELP) > ■
```

Figure 3

Menu of a number of charts that may be displayed or printed as selected by operator. These charts show current values of computed variables organized by body function. Figures 5 and 6 illustrate two of these charts. Those choices marked with asterisk (*) are ordinarily not available during patient simulations.

### Exercise

The response to exercise involves all of the organ systems described in the model and serves as a good illustration of the integrative aspects which can be studied by simulation. In HUMAN we simulate exercise using two parameters: EXER defines the intensity in liters of oxygen consumed per minute by skeletal muscle; EXERMIN defines the duration in minutes

The primary cardiovascular effect is to reduce the resistance to blood flow through the skeletal muscle, with additional actions on the sympathetic outflow and on the level of ventilation. Note that exercise is terminated when oxygen debt exceeds 10 liters. One possible manipulation is to adjust the intensity of exercise to different values in an attempt to see how long that level can persist. Does breathing of 100% oxygen prolong this? Does infusion of high-hematocrit blood help?

Figure 4 shows the printer output after changing the exercise intensity from 0.0 to 1.0 liters $O_2$/min for the same five variables shown in the steady state in Fig. 2. The printout interval has been set at 0.5 min to follow the rapid changes.

This simulated response shows an increase in cardiac output, large muscle blood flow, and a fall in venous oxygen content. Comparable responses have been observed in exercising humans (2, 12). The displayed variables have approached an apparent steady state during which increased ventilation balances the increased oxygen extraction. Alternative choices for the tabular columns could have been total peripheral resistance, individual organ flows, alveolar ventilation, oxygen debt, heat production, sweat, or any of the other 150 computed variables.

The overall view at some instant in the simulation is presented by looking at the charts as selected from the menu in Fig. 3. Circulation, respiration, and muscle metabolism might be of particular interest after 5 min of exercise.

Figure 5 shows the normal and current values for the pressure and regional blood flows. Note the increase in systolic and pulse pressures consistent with increased stroke volume. Also, the skeletal muscle flow increases in absolute terms and now gets over 60% of the cardiac output, while other organs show only minor changes in flow.

Figure 6 shows the metabolic state of muscle after 5 min of exercise. If the value of the variable EXER is other than 0.0, a message to that effect is displayed. Besides flow to the organ, oxygen delivery and oxygen utilization are given, as are arterial and muscle venous partial pressures. Although heat production is five times normal, temperature rise is slight during this time because of the large heat capacity of the body.

## Hemorrhage

Another demonstration involving several modules in the model is the response to hemorrhage. Figure 7 shows

```
Value of EXER is 0.00
New Value of EXER is 1.0

DAY = 1 -- TIME = 12:10 AM
```

| TIME | AP | CO | MUSFLO | VENT | O2V |
|---|---|---|---|---|---|
| 12:10 | 99.2 | 5444. | 1113. | 5.736 | .147 |
| 12:10 | 107. | 6496. | 1749. | 7.229 | .143 |
| 12:11 | 111. | 7877. | 3082. | 9.206 | .131 |
| 12:11 | 111. | 9595. | 4950. | 11.061 | .119 |
| 12:12 | 112. | 11052. | 6573. | 14.995 | .111 |
| 12:12 | 111. | 11874. | 7488. | 16.821 | .107 |
| 12:13 | 112. | 12505. | 8157. | 18.941 | .105 |
| 12:13 | 111. | 12779. | 8496. | 19.660 | .103 |
| 12:14 | 111. | 13065. | 8856. | 20.5 | .102 |
| 12:14 | 111. | 13155. | 8967. | 21.7 | .101 |
| 12:15 | 111. | 13253. | 9091. | 21.7 | .101 |

### Figure 4

Continuation of simulation in Fig. 2 after exercise parameter has been set. Magnitude of exercise is expressed as an increase in oxygen utilization by skeletal muscle, 1 l/min in this case. Variables displayed are the same as in Fig. 2. Computation interval was selected as 0.5 min, though value is printed to nearest minute. Note responses, such as increase in cardiac output and ventilation, redistribution of cardiac output to skeletal muscle, and greater extraction of oxygen.

```
. . . .  CIRCULATION  . . . .

PRESSURES (mm Hg):
   Mean Art. (100)          111.
   Sys/Dia (120/80)      158./80.
   Pulm.Art.                27.
   Rt.Atrial ( 0)            5.1
   Lft.Atrl  ( 6)           17.8

Flow (ml/min):
   Cardiac Output        13253.
   L-to-R Shunt              0.
   R-to-L Shunt              0.

Regional Flows (ml/min):
   Brain        (750)       817.
   Coronaries   (225)       372.
   Muscle      (1100)      9091.
   Renal       (1200)      1056.
   Skin         (400)       391.
   Other       (1825)      1529.
Peripheral A-V Fistula        0.
```

### Figure 5

Circulatory variables after 5 min of exercise. Normal values are included within parentheses for comparison.

```
. . . . MUSCLE AND OXYGEN DEBT . . . .

Exercise is underway

Muscle:
  Flow          (1100)      9091.  ml/min
  O2 Del          (64)      1038.  ml/min
  O2 Used         (64)      1038.  ml/min
 PO2: Art         (98)        88.   mm Hg
  Mus Ven         (33)        14.   mm Hg

Oxygen Debt                   .1 liters
Temperature                 37.4  C
Cal Produced    (1.17)        5.9  /min
Sweat Prod      ( .5 )         .7 ml/min
Skin Bl.Flow    (400)       391.  ml/min

Plasma PH       (7.4)         7.39
   Bicarb       ( 24)        24.   meq/l
   Lactate      ( 1)          1.   meq/l

Brain Oxygen Debt             0.   ml O2
```

### Figure 6

Metabolic variables after 5 min of exercise. Note that total calories produced per minute are 5 times resting values, but oxygen utilization by muscle is increased much more. Oxygen delivery to muscle is muscle flow times oxygen extraction. After exercise, oxygen delivery may exceed utilization as oxygen debt is repaid.

| TIME | RCM | PV | HCT | PO2V | ERYTH |
|---|---|---|---|---|---|
| 01:00 AM | 2251. | 2717. | 45.31 | 38.08 | 1.096 |
| 01:10 AM | 2137. | 2600. | 45.11 | 37.54 | 1.123 |
| 01:20 AM | 2025. | 2544. | 44.32 | 36.59 | 1.171 |
| 01:30 AM | 1915. | 2496. | 43.41 | 34.87 | 1.257 |
| 01:40 AM | 1915. | 2567. | 42.72 | 33.87 | 1.306 |
| 01:50 AM | 1915. | 2578. | 42.62 | 33.31 | 1.334 |
| 02:00 AM | 1915. | 2579. | 42.61 | 32.99 | 1.350 |

### Figure 7

Blood responses to 750 ml hemorrhage over 30 min: RCM, red cell volume in ml; PV, plasma volume in ml; HCT, hematocrit in %; PO2V, partial pressure of venous oxygen in mmHg; and ERYTH, erythropoiesis as times normal. Fall in hematocrit illustrates replacement of plasma by absorption of extravascular fluids. In model, erythropoiesis is a function of venous oxygen.

the redistribution of body fluids following hemorrhage, changes not easily discerned in laboratory exercises. The variables shown in Fig. 7 are red cell mass (RCM), plasma volume (PV), and hematocrit (HCT) following a hemorrhage of 750 ml over a period of 30 min.

Note that the red blood cells decrease at a constant rate over 30 min, but that the hematocrit does not stay constant because of the replacement of plasma volume by absorption of extravascular fluids. These responses are similar to those observed by Chien (3). Also, the venous oxygen partial pressure (PO2V) falls because of the greater extraction at the reduced cardiac output. In the model the low venous oxygen is the stimulus to increased erythropoiesis (ERYTH), shown in the last column. Over a simulated period of days the red cell mass will gradually be restored.

Other responses of the model to this disturbance include an increase of plasma renin activity, neural involvement (tachycardia and other sympathetic activity), blood flow redistribution, and renal involvement (reduced sodium excretion).

## Patient Encounters

Many of the parameters within the model may be changed to simulate disease. Stored patient simulations are to be diagnosed using only routine clinical data. In many cases the patient's condition can be improved or stabilized by therapeutic interventions, such as drugs, transfusions, artifical respiration, or artifical hemodialysis. After such a simulated patient has been thoroughly studied, it is possible to expose the full physiological data in order to gain more insight about the mechanisms involved.

The parameters modified for pathology include coronary artery resistance, right and left heart strength, right and left myocardial infarctions, ventricular septal defects, pulmonary surface area, pulmonary dead space, functional renal mass, renal artery stenosis, pheochromocytoma, primary aldosteronism, thyroxine secretion, and hemorrhage.

In addition, secondary pathologies may be induced, such as hypertrophy following long-term elevation of ventricular work load, elevated left atrial pressure and pulmonary edema following left ventricle failure, generalized edema, muscular weakness, and cardiac fibrillation. Many of these are indicated as messages at autopsy.

One simulated patient, having coronary artery disease, will be described as an illustration. The tabular outputs, shown in Fig. 8, are originally limited to the common clinical observations of systolic and diastolic pressure, heart rate, respiration rate, and temperature. In this case the tachycardia and marginally low systolic pressure are not specific enough to be of much diagnostic help.

Display of the data variables in chart format is limited to these same routine observations, plus the blood chemistry and urine specimen. However, there is a short history for the specific patient along with symptom messages displayed when the related variables become abnormal. Figure 9 shows the display for this patient at the start of the simulation. This is personalized by adding name, age, sex, and weight. The history of intolerance to exercise is suggestive. The malaise could be set by any of a number of variables reaching the limits of their normal range.

| TIME | SBP | DBP | PULSE | RESPRT | TEMP |
|---|---|---|---|---|---|
| 12:00 AM | 102. | 80.3 | 95.5 | 12.33 | 37.6 |
| 12:05 AM | 102. | 80.3 | 95.5 | 12.33 | 37.6 |

Figure 8

Systolic (SBP) and diastolic (DBP) pressure in mmHg; pulse rate in beats/min; RESRT, respiration rate/min; and TEMP, temperature in °C for a simulated patient.

```
Charles Clinton
Day: 1 -- Time: 12:05 AM

This man has a history of aches and pains
and intolerance to exercise.

I don't feel all that good.
```

Figure 9

Subjective messages for simulated patient. Short histories, such as this one, can be entered when instructor creates the related set of abnormal parameters. Symptom messages are turned on by related variables that are out of the normal range of values.

Following up on the exercise clue, the operator could simulate exercise at different levels. For this particular patient the finding would be that even the lowest intensity of exercise would be terminated abruptly and the following message would be added to the display in Fig. 9: "I just had a pain in the chest."

By adjusting two parameters it is possible to turn on the nitroglycerine prescription (software) switch and to set the size of the dose. Then the patient is able to handle at least a modest level of exercise. As an illustration, let us examine how the model implements this situation.

During each iteration of the heart-reflex module, the coronary flow is computed from the arterial pressure and the coronary resistance. The resistance calculation takes into account the degree of the disease, blood viscosity, vasodilator agents, and the metabolic dilation depending on cardiac work, blood oxygen content, and digitalis level. Coronary flow, in the model, is ordinarily determined by the metabolically determined resistance, but the flow can never be greater than that allowed by the mechanically limited coronary resistance. When disease, without dilators, raises the minimum possible resistance above that which metabolic demands dictate, exercise is terminated and the message of a chest pain is given.

## Conclusion

Besides the need for validation and improvements in individual modules, there are other avenues for continuing development of this particular model. Graphic displays, some with animation, would offer advantages over the columns of numbers. There is need for the development of clinical examples by teachers having that perspective. Also, as with all digital simulations, HUMAN is constrained in that it is approximating continuous processes by a series of discrete steps. In some cases stability has been achieved at the expense of a faithful transient response. Hardware developments, combined with user interest, suggest that each of these needs will be addressed during this decade.

In its present form HUMAN does illustrate that it is possible to simulate the time-dependent interactions between several body organ systems in a form suited for student use. The convenience of teaching simulations of

this scope running on microcomputers is especially significant. Not only can integrative simulations illustrate the dynamic essence of homeostasis to new students, but the exercises may also nurture a positive attitude toward explicit formulations of physiology in general.

We have no quantitative estimate of the value or ultility in using this, or other, simulation models in teaching physiology. We interpret the enthusiasm with which HUMAN has been received by our own students and by faculty at other institutions as evidence that simulation provides a unique extension to other modes of teaching physiology.

Though the number of factors included makes this model vulnerable, it does seem to give reasonable responses to a number of forcings. No doubt part of its success arises from the homeostatic nature of the system being simulated. Rough approximations, combined in concert, establish characteristics of the whole. Though the model is far from its final form, the fact that the calculated global properties are as good as they are is most exciting. To the authors, it presents physiology in an operational form, even though not all inclusive.

## Appendix

Copies of the HUMAN program, documentation, and teaching manual are available from the authors for the cost of duplication. T. G. Coleman can provide software on conventional magnetic tape for mainframe computers. J. E. Randall has a CP/M-80 version that will run on an Apple II microcomputer which has the Z-80 interface card and a full 64K of random access memory (RAM). A version is also available for IBM Personal Computer.

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# The Regulation of Acid-Base Balance—A Microprocessor Simulation

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Teaching physiology to medical students as a discipline that deals with regulatory phenomena, rather than as a colorful embellishment of anatomy, can be difficult. Much of the difficulty in understanding regulatory phenomena probably arises from a lack of facility in dealing with many variables at the same time and having no easy way to relate the variables to each other. We forget that many students lack the ability to read meaning from graphic data because of insufficient experience.

The regulation of acid-base balance is an area of physiology where it can be most difficult to direct attention to the mechanisms that the organism uses to adjust the pH of plasma. The students get diverted by their mystification of "pH" and the details of the many physical buffers involved. Many of the texts make loose statements about buffer base and tend to equate it to the bicarbonate content of plasma. The students retreat from the barrage of verbiage and quickly tire of trying to "figure it out"; they resort to memorizing the Davenport diagram as an aid to answering test questions. Clinicians forget that the calcium content of bone becomes active in the buffering process during long-term disorders such as chronic renal disease. The following computer simulation of the regulation of acid-base balance was developed to try to counter the above natural tendencies.

The simulation model is simple and was developed by Peters and Van Slyke and later modified by others (1). It assumes the following.

1. The principal buffer is protein, most of it inside of cells.
2. Regulation is either respiratory (fast) or renal (slow).
3. The sensor of feedback for respiratory regulation is arterial pH and $P_{CO_2}$. No attempt is made to incorporate the medullary sensors into the model; nor do we deal with the paradoxic shift during metabolic changes in acid-base balance. However, we do have plans to add this to the model in the future. The compromise required by the interaction of these two variables as they play their role in regulating ventilation is achieved by a simple averaging process in line 1190.
4. The sensor for renal regulation is not specified; it is assumed to respond to pH only, and it increases or decreases the amount of acid excreted by the kidney. It continues to operate slowly until the pH is restored to normal. The effect of acid excretion by the kidney is to increase the amount of sodium proteinate available to act as a buffer for hydrogen ions.

The emphasis of the simulation is on the regulatory compensations that are involved in the total process. The sample run (Fig. 1) illustrates the kinds of experiences provided. There is an attempt to distinguish between the simple physical buffering phenomena by the protein buffer reaction and the changes in $P_{CO_2}$, $HCO_3^-$, and $Cl^-$ brought about by the respiratory or renal regulatory systems. Each step of the process is explicitly stated as it occurs. The regulated parameters are restated at each step of the regulatory process.

## Equations

Buffer base (sodium proteinate) interacts with hydrogen ions from carbon dioxide gas in the following manner:

$$CO_2 + H_2O = H_2CO_3$$

$$H_2CO_3 = H^+ + HCO_{3_i}^-$$

$$H^+ + \text{Proteinate}^- = \text{HProteinate}$$
(physical buffer reaction)

$$HCO_{3_i}^- + Cl_o^- = Cl_i^- + HCO_{3_o}^-$$
(the chloride shift)

adding the above equations results in

$$CO_2 + H_2O + \text{Proteinate}^- + Cl_o^- = HCO_{3_o}^- + Cl_i^- + \text{HProteinate}$$

It is this last equation that is used to follow the buffer base changes. It is written as a mass-action reaction equal to KEQ, the equilibrium constant.

$$KEQ = X^3/55.5\ (Pr^- - X)\ (Cl^- - X)\ ALPHA\ PCO_2$$

where X represents the bicarbonate concentration in plasma at equilibrium. This equation is solved in the routine that starts at line 400. This allows the calculation of the bicarbonate content at a given proteinate concentration and $PCO_2$. The standard bicarbonate content is calculated with this equation by setting the $PCO_2$ at 40 torr and then solving for the bicarbonate content. All of the variables in the program are given English names so that persons not experienced with BASIC Program statements should be able to understand the calculations as done in the program. Some simplifying assumptions allow for ease of calculation. It is assumed that all bicarbonate in plasma comes from carbon dioxide and that all intracellular chloride ions come from the extracellular fluid during the chloride-bicarbonate exchange. It is assumed that there is an unlimited supply of carbon dioxide and water for these reactions, whereas supplies of chloride and proteinate ions are limited. The above assumptions reduce the solution of the mass-action equation to finding a cube root in the routine at line 400. The speed of this calculation is affected by the degree of precision required, and the program documentation describes the changes that are necessary to sacrifice precision for speed.

## Figure 1

This is a sample run of the ACIDBASE program:

```
NOTE: USER INPUT IS UNDERLINED

                ACIDBASE BALANCE
                  <<< MENU >>>

1- Simulate a Metabolic Acidosis
2- Simulate a Metabolic Alkalosis
3- Simulate an Uncompensated Respiratory Acidosis
        then provide a SLOW renal compensation
4- Simulate an Uncompensated Respiratory Alkalosis
        then provide a SLOW renal compensation
5- EXIT from this Program.

Type the number of your choice 3

              <<<RESPIRATORY ACIDOSIS>>>

Add how many torr of CO2? [3 <==> 30] 20
Bicarbonate =   27.1
pH = 7.27 this is without Renal Compensation
The Proteinate Buffer is currently at a
concentration of
0.042 meq/L.
With the lowered pH as an error signal the kidney
is now excreting acid.
This will raise the Standard Bicarbonate Level to
buffer excess carbonic acid.

Follow the pH to slow correction ===>   7.273
7.279    7.286    7.292    7.298    7.304
7.310    7.315    7.321    7.327    7.332
7.337    7.342    7.347    7.352    7.357
7.362    7.366    7.371    7.376    7.380
7.384    7.389    7.393    7.397    7.401

New Standard BICARBONATE =   34.0
pH =   7.41 which may compensate for the added
carbon dioxide.
Potassium Proteinate has been increased to 0.069
meq/L.
The Respiratory Defect is still present
and PCO2 is still  60  torr.

DEPRESS  Q  TO QUIT ANY OTHER KEY TO CONTINUE Q

                ACIDBASE BALANCE
                  <<< MENU >>>

1- Simulate a Metabolic Acidosis
2- Simulate a Metabolic Alkalosis
3- Simulate an Uncompensated Respiratory Acidosis
        then provide a SLOW renal compensation
4- Simulate an Uncompensated Respiratory Alkalosis
        then provide a SLOW renal compensation
5- EXIT from this Program.

Type the number of your choice 1
              <<<METABOLIC ACIDOSIS>>>
Add how many meq/L of acid? [.003 <==> .025] .010
Standard Bicarbonate =   21.0
pH= 7.33 this is without Respiratory Compensation
PCO2 adjusted to:  36 torr  by increasing
ventilation
New BICARBONATE =   20.6
pH =   7.37 which may compensate
for the added acid

DEPRESS  Q  TO QUIT ANY OTHER KEY TO CONTINUE Q

                ACIDBASE BALANCE
                  <<< MENU >>>
1- Simulate a Metabolic Acidosis
2- Simulate a Metabolic Alkalosis
3- Simulate an Uncompensated Respiratory Acidosis
        then provide a SLOW renal compensation
4- Simulate an Uncompensated Respiratory Alkalosis
        then provide a SLOW renal compensation
5- EXIT from this Program.
     Type the number of your choice 5
```

PROGRAM LISTING

The program is written in MicroSoft Basic and can be compiled in its present form by the MicroSoft Compiler to speed up the calculations. The version, as listed, can be speeded up by the removal of all REM statements. The program can be obtained on 8" disks in the CP/M format by sending a blank disk to the author in a return addressed mailer. I will supply both the MicroSoft BASIC source and the compiled version of the program. The program will contain no cursor addresses. The program can also be supplied on 5 1/4" hard sectored disks for the Heath 89 (with the cursor addresses for the H19 terminal). This can be a menu-driven unit that also has a Cardiovascular System Simulation. Specify if you desire the faster running compiled version with cursor addresses. Please send the disk and mailer with return address and postage.

```
10 REM PROGRAM ACIDBASE.BAS
20 REM AUTHOR ROBERT W. RASCH BOX 19780A
25 REM QUILLEN-DISHNER COLLEGE OF MEDICINE
30 REM JOHNSON CITY, TN 37614
40 REM PHONE (615)-928-6426 x234
50 REM May be copied freely for non-commercial
uses
60 REM This version has all cursor commands
removed
80 DIM D(3)
90 ALPHA=.0308:PR=.042:CL=.103:KEQ=.172335
95 PCO2=40'NORMAL VALUES
100 DEF FNR(N,D)=FIX(N*10^D+.5)/10^D'ROUNDS N TO D
PLACES
110 PRINT"              ACIDBASE BALANCE"
120 PRINT
130 PRINT"                <<< MENU >>>"
140 PRINT
150 PRINT"  1- Simulate a Metabolic Acidosis"
160 PRINT"  2- Simulate a Metabolic Alkalosis"
170 PRINT"  3- Simulate an Uncompensated
               Respiratory Acidosis"
180 PRINT"       then provide a SLOW renal
                      compensation"
190 PRINT"  4- Simulate an Uncompensated
                  Respiratory Alkalosis"
200 PRINT"       then provide a SLOW renal
                  compensation"
210 PRINT"  5- EXIT from this Program.
220 PRINT
230 PRINT"     Type the number of your choice"
240 A$=INPUT$(1)
250 A=VAL(A$):IF A<1 OR A>5 THEN 240
300 REM JUMP TO OPERATING MODES FOR VARIOUS
ROUTINES AT THIS POINT
```

---

It is conventional to underline user imput.

```
310 ON A GOTO 1000,2000,3000,4000,320
320 END
330 REM*********ALL ROUTINES BELOW THIS
POINT*********
400 'ROUTINE TO CALCULATE POSITION ON CO2
ABSORPTION CURVE
410 ' ENTER WITH VARIABLES SET AND CALCULATE
BICARBONATE AS Y
420 '
430 K1=KEQ*.0555*ALPHA*PCO2:K2=(PR+CL)*K1
435 K3=K1*PR*CL
440 DEF FNF(X,K1,K2,K3)=X^3-X^2*K1+X*K2-K3
450 REM -ESTABLISH INTERVAL OF RANDOM SEARCH
460 A=.006:B=.05
470 A1=SGN(FNF(A,K1,K2,K3))
480 B1=SGN(FNF(B,K1,K2,K3))
490 REM- TEST FOR ROOT AT EITHER LIMIT
500 IF A1*B1=0 THEN 830
510 REM- TEST FOR OPPOSITE SIGNS AT INTERVAL
LIMITS
520 IF A1*B1<0 THEN 690
530 REM-LOOP TO SEARCH 1000 NUMBERS FOR OPPOSITE
SIGNS IN FUNCTION
540 FOR I=1 TO 1000
550 X=A+RND(2)*(B-A)
560 X1=SGN(FNF(X,K1,K2,K3))
570 REM - TEST FOR ROOT AT RANDOM NUMBER; IF YES,
END SEARCH, PRINT
580 IF X1=0 THEN 870
590 REM- TEST FOR OPPOSITE SIGNS AT RANDOM NUMBER
AND LOWER LIMIT
600 IF A1*X1<0 THEN 660
610 REM- TRY ANOTHER RANDOM NUMBER
620 NEXT I
630 PRINT"NO CHANGE OF SIGN FOUND"
640 GOTO 870
650 REM - CHANGE SIGN FOUND; CALCULATE ROOT
660 B=X
670 REM - STORE POSITIVE POINT IN D(3), NEGATIVE
POINT IN D(1)
680 REM - D(1) AND D(3) BECOME INTERVAL LIMITS
690 D(2+A1)=A
700 D(2-A1)=B
710 REM- CALCULATE MIDPOINT BETWEEN THE TWO LIMITS
720 Y=(D(1)+D(3))/2
730 Y1=SGN(FNF(Y,K1,K2,K3))
740 REM - TEST FOR ROOT AT MIDPOINT
750 IF Y1=0 THEN 870
760 REM- TEST A NEW LIMIT TO CLOSE IN ON ROOT
770 D(2+Y1)=Y
780 REM- TEST FOR A VALUE CLOSE ENOUGH TO ZERO TO
ASSUME A ROOT
790 IF ABS(D(1)-D(3))/ABS(D(1)+ABS(D(3)))<.0005
THEN 870'CONTROL SPEED AND ACCURACY OF CALCULATION
WITH VALUE HELD HERE=>.00005 MORE ACCURATE
800 REM- RETEST WITH NEW LIMITS
810 GOTO 720
820 REM- ROOT AT AN INTERVAL LIMIT; FIND WHICH
LIMIT, PRINT
830 IF A1=0 THEN 860
840 Y=B1
850 GOTO 870
860 Y=A1
870 RETURN'Y IS THE ROOT
900 REM *** ROUTINE CALCULATES THE pH ***
910 '      enter with HCO3=Y AND pCO2 SET
920 PH= 6.1 + LOG(Y*1000/(ALPHA*PCO2))/LOG(10)
930 RETURN
1000 PRINT"         <<<METABOLIC ACIDOSIS>>>"
1010 PR=.042:CL=.103:PCO2=40'NORMAL VALUES
1020 INPUT "Add how many meq/L of acid? [.003
     <==>.025] ",ACID
1030 IF ACID>.025 THEN PRINT"TOO MUCH":GOTO 1020
1040 IF ACID<.003  THEN PRINT "TOO LITTLE":GOTO
          1020
1050 CL=.103-ACID'WHEN ACID IS ADDED IT AFFECTS
CHLORIDE TOO!
1060 PR=.042-ACID:PCO2=40'FIND STANDARD
BICARBONATE
1070 GOSUB 430'FINDS LOCATION ON CARBON DIOXIDE
ABSORPTION CURVE
1080 PRINT
1090 PRINT "Standard Bicarbonate ="; USING
          "#####.#";Y*1000
1100 GOSUB 920'CALCULATE pH
1110 PRINT "pH = "; USING "###.##";PH;
1120 PRINT " this is without Respiratory
          Compensation"
1130 'NOW MAKE THE pH 7.41 by setting PCO2
1140 IF FNR(PH,2)>=FNR(7.41,2) THEN GOTO
1190'FINISHED MAKE COMPROMISE
1150 PCO2=PCO2-1
1160 GOSUB 430
1170 GOSUB 920
1180 GOTO 1140'TRY ANOTHER ADJUSTMENT
1190 LET PCO2=(PCO2+40)/2'MAKE THIS COMPROMISE
1200 PRINT"PCO2 adjusted to: ";PCO2;"torr  by "
1210 PRINT "increasing ventilation"
1220 GOSUB 430'FIND THE COMPROMISE BICARBONATE
1230 GOSUB 920'GET THE COMPROMISE PH
1240 PRINT "New BICARBONATE ="; USING
          "#####.#";Y*1000
1250 PRINT "pH = "; USING "###.##";PH;:PRINT "
          which may compensate "
1260 PRINT "for the added acid"
1270 PRINT"DEPRESS  Q  TO QUIT ANY OTHER KEY TO
          CONTINUE"
1280 A$=INPUT$(1)
1290 PRINT
1300 IF A$="Q" THEN 110
1310 GOTO 1010'TRY ANOTHER
2000 PRINT "<<<METABOLIC ALKALOSIS>>>"
2010 PR=.042:CL=.103:PCO2=40'NORMAL VALUES
2020 INPUT "Add how many meq/L of
alkali?[.003<==>.025] ",ALK
2030 IF ALK>.025 THEN PRINT"TOO MUCH":GOTO 2020
2040 IF ALK<.003 THEN PRINT "TOO LITTLE":GOTO 2020
2050 CL=.103+ALK'CHLORIDE IS AFFECTEF ALSO!!
2060 PR=.042+ALK:PCO2=40'FIND STANDARD BICARBONATE
2070 PRINT
2080 GOSUB 430'FINDS LOCATION ON CARBON DIOXIDE
ABSORPTION CURVE
2090 PRINT "Standard Bicarbonate ="; USING
          "#####.#";Y*1000
2100 GOSUB 920'CALCULATE pH
2110 PRINT "pH = "; USING "###.##";PH;
2120 PRINT " this is without Respiratory
          Compensation"
2130 'NOW MAKE THE pH 7.41 by setting PCO2
2140 IF FNR(PH,2)<=FNR(7.41,2) THEN GOTO
2190'FINISHED MAKE COMPROMISE
2150  PCO2=PCO2+1'THIS SHOULD DECREASE PH
2160 GOSUB 430'FIND BICARBONATE ON CO2 ABSORPTION
CURVE AT THIS PCO2
2170 GOSUB 920'FIND PH AT THAT BICARBONTE
2180 GOTO 2140'TRY ANOTHER ADJUSTMENT
2190 LET PCO2=(PCO2+40)/2'MAKE THIS COMPROMISE
2200 PRINT"PCO2 adjusted to: ";PCO2;"torr  by "
```

```
2210 PRINT "decreasing ventilation"
2220 GOSUB 430'FIND THE COMPROMISE BICARBONATE
2230 GOSUB 920'GET THE COMPROMISE PH
2240 PRINT "New BICARBONATE ="; USING
        "#####.#";Y*1000
2250 PRINT "pH = "; USING "###.##";PH;:PRINT "
        which may compensate "
2260 PRINT "for the added alkali"
2270 PRINT"DEPRESS  Q  TO QUIT ANY OTHER KEY TO
        CONTINUE"
2280 A$=INPUT$(1)
2290 PRINT
2300 IF A$="Q" THEN 110
2310 GOTO 2010'TRY ANOTHER
3000 PRINT "         <<<RESPIRATORY ACIDOSIS>>>"
3010 PR=.042:CL=.103:PCO2=40'NORMAL VALUES
3020 INPUT "Add how many torr of CO2? [3 <==> 30]
        ",TORR
3030 IF TORR>30 THEN PRINT"TOO MUCH":GOTO 3020
3040 IF TORR<3 THEN PRINT "TOO LITTLE":GOTO 3020
3050 PRINT
3060 PCO2=40+TORR'FIND LOCATION ON NORMAL STANDARD
BICARBONATE CURVE
3070 GOSUB 430'FINDS LOCATION ON CARBON DIOXIDE
ABSORPTION CURVE
3080 PRINT "Bicarbonate ="; USING "#####.#";Y*1000
3090 GOSUB 920'CALCULATE pH
3100 PRINT "pH = "; USING "###.##";PH;
3110 PRINT " this is without Renal Compensation"
3120 PRINT "The Proteinate Buffer is currently at
        a concentration of ";
3130 PRINT USING "#.###";PR;:PRINT " meq/L."
3140 PRINT "With the lowered pH as an error signal
        the kidney is now"
3150 PRINT " excreting acid."
3160 PRINT "This will raise the Standard
        Bicarbonate Level to buffer"
3170 PRINT " excess carbonic acid."
3180 PRINT "Follow the pH to slow correction ===>"
3190 N9=0:PH=0
3200 'NOW MAKE THE pH 7.41 by setting PR with the
        excretion of acid
3210 IF FNR(PH,2)>=FNR(7.41,2) THEN 3300'FINISHED
COMPENSATED!
3220  PR=PR+.001:CL=CL+.001'EXCRETING ACID
3230 IF PH=0 THEN 3260
3240 PRINT USING "#.###     ";PH;:N9=N9+1
3250 IF N9>=8 THEN N9=0:PRINT
3260 GOSUB 430'FIND BICARBONATE AT THIS PCO2, PR
AND CL
3270 GOSUB 920'NOW GET THE PH FOR THIS BICARBONATE
3280 GOTO 3210'TRY ANOTHER ADJUSTMENT
3290 'THE PH HAS BEEN ADJUSTED TO NORMAL BY THE
ADJUSTMENT OF BASE

3300 PRINT
3310 SPCO2=PCO2'SAVE THIS VALUE FOR LATER
3320 PCO2=40'FIND THE STANDARD BICARBONATE FOR
THIS NEW CURVE
3330 GOSUB 430
3340 PRINT "New Standard BICARBONATE ="; USING
        "#####.#";Y*1000
3350 PRINT "pH = "; USING "###.##";PH;:PRINT "
        which may compensate "
3360 PRINT "for the added carbon dioxide."
3370 PRINT "Potassium Proteinate has been
        increased to "
3380 PRINT USING "#.###";PR;:PRINT " meq/L."
3390 PRINT "The Respiratory Defect is still
present and PCO2 is still ";SPCO2;
3400 PRINT " torr."
3410 PRINT"DEPRESS  Q  TO QUIT ANY OTHER KEY TO
     CONTINUE"
3420 A$=INPUT$(1)
3430 PRINT
3440 IF A$="Q" THEN 110
3450 GOTO 3010'TRY ANOTHER
4000 PRINT "<<<RESPIRATORY ALKALOSIS>>>"
4010 PR=.042:CL=.103:PCO2=40'NORMAL VALUES
4020 INPUT "Subtract how many torr of CO2? [3 <==>
        29] ",TORR
4030 IF TORR>29 THEN PRINT"TOO MUCH":GOTO 4020
4040 IF TORR<3 THEN PRINT "TOO LITTLE":GOTO 4020
4050 PRINT
4060 PCO2=40-TORR'FIND LOCATION ON NORMAL STANDARD
BICARBONATE CURVE
4070 GOSUB 430'FINDS LOCATION ON CARBON DIOXIDE
ABSORPTION CURVE
4080 PRINT "Bicarbonate ="; USING "#####.#";Y*1000
4090 GOSUB 920'CALCULATE pH
4100 PRINT "pH = "; USING "###.##";PH;
4110 PRINT " this is without Renal Compensation"
4120 PRINT "The Proteinate Buffer is currently at
        a concentration of ";
4130 PRINT USING "#.###";PR;:PRINT " meq/L."
4140 PRINT "With the elevated pH as an error
        signal the kidney is now"
4150 PRINT " conserving acid."
4160 PRINT "This will lower the Standard
        Bicarbonate Level to buffer"
4170 PRINT " the decrease in carbonic acid."
4180 PRINT "Follow the pH to slow correction ===>"
4190 N9=0:PH=8
4200 'NOW MAKE THE pH 7.41 by setting PR with the
        conservation of acid
4210 IF FNR(PH,2)<=FNR(7.41,2) THEN 4300'FINISHED
COMPENSATED!
4220  PR=PR-.001:CL=CL-.001'CONSERVING ACID
4230 IF PH=8 THEN 4260
4240 PRINT USING "#.###     ";PH;:N9=N9+1
4250 IF N9>=8 THEN N9=0:PRINT
4260 GOSUB 430'FIND BICARBONATE AT THIS PCO2, PR
AND CL
4270 GOSUB 920'NOW GET THE PH FOR THIS BICARBONATE
4280 GOTO 4210'TRY ANOTHER ADJUSTMENT
4290 'THE PH HAS BEEN ADJUSTED TO NORMAL BY THE
ADJUSTMENT OF BASE
4300 PRINT
4310 SPCO2=PCO2'SAVE THIS VALUE FOR LATER
4320 PCO2=40'FIND THE STANDARD BICARBONATE FOR
THIS NEW CURVE
4330 GOSUB 430
4340 PRINT "New Standard BICARBONATE
        =";USING"#####.#";Y*1000
4350 PRINT "pH = "; USING "###.##";PH;:PRINT "
        which may compensate ";
4360 PRINT "for the decreased carbon dioxide."
4370 PRINT "Potassium Proteinate has been
        decreased to ";
4380 PRINT USING "#.###";PR;:PRINT " meq/L."

4390 PRINT"The Respiratory Defect is still present
        and PCO2 is still ";SPCO2;
4400 PRINT " torr."
4410 PRINT"DEPRESS  Q  TO QUIT ANY OTHER KEY TO
        CONTINUE"
4420 A$=INPUT$(1)
4430 PRINT
4440 IF A$="Q" THEN 110
4450 GOTO 4010'TRY ANOTHER
```

## The Major Program Variables

ALPHA is the coefficient of carbon dioxide absorption in plasma.

PR is the potassium proteinate concentration inside cells (mostly).

CL is the chloride ion concentration in the extracellular fluids.

KEQ is the mass-action equilibrium constant.

$PCO_2$ is the partial pressure of carbon dioxide.

ALK is the amount of base added in terms of changes in milliequivalents per liter.

ACID is the amount of acid added in terms of changes in milliequivalents per liter.

K1, K2, and K3 are arbitrary constants arranged to simplify the location of a cube root.

DEF FNF(X, K1, K2, K3) = $X^3 - X^{2*} K1 + X^* K2 - K3$ is the mass-action equation arranged for a cube root solution.

pH = 6.1 + LOG [Y*1000/(ALPHA*$PCO_2$)]/LOG (10) calculates the pH.

## Method of Presentation

We have not objectively tested the effect of this kind of computer simulation on student learning. So far, we have tried only one format of presentation. Our student laboratory has several sessions where the students are involved in a variety of activities as small groups. One of the small groups consists of about eight students around the microprocessor. We have a brief handout that describes a series of simulations and provides some suggestions to start them off. The students appeared to enjoy the session, and the general attitude at the time suggested that they would be interested in increasing the amount of such activity. We hope to augment the number of microprocessors so that a group of two or three can interact with the simulations at a session.

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# RECENT ADVANCES IN PHYSIOLOGICAL MONITORING
## OPENING REMARKS

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The past several decades have seen remarkable changes in our understanding of physiologic processes - much through the improved ability to monitor changes in an awake unanesthetized state. Applications of innovative technology have received major support from parallel advances in microelectronics, computerized signal processing and software development for quantitative measurement and analysis. The result has been new invasive and non-invasive methods for studying body function.

The present symposium has been organized with the purpose of reviewing selected relatively new instrumentation methods which have applications for monitoring both animals and man. Emphasis has focused on the cardiovascular system. Such a selection was predicated on the vast amount of work that has already been accomplished and is on-going in this area. Cardiovascular disease presently represents the major cause of death and illness in this country. Review of cardiovascular methodologies would then provide maximal coverage of principals in a short review. Six techniques for non-invasive evaluation of the cardiovascular system will be discussed, several in detail, and include: digital angiography, X-ray computed tomography, ultrasound, heavy ion radiography, emission tomography and nuclear magnetic resonance. Certain techniques, such as digital radiography, still require injection of contrast material in order to obtain quantitative measurements, but with improved detection methods such injections need not be made selectively into heart chambers, but into a peripheral vein. Analysis relies on television or equivalent recordings of images which are then computer processed for extraction of data content. Contrast levels undetectable or marginal in individual frames may be enhanced or superimposed sequentially over a cardiac cycle or repeatedly at a designated time such as end diastole to provide useable delineation of structures. Other methods such as emission tomography rely on injection of radionuclides but provide invaluable data on tissue metabolic processes, receptor site concentrations, blood flow and tissue profusion. More recently use of methods such as nuclear magnetic resonance (NMR) promise still more important information related to free water content of tissues, relative flow in large vessels and the molecular distribution $^{13}C$ and $^{31}P$. Recent data demonstrates that NMR recordings provide a means of *in vivo* spectroscopy, where frequency of the received signal can be shifted by a few parts per million depending on the chemical state of the nuclei of a tissue. Such measurements show great promise in evaluating ischemic states of brain and other tissues, including the heart. Use of ultrasound has increased markedly over the past decade. Received signals have been shown to depend on the acoustic impedance mismatch of tissues and sound propagation velocity and attenuation in the body as well as frequency shifts due to organ motions. Ultrasound applications have particularly benefitted from effective application of integrated circuit technology. These have enabled studies for accurate 2- and 3-D reconstructions of organ size and shape over the cardiac cycle as well as calculation of blood flow. This has been made possible by incorporating digital processing capability within the instruments themselves as well as computer processing of resultant signals. Previous large and bulky units weighing hundreds of pounds have now been collapsed into average briefcase-sized models weighing no more than 30 or 40 lbs., some even battery operated.

Three forms of monitoring procedures are also discussed and include long-term recording of variables such as ECG, invasive bedside measurements in post-operative or ill patients and use of biotelemetry methods. These techniques first developed in animals are also finding increasing application for man. Registration of large volumes of data have required careful attention to analytic methods and reliance on computer processing. Resultant ability to register heart rate and representtive ECG waveform over 24-hour periods has provided important new approaches for understanding normal heart function and subsequent effect of pathologic processes, particularly coronary artery disease. Developments in bedside monitoring have relied heavily on new devices such as balloon tipped (Swan-Ganz) catheters. Ease of application has reached the point where such catheterizations are being increasingly used in completely normal individuals. Such an approach will be employed for at least one passenger aboard the forthcoming Spacelab mission to be flown by 1984. Catheters have been tolerated from several days to weeks in man and for months in animals. Biotelemetry has also become increasingly used to free animals or man from effects of anesthesia, tranquilization or the constraints of a normal laboratory environment. Application of microelectronic methods using IC techniques are providing increasingly smaller and more reliable devices, whether transducer, signal conditioner or transmitter. Decreases in size have allowed for use of far more complicated circuitry, increasing

the range and capability for monitoring. Of particular importance has been the development of multichannel capability. Miniaturization methods have not been solely limited to obtaining data from the body, but has allowed opening of avenues for communication into the body through the intact skin. Heart pacemakers represent a classic example of this latter approach. Other newer systems are also available which include nerve stimulators, devices to measure cerebral spinal fluid pressure and drug delivery systems. Power supply has been a severely limiting factor for all telemetry applications, particularly for experimental designs which require reception of data for periods in excess of a few weeks or months. Use of newer type batteries such as lithium cells, have proved beneficial. Battery elimination and replacement by RF power induction through the skin has provided an encouraging alternative and makes energizing possible for an indefinite period. RF sources may be provided by coils placed in a vest worn by a patient or animal or situated in the walls of an animal's cage. They may also be used to recharge previously implanted batteries. Improvements in long-term reliability of sensors and transmitters still need attention. Present advances in technology open the possibilities of extending available continuous or intermittent biotelemetry monitoring capabilities of 1-2 years duration to even longer term sampling of organ function or parameters for the life time of instrumented subjects.

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# POSITRON EMISSION TOMOGRAPHY OF THE HEART

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## INTRODUCTION

Positron emission tomography (PET) of the heart can measure blood perfusion, metabolism of fatty acids, metabolism of sugars, uptake of amino acids and can quantitate infarction volume. This paper reviews the principles which are basic to PET instrumentation and procedures for quantitative studies of human physiology with examples of measurements of myocardial flow and metabolism.

## PET PRINCIPLES

Positron emission tomography involves the use of radionuclides which emit two 511 keV photons after the annihilation of a positron (positive electron) with an electron. Positrons are emitted from isotopes (Fig. 1A) such as carbon-11, nitrogen-13, rubidium-82, iron-52, etc. Carbon-11, produced by a cyclotron, has 6 protons and only 5 neutrons. The tendency is for one of the protons to become a neutron, losing its positive charge in the form of a positron. When the positron moves a short distance from the nucleus, it encounters a negative electron and there is a resulting annihilation of this matter and anti-matter leaving 2 high energy photons. These photons fly off at 180° from one another and are detected by an array of scintillation crystals and phototubes in time coincidence. If 2 photons are detected within a few nanosec, it is assumed that the activity exists along some line between those 2 detectors. The methodology of positron tomography is somewhat different than that of single photon tomography because for positron tomography lead collimators are not needed to focus the information from the patient onto the detector material. The positron tomograph is comprised of an array of detectors which surround the subject (Fig. 2). If enough coincidence events are collected, reconstruction of the distribution of the radionuclide can be made by computer in much the same fashion as X-ray computed tomography except that accommodation for attenuation must be made (1). By using special high-speed detectors and timing electronics to measure the small difference in the time of detection of the 2 photons, time-of-flight can be used to give some improvement in statistical performance.

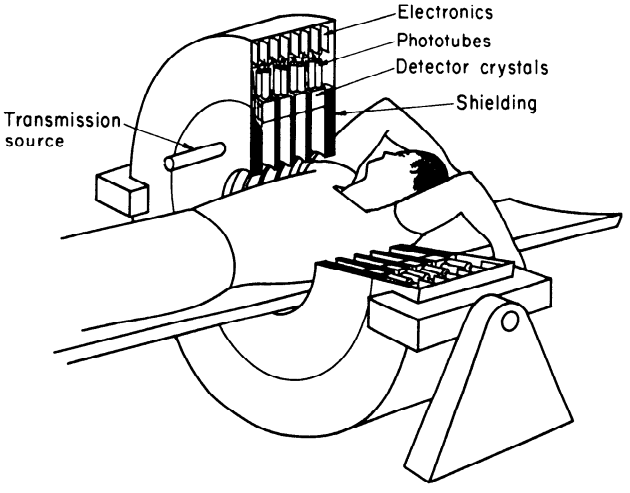
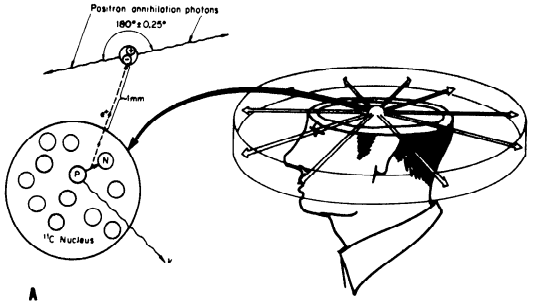



Fig. 2. Schematic of PET device for imaging the thorax. Present plans are for devices with 2000 detectors or more.



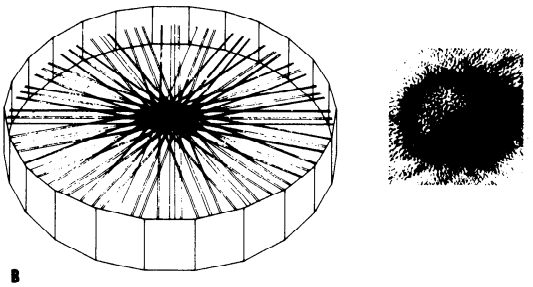




Fig. 1. A. PET relies on the time coincidence detection of annihilation photons from the interaction of a positron with an electron.

B. Scintillation crystals and phototubes detect the co-linear photons.

## MYOCARDIAL PERFUSION

For tracers such as $^{82}Rb$, $^{52m}Mn$, and $^{13}NH_3$, with high extraction coefficients and low tissue clearance, flow can be deduced from the quotient of the amount accumulated in the myocardium at any time and the amount that has been available to the myocardium (Eq. 1). The latter can be deduced from the concentration in the left ventricular blood pool measured tomographically.

$$F \times E = \frac{Q(T)e^{\lambda T}}{\int_0^T A(t)e^{\lambda t}dt} \quad ; \qquad (1)$$

where Q(T) is the amount in the myocardium at time T, F is flow, E is the tissue extraction, A is the arterial concentration, and $\lambda$ is the physical decay constant. A major asset of dynamic positron tomography is the fact that both Q(t) and A(t) can be measured simultaneously, in the PET images. The PET system used for our studies has a resolution of 9mm FWHM and can acquire complete angular sampling without motion of the detectors (4). A limitation of this procedure is the fact that extraction is a decreasing function of flow for a diffusion limited tracer such as rubidium (Fig. 3); however, over the flow range 0 to 2 times normal flow the F x E values from Eq. 1 can be related to specific volume flow. This general model allows measurement of specific volume flow using bolus injection or constant infusion of $^{82}Rb$ (76 sec) from a $^{82}Sr/^{82}Rb$ generator (2,19).

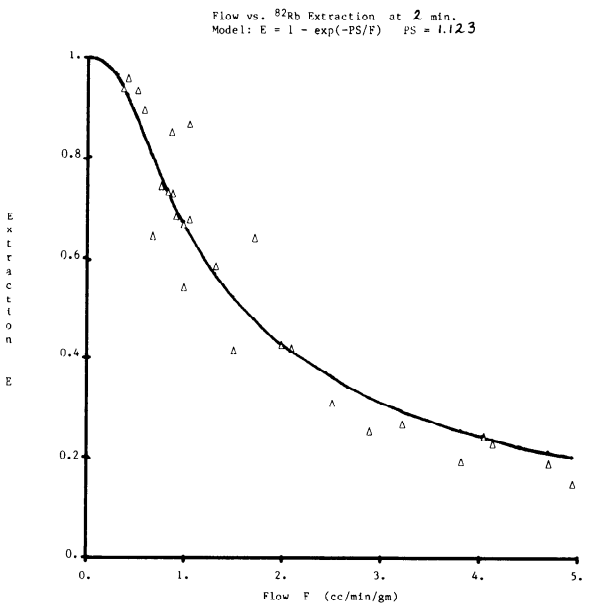



Fig. 3. Tracers such as $Rb^+$ measure relative perfusion by the amount accumulated in the myocardium. Dynamic measurements depend on flow times extraction but extraction is a function of flow as shown here.

Infarction detection and sizing can be accomplished by static imaging of the accumulation of a number of positron emitters (e.g, $^{13}NH_3$ (8), $^{82}Rb$ (1), $^{11}C$-palmitic acid (17), and $^{18}F$-fluoro-deoxyglucose (13).

## FATTY ACID METABOLISM

The major fuel for metabolism of the nonischemic myocardium is fatty acids, although glucose plays a significant role when glucose and insulin are present. Palmitic acid labelled with carbon-11 in the carboxyl position has been used to evaluate the rate of ß-oxidation by examination of the rate of disappearance of the activity as a function of time (7,18). Under ischemic conditions, the rate of clearance is decreased. In the normal myocardium the rate of clearance is proportional to cardiac work. The residue function (uptake-clearance curve) contains unique information on the ß-oxidation of free fatty acids for the production of high energy phosphates (Fig. 4). However, the detailed shape of the residue function will depend very much on the input function as well as on the ß-oxidation rate. Using dynamic PET, this input function can be evaluated and ß-oxidation rate determined using the model of Fig. 4. Having measured the input function, the parameters of the model are determined by an iterative least squares fit to the residue function. This method provides a quantitative technique for evaluation of myocardial metabolism, but requires a dynamic PET system for acquisition of gated images collected for 5 sec intervals during the early part of the study.

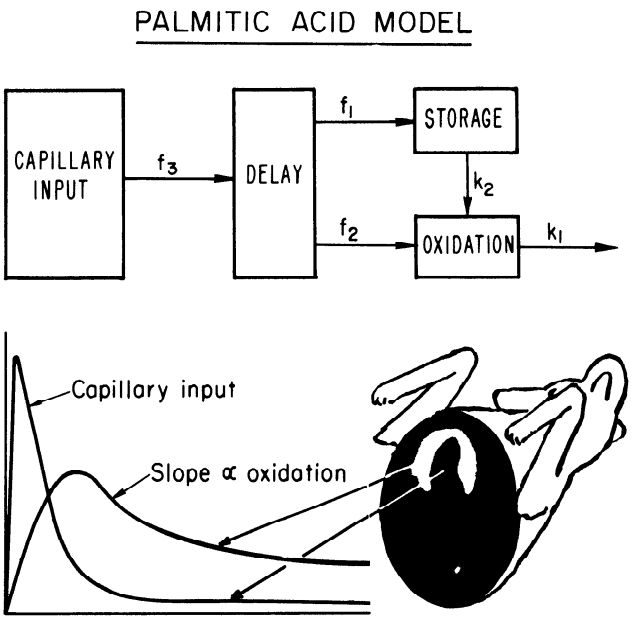



Fig. 4. Model used to describe fatty-acid oxidation using the non-invasively detected ventricular blood concentration and the residue curve extracted from a sequence of PET images after i.v. injection of $^{11}C$-palmitic acid.

## GLUCOSE METABOLISM OF THE MYOCARDIUM

The accumulation of $^{18}$F-fluoro-deoxyglucose in the heart makes this agent well suited for imaging the distribution of functional muscle, as well as for metabolic studies. High resolution static images of the myocardium can be obtained with good statistics in a 5 min. data accumulation interval, 40 min. after injection of 4-8 mCi of $^{18}$F-fluoro-deoxyglucose. Fluoro-deoxyglucose is transported between blood and the myocyte by the same saturable carrier that transports glucose. Fluoro-deoxyglucose-6-phosphate is not further metabolized and accumulates in the myocardium without significant loss for as long as 90 min.

The rate of glycolysis is determined using the moment-to-moment concentration changes in the myocardium and a compartment model similar to that employed for brain studies (12). The first studies of the myocardium using $^{18}$F-fluoro-deoxyglucose showed that the rate constants for myocyte glycolysis are similar to those for the brain (12,16). However, unlike the brain, the membrane transport of glucose in the myocardium is mediated by insulin, and perhaps by non-specific permeability changes during ischemia. Thus, it appears that the short-cut of assuming average values for the rate constants will lead to serious errors. A dramatic example of the effects of insulin on glucose transport into skeletal muscle is shown in Fig. 5 wherein glucose uptake at low and high insulin levels is shown. If the moment-to-moment data from the blood pool in the left ventricle and the myocardium are observed it is possible to experimentally derive the transport and phosphorylation rate constants for each subject rather than rely on assumed values.

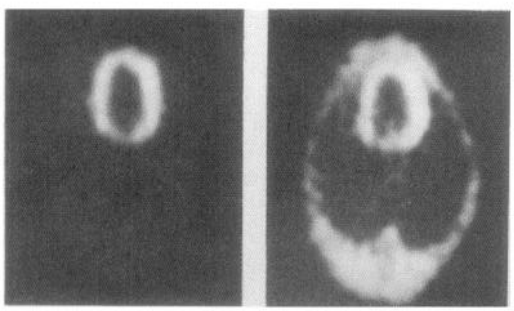



Fig. 5. $^{18}$F-2-fluoro-2-deoxyglucose accumulation depends on the metabolic demands of the heart and the availability of insulin. The accumulation after 48 hr. fast (left) is less than that after infusion of insulin and glucose (right).

Increased glycolysis during ischemia has been thought to explain the observation that there is a less marked decrease in fluoro-deoxyglucose uptake than there is a decrease in flow measured using $^{13}NH_3$ in the compromised myocardium (16). Glycolytic flux is increased only during a short period (9), and depends upon the glucose-insulin state of the subject. Furthermore, it is still not clear to what extent $^{13}$N-ammonia extraction and accumulation in the heart is dependent on the state of myocardial protein metabolism (Schelbert et al, 1980, 16). Should glucose uptake actually increase relative to flow as a reliable indicator of myocardial ischemia, then it is possible to use $^{82}$Rb from a generator system to measure relative flow and then $^{18}$F-fluoro-deoxyglucose to examine the state of the myocardial metabolism. The availability of $^{18}$F (1.8 hr. half-life) regionally and $^{82}$Rb (76 sec half-life) locally from a table-top generator (19), can make this dual approach a practical method for detecting ischemia in patients.

## AMINO ACID METABOLISM

Amino acid kinetics of the human myocardium can be studied using $^{13}$N or $^{11}$C labelled amino acids. The amino acid with the highest demonstrated uptake in the myocardium is asparagine (5). Its uptake of 13.7 percent of the injected dose in the dog is about four times higher than that of potassium, rubidium, glucose, and fatty acids; however, the uptake in man is low (10). Glutamate has a higher extraction in the ischemic myocardium than in the normal myocardium according to measurements made during coronary catheterization in man (11). A high extraction of 5.6 percent of the injected dose has been observed in patient studies (6). $^{13}$N-alanine is also known to localize in the heart, but the possibility exists that after peripheral injection the $^{13}NH_3$ from metabolized alanine is the actual tracer in the heart.

Our studies of amino acid metabolism focused initially on $^{11}$C-valine, one of the branched-chain amino acids oxidized by muscle (3). We observed less than 1 percent of the injected dose in the myocardium and no significant increase in accumulation during fatty acid infusion (1). Studies on methionine and taurine accumulation are now underway. In man and dogs about 1 percent of the injected dose of these compounds goes to the myocardium where the concentration is 2 times that in skeletal muscle.

## CONCLUSION

Experience has shown that quantitative studies of myocardial perfusion and metabolism can be made by measurement of the input function and residue function from sequential PET images.

Rubidium-82, delivered from a table-top generator is a practical tracer for relative flow measurents. The metabolism of glucose can be evaluated by $^{18}$F-fluoro-deoxyglucose accumulation kinetics and fatty acid metabolism can be measured by modelling the disappearance of label from the myocardium due to β-oxidation. Amino acid kinetics can be followed using $^{11}$C or $^{13}$N labels (14).

Practical clinical applications require a tomograph with at least 3 levels of data taken simultaneously with a resolution less than 8 mm FWHM. Gating of the transverse section data, and

measurement of the input function are the two additional requirements for quantitative studies of perfusion and metabolism. Gating is necessary during acquisition of the residue curve because the high activity of the ventricular blood pool will seriously distort the information from the region of interest over the left ventricle.

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# DIGITAL RADIOLOGIC MONITORING OF RENAL PHYSIOLOGY

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## ABSTRACT

Digitization of radiographic information permits direct quantitation of physiologic processes for which radiographic contrast material may serve as a marker. Investigations are described in which conventional and experimental X-ray equipment are applied to determining renal microcirculatory and excretory function. These techniques have the advantage of being relatively non-invasive and permitting sequential, instantaneous measurements during the experimental process.

## INTRODUCTION

Recent advances in radiologic technology have applied the digital computer to medical imaging. The main advantages of these modalities - including computerized tomography (CT), digital subtraction angiography (DSA), and nuclear magnetic resonance (NMR) - have been increased contrast resolution of anatomic detail, increased flexibility in extracting additional morphologic data, and decreased patient risk. Perhaps even more importantly, however, digitization of radiographic information has raised the possibility of application to evaluation of organ function. This is possible because the numerical representation of focal density on X-ray images are directly related to radiation absorption at discrete points. Thus, if sequential images are exposed prior to and at intervals following intravascular administration of radiographic contrast material, information may be derived concerning passage of contrast through various anatomic compartments.

A particular interest of our research group has been development of digital imaging modalities and their application to the study of renal circulation and excretion in experimental settings. The following represents a summary of investigations demonstrating a portion of the range and potential of these techniques. We expect that increasing sophistication of technology and, hopefully, our own inventiveness in its application will expand the utility of this approach.

## EVALUATION OF NORMAL AND ABNORMAL CONTRAST EXCRETION BY FILM-RECORDED AXIAL TOMOGRAPHY (1,2)

Conventional radiographic contrast agents contain iodine and are 99% excreted by renal glomerular filtration. Thus, evaluation of excretion dynamics of excretion should reflect glomerular function and tubular transit. A recent innovation in our department has been the development of a unique axial tomographic scanner, which we have applied to imaging of small animals and investigation of contrast excretion. The system employs traditional X-ray film as the receptor, with subsequent digitization. An X-ray fan beam is passed through a scatter rejecting slit to a horizontally rotating turntable on which lays the experimental animal. The beam traverses the animal's kidneys, passes another scatter rejecting slit, and is received by a vertically moving film cassette. Geometric magnification is performed simply by separating the components. The pulsations of the X-ray beam and the stepwise motions of the animal turntable and film cassette occur in synchrony, such that a collection of sine waves are imprinted on the developed radiograph. Each sine wave is representative of an anatomic locus, such that the amplitude and density of the wave are related to the position and X-ray absorbing capacity of the point respectively. Figure 1 shows the schema for processing the X-rays. Digitization is by scanning microdensitometry. Generated data is condensed by center-weighted averaging, filtered, and back projected. Recontructed images are displayed on a CRT screen.

Figure 2 depicts a renal scan of a rat obtained in this manner. It has a spatial resolution of 150 microns; potentially the method has the capacity for resolving structures as small as 50 microns (3). Scanning was performed prior to and 2, 15, 30, 60, and 120 minutes following the administration of contrast material (60% sodium-meglumine diatrizoate, 2 cc/kg).

Densitometry of cortical and medullary compartments was accomplished in the manner shown in Figure 3. Alterations in compartment densities - as represented by the CT numbers - is directly related to the amount of contrast present, and provides information concerning the passage of contrast through the cortex and medulla.

Following initial successful experience with the equipment and technique, attention was turned to evaluating differences in excretion occurring during induction of a pathologic process. In the past, we have focused special interest on the myoglobinuric model of acute renal failure (ARF) in the rat. ARF was induced in five rats by initial 24-hour dehydration, followed by intramuscular injection of glycerol, 5 gm/kg. CT scans were obtained on these rats 24 hours after glycerol injection and on three normal rats as well. Density values for renal cortex and medulla were plotted

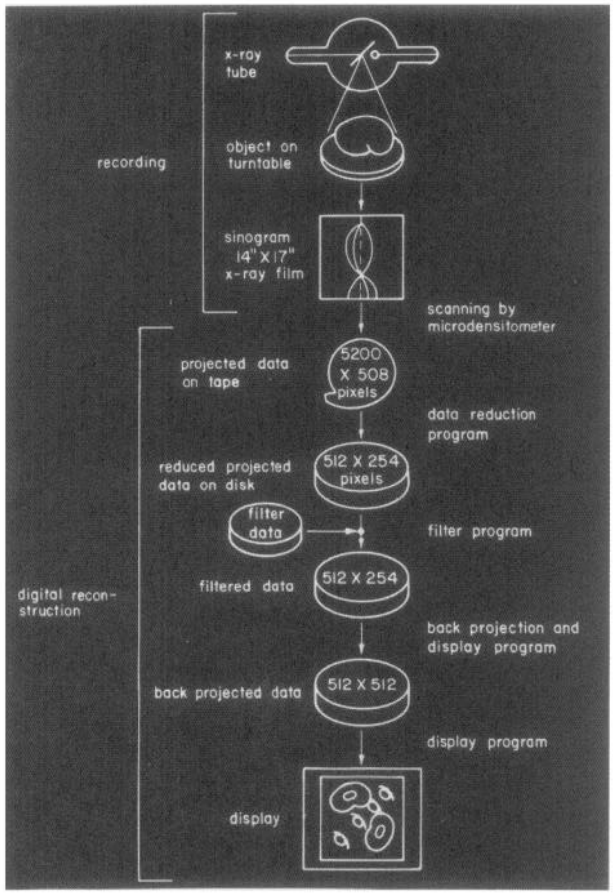


Figure 1: Method for Film-Recorded Axial Tomography

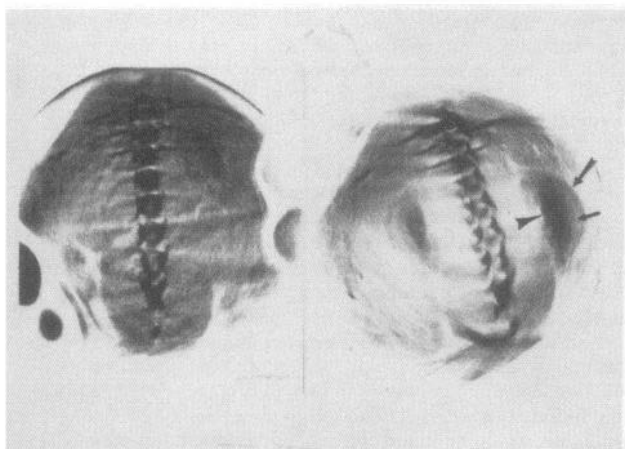

Figure 2. Pre-(left) and Post-(right) Contrast Film-Recorded Axial Tomographic Images Through the Region of a Rat's Kidneys

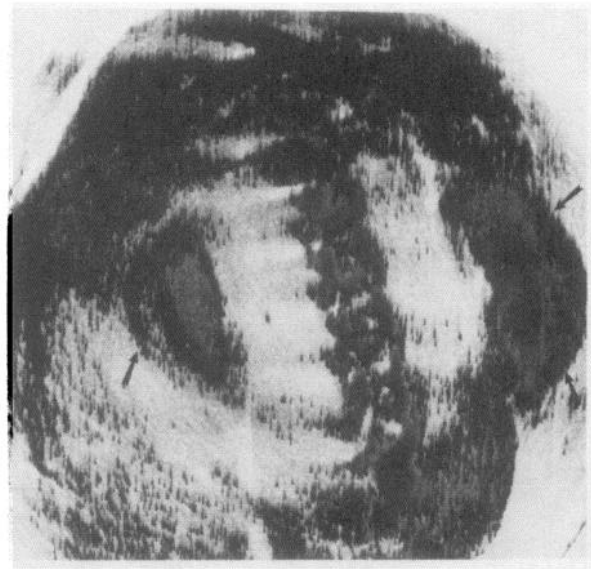

Figure 3: Densitometric Values for Renal Cortex (Arrows)

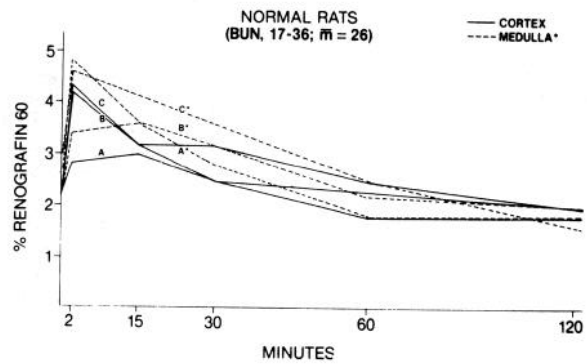


Figure 4: Time-Density Curves in Normal Rats

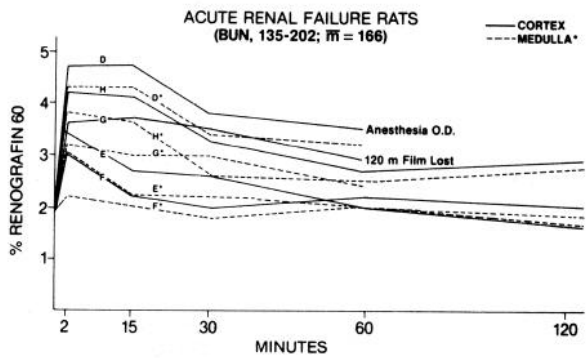


Figure 5: Time Density Curves, Acute Renal Failure

against time, so that the resultant time-density curves for normal and ARF-affected animals might be compared.

Figures 4 and 5 depict these curves. It is evident that medullary contrast concentration is initially greater than cortical in all normal animals, whereas for ARF-affected animals, the converse is the case. Prompt contrast excretion is seen in normal rats, such that cortical and medullary density returns to normal within 120 minutes. This was not true in ARF-affected animals, where two excretory patterns were observed. Two rats manifested only minimal initial alterations in density; density values returned almost immediately to baseline, suggesting that all alterations were related to intravascular contrast material and nearly no filtration occurred. The three other ARF-affected rats demonstrated prolonged cortical and medullary retention of contrast agent in tubules, perhaps secondary to tubular obstruction. These results serve to point out the variability inherent in this model and may help to explain the disparate results obtained using other, often non-invasive, techniques.

## COMPUTED TOMOGRAPHIC ESTIMATION OF THE FRACTION OF AN ORGAN COMPOSED OF BLOOD VESSEL LUMEN (4)

Much of our information concerning microcirculatory alterations during disease pathogenesis has been derived from application of time consuming and invasive procedures, which themselves may impinge upon and alter homeostasis. The value of these digital radiographic techniques is that they require only minimal animal manipulation, and measurements may be made instantaneously. Believing that alterations in organ vascular volume might occur during circulatory disorders and affect blood flow, we moved to develop a radiologic method with the above qualities to quantitate these changes.

The method combines the quantitating facility of conventional computerized tomography with the unique properties of the experimental contrast agent, perfluoroctylbromide (PFOB). This agent, which has undergone development and extensive investigation by Long et al., remains wholly intravascular during our scanning period, is not renally excreted, and is not detrimental to cardiovascular status in the doses used for this experiment (5).

The method for determining the fraction of renal parnechyma occupied by blood vessels at an instant in time during CT scanning is as follows:

$$u_K = u_{Kp}\,(1\text{-}FVV_K + u_B\,(FVV_K) \qquad \text{eq (1)}$$

$FVV_K$ is the fraction of kidney volume occupied by vascular lumina and $1 - FVV_K$ is the fractional volume of all other renal parenchymal constituents, and after intravenous administration of PFOB:

$$u_K' = u_{Kp}\,(1\text{-}FVV_K) + u_B'\,(FVV_K) \qquad \text{eq (2)}$$

where u = CT attenuation coefficient prior to serially PFOB administration, $u'$ = CT attenuation coefficient following PFOB administration, K = kidney, Kp= kidney parenchyma, excluding vascular lumen, and B = blood.

Since PFOB is entirely intravascular, $u_{Kp}$ remains unaltered. Subtracting eq (1) from eq (2):

$$FVV_K = \frac{(u_K' - u_K)}{(u_B' - u_B)} \qquad (3)$$

Since the CT number of a tissue is directly related to its u :

$$FVV_K = \frac{(CT_K' - CT_K)}{(CT_B' - CT_B)} \qquad (4)$$

CT numbers may be read from the CRT screen.

To apply this method we performed conventional 1 cm CT scans through rats' kidneys prior to and following the injection of PFOB, 3 cc/kg. CT density numbers for blood and kidney were obtained using a cursor method to outline the vena cava and renal parenchyma respectively. The computer then calculated the average density of all pixels contained within the region of interest. Scans and densitometry were performed in this fashion for normal rats and rats which had received an intramuscular injection of glycerol 20-50 minutes or 60-120 minutes previously. The density values thus obtained were used to calculate fractional vascular volumes ($FVV_K$) for normal animals and those undergoing acute renal failure. The results were then compared among the three groups and correlated with any histologic alterations.

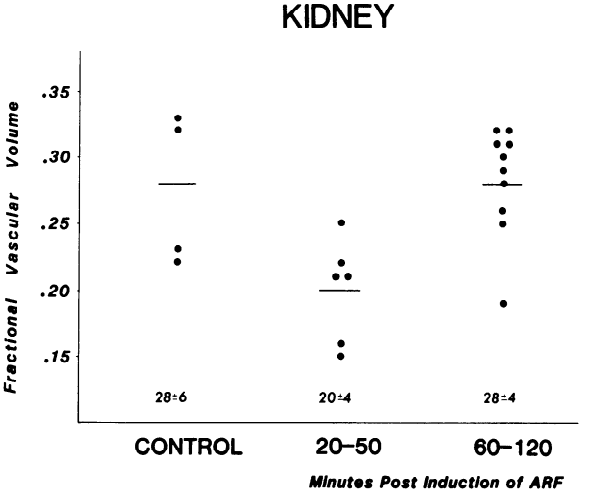


Figure 6: Mean Fractional Vascular Volume of Kidney

Figure 6 shows that the mean $FVV_K$ for normal animals was .28. This declined significantly to .20 among those animals scanned 20-50 minutes following glycerol injection ($p<.02$). A return to pre-injection levels of $FVV_K$ was seen in ARF affected rats scanned later in their course. This, too, was a statistically significant alteration when compared with those animals scanned earlier ($p<.01$). This result is particularly interesting since it suggests that microcirculatory alterations may play a role in initiation of this disorder, but only very early in its course. This is a period which

might be more difficult to study by traditional means, and one which might be particularly sensitive to change by invasive techniques. Again, the advantages of this radiographic method - and of our new physiologic parameter which we have termed fractional vascular volume - are threefold: (1) is non-invasiveness method, (a) follows alterations sequentially and nearly instantaneously, and (3) absence of sampling error, since an overview of all of the renal parenchyma is obtained. These qualities should prove advantageous in investigating processes where rapid microcirculatory alterations may be important in pathogenesis.

## DIGITAL SUBTRACTION ANGIOGRAPHY AND THE EVALUATION OF RELATIVE RENAL ARTERY TRANSIT (6)

Digital subtraction angiography is a new, clinically applicable, radiographic method designed for minimally invasive imaging of the circulation. Its technology combines image intensifier high contrast sensitivity as the X-ray receptor with post-processing capability of the digital computer. As a result, arteriography may be performed using a simple intravenous injection of contrast material.

Briefly, X-rays traverse an object to an image intensifier. A video camera with high signal:noise properties transmits the image to an analog-digital converter and hence to memory storage. These functions and image reconstruction are computer-controlled. Subsequent image subtraction and image processing are computer-mediated under interactive operator control (7).

Again, digital quantization of radiographic density information permits extraction of physiologic information. In this case, greyhound dogs were anesthetized and placed on a respirator. A flow probe was placed proximally on their left renal arteries just prior to injecting 60% sodium-meglumine diatrizoate, 3 cc/sec for four seconds, a flow reading was recorded. Contrast injection was followed by recording images at 2/sec for 10 seconds. The initial injection-exposure sequence under control conditions were compared to subsequent sequences of simulated stenosis and resulted in measurements reflecting decreased flow.

Five dogs were imaged in this fashion, with three to five injection-exposure sequences being obtained in each animal. Renal artery density was measured on each image using a cursor placed over the opacified renal artery. These measurements were then used to generate time-density curves as shown for one animal in Figure 7. A graphic relationship exists between the level of blood flow and configuration of the time-density curves. For more objective evaluation, we empirically derived from these curves a parameter we termed "average slope."

The average slope is representative of a line drawn from the origin - just prior to the arrival of contrast in the renal artery - to the point of peak density on the curve. The average slope is thus time and density dependent and is representative of the velocity of flow. The average slope diminished in steepness with corresponding decrements of flow. This same relationship was upheld, nearly without exception, among the animals studied.

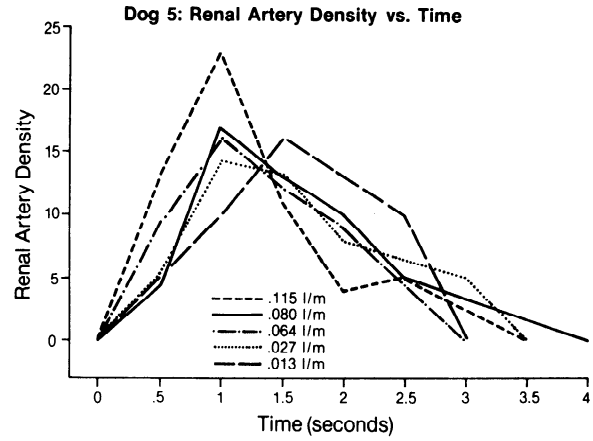


Figure 7: Dog 5: Renal Artery Density vs. Time

## SUMMARY

This text was presented as a series of vignettes in order to illustrate themes common to application of various digital radiographic methods to physiologic studies. These include the following:

1. Sequential alterations in imaged density of a structure of interest are related to the amount of a radiographic marker (contrast material) present and to its passage through the structure.

2. Measurements of this nature are obtained easily, quickly, and with minimal alteration in homeostasis.

3. These techniques permit relatively accurate quantitation of physiologic processes.

While we are encouraged by our own investigations and those of others employing these modalities, we recognize that their scope and potential is considerably greater than presented here. Rather, these investigations are intended to serve only as examples of the utility of these and, as yet, other undescribed techniques employing digital radiographic parametric imaging.

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# AMBULATORY MONITORING OF ELECTROCARDIOGRAMS - CURRENT TECHNOLOGY OF RECORDING AND ANALYSIS

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## ABSTRACT

With technological advances, manufacturers have designed medical equipment which is smaller, faster, less expensive and more sophisticated than that previously available. These features have been widely applied to equipment for recording ECGs in ambulatory patients. This paper describes the types of devices available including continuous Holter systems, real-time or event recorders, transtelephonic units and hybrids of these. We will also discuss analytic methods implemented for detecting arrhythmias, heart rate changes and ST segment shifts.

## INTRODUCTION

For years, there has been investigator interest in recording electrocardiograms in an ambulatory setting. This type of monitoring has been used to study normal populations as well as groups or individuals with known cardiac problems. This type of monitoring enables study of individuals during their normal daily activities. Through recordings made for up to 24 hours, data have been collected and studied about circadian rhythm, normal ECG variation, drug efficacy, ST segment variation, and sleep-related changes.

Since the first "Holter" recording was done, advances in technology have produced smaller and more sophisticated electronic equipment. This technology has been incorporated into such ambulatory designs as:

1) continuous Holter systems that record the ECG on tape and later analyze the data by fast versatile scanners,

2) real-time systems that analyze and selectively store ECG data in solid-state memory or onto tape while the patient is being monitored,

3) transtelephonic recorders that transmit a patient's ECG over the phone, either in real-time or from pre-recorded units,

4) hybrids of the real-time and transtelephonic units,

5) units that record signals such as esophageal leads, blood pressure, or pacemaker spikes in addition to surface ECGs.

In this paper, we describe each of these units and the situations in which they are used. We also explain the various methods of analysis and the resultant information.

## CONTINUOUS OR TRADITIONAL HOLTER SYSTEMS

The continuous or traditional Holter systems consist of a small recorder (1-2 lbs) worn by the patient on a belt or shoulder strap. Typically two channels of the patient's surface ECG are directly recorded. The recorder can operate for a period of 24 (some up to 48) hours, powered by a disposable or rechargeable battery. The entire 24 hours are recorded on a cassette or reel-to-reel audio tape. No analysis is done by the recorder; instead all data are recorded for later playback and analysis by a separate scanner. If more than 24 hours of data are needed, the tape and battery must be changed. These recorders often include: (1) a 1 millivolt calibration signal, (2) a timing reference (sometimes related to the patient's clock), (3) an event marker used by the patient.

Completed recordings are played back through a corresponding scanner/analyzer. The scanner unit consists of a tape playback, operator control modules, a video screen for display and edit, and a printer/plotter for reports. The level of automation of the analysis depends on the manufacturer and the model chosen. Some models only display superimposed QRS complexes and/or histograms of R-to-R intervals for the technician. Any "abnormal events" must be recognized and manually verified. These events may then be plotted on the strip chart recorder. Other models contain more automated analysis. In such a scanner, the operator initially "dials in" certain parameters, usually a prematurity range and an area range that describe the patient's normal QRS complexes. The scanner then analyzes the data automatically using these criteria to recognize and quantitate "abnormal beats." Times for pauses, bradycardia, tachycardia, and ST segment changes are also quantitated. Summaries of these events are presented to the technician for review and print-out.

The continuous Holter system is still the most commonly used monitor because all of the data are available to the physician for review. Twenty-four hour recordings can be used to: (1) evaluate the efficacy of antiarrhythmic drugs for clinical and research patients, (2) study a given drug's ability to suppress premature ventricular activity, (3) monitor patients who have sudden and frequent (greater than 1/24 hours) syncopal episodes to determine if the episodes relate to a cardiac phenomenon, (4) identify and study episodes of bradycardia, tachycardia, or supraventricular activity, (5) follow therapy of any event by serial recordings to evaluate effectiveness. By recording all ECG complexes, the continuous recording systems enable the scanner and/or technician to extract the significant episodes.

## REAL-TIME OR EVENT SYSTEMS

The real-time or event systems are a relatively

new technology for ambulatory monitoring. These units consist of a microprocessor system within the recorder which analyzes 1 or 2 channels of ECG while the patient is being recorded. When an event of interest is detected, the microprocessor stores the relevant information in solid-state memory or in a combination of memory and audio tape. Usually the time and type of event are saved as well as the event's frequency of occurrence and a sample of the ECG. Unlike the continuous systems, the event recorders only store selected information for subsequent printing and display of relevant ECG waveforms.

In newer versions of real-time systems, the office unit may be used to "program" the recorder. The patient's "normal" QRS complex is provided to the recorder as well as criteria for brady- and tachy-cardia. Limited recorder storage capacity can be used with maximum efficiency enabling detection of bigeminy, pauses, or other events that the patient experiences frequently or are already known to the physician.

Some of these recorders can collect data for more than 24 hours. In fact, the battery unit must have a longer life-time than those of continuous systems since battery failure or run-down results in loss of information stored in the memory. In addition to limitations imposed by battery use, the recorder can only store data if there is available memory. When the memory is full, the recorder either stops further data storage or uses a priority system to replace old event information with a new, higher-priority event.

Advantages of the real-time systems over continuous systems are availability of immediate results for review as soon as the recorder is removed from the patient and very little involvement of technician time. A disadvantage is that the analysis is only as accurate as the software algorithm within the recorder. Therefore, if an event is undetected by the algorithm, it will not be stored for review and go undetected.

TRANSTELEPHONIC UNITS

Another type of ambulatory ECG monitoring device is a transtelephonic unit. This device transmits one channel of ECG over the phone to a receiving unit which plots the signal on a strip chart recorder. Earlier devices had no internal storage and required the patient to be experiencing an episode while he was transmitting his ECG over the phone. Newer designs have memory that records the signal and plays back the recorded ECG after the patient can reach a phone. Both types may be used by patients who have sustained episodes lasting long enough to be recorded and/or sent via phone. If the patient experiences these episodes less than once a day, a transtelephonic device would be more practical than a continuous Holter. A disadvantage of this system is that the ECG information prior to the event will not be recorded. Another disadvantage is the episodic nature of the analysis tailored to recording single rather than multiple events.

HYBRIDS OF REAL-TIME AND TRANSTELEPHONIC UNITS

The newest units combine the real-time recorder with transtelephonic capability. This recorder analyzes the ECG as it is being recorded and stores significant events. If the memory becomes filled, the unit signals the patient to phone the office unit to "dump" the information and reuse the memory. It also signals the patient if a "serious" episode is detected that should be communicated to a physician as soon as possible. Certain of these devices allow reprogramming of the recorder's algorithm over the phone. Although these devices are still under development, they offer the possibility of maximum flexibility and efficiency for the patient, technician and physician. However, one must keep in mind that the accuracy is still dependent upon the software algorithm.

OTHER AMBULATORY MEASUREMENTS

In addition to recording 1 to 2 surface ECG signals, some continuous Holter systems can record blood pressure, pacemaker activity, and/or esophageal ECG signals. Pacemaker activity can also be examined with some of the transtelephonic devices.

Cuff blood pressure can be automatically measured and recorded by coupling the Del Mar Avionics blood pressure module with their continuous recorder. Special decoding units in their scanner retrieve the pressure information from tape for review and reporting. Although simultaneous ECG/blood pressure information can be useful, the accuracy of the pressure readings is very dependent on the sensing unit and placement of the cuff.

Pacemaker activity can also be evaluated on an ambulatory basis. Units that detect pacemaker stimulus voltage spikes usually have filtering circuitry that apply specifically to the frequency of the spikes. The channel detecting the ECGs usually attenuates or eliminates the high frequency spikes. If the spike is recorded on tape, the scanner's sampling rate may be too slow to consistently digitize it. Del Mar Avionics has a special Holter recorder in which one channel is devoted to a surface ECG lead and the other channel records the time its high frequency circuitry detects a pacemaker spike. Special units in their scanner decode and present the information for reporting.

Since surface ECG recordings do not reveal atrial activity reliably, some groups are recording an esophageal ECG as well as a surface ECG with continuous Holter recorders (1). The esophageal signal is obtained with a small bipolar electrode positioned in the esophagus behind the atria. The electrode is connected to a preamplifier via a pair of teflon-coated wires. The patient swallows the gelatin-encapsulated electrode which is then positioned behind the atria after the gelatin capsule dissolves. The wire is secured close to the mouth with a piece of tape.

By recording simultaneous surface and esophageal signals, atrial and/or ventricular activity can be more clearly evaluated. An example of a tracing is shown in Figure 1. Notice the P and R waves on the surface lead that correspond to the atrial (A) and ventricular (V) activity on the esophageal lead. This method can be used to determine if a rhythm is supraventricular or ventricular tachycardia.

FEATURE EXTRACTION

Analysis of ambulatory data, is usually one of two types. The first type is termed "feature extraction" (2,3). With this algorithm, each QRS complex is represented by a few "features" or measurements (usually 2 to 4). These measurements can include QRS width, prematurity (the time since the last QRS complex relative to the average time),

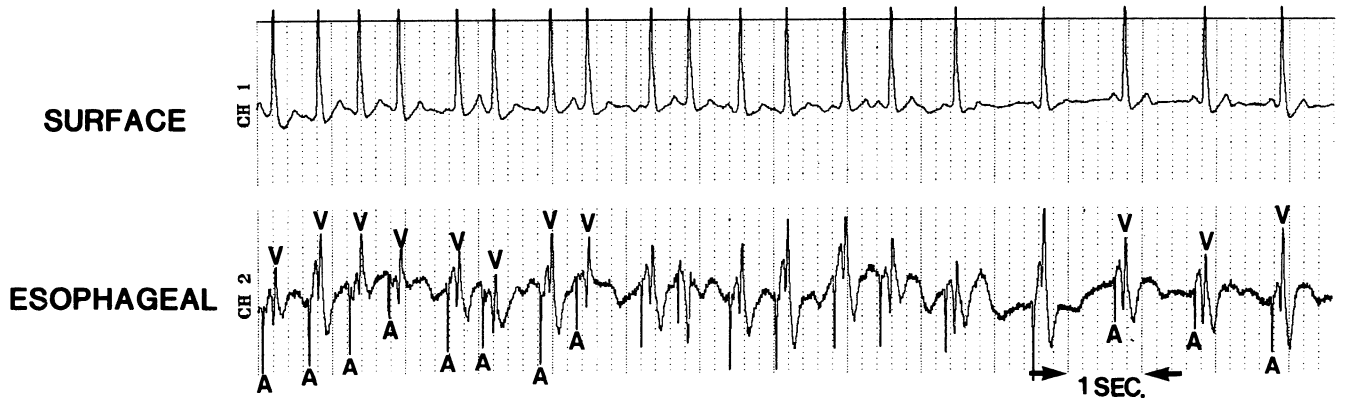


Figure 1

area under the curve, direction of main deflection, and number of times the signal changes direction (see Figure 2).

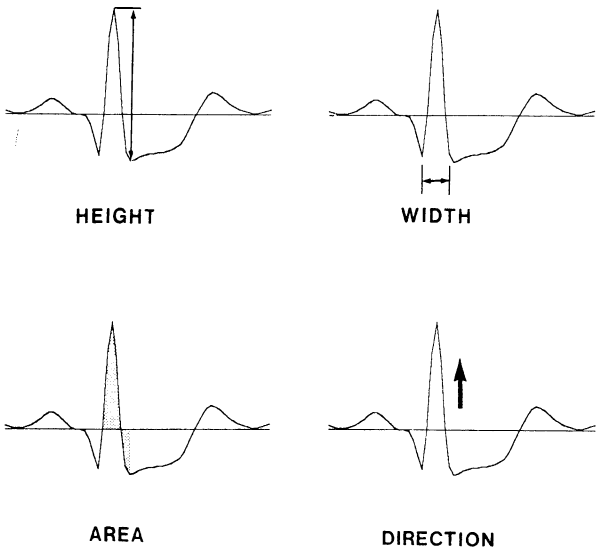


Figure 2

Although these types of measurements can be made with a digital computer, they can also be determined by analog circuitry, making the analysis fast and fairly straightforward.

In most continuous Holter scanners, the operator selects the range of measurements that will include normal beats and exclude abnormals. Typically, prematurity (time in the heart cycle) and QRS area (or width) are used. If the beat measurements are outside normal limits for both ranges, the beat will be called abnormal, an example being a premature ventricular contraction (PVC).

Some manufacturers, especially those of "real-time" systems, establish the "normal" values and ranges for these measurements automatically. By assuming the first group of beats recorded (10, 20, 30, etc.) are predominately normal sinus, average values are determined, and the values are updated throughout the recording. These values may be inaccurate if the recording contains bigeminy, atrial fibrillation, or other rhythm abnormalities. Other systems may have the technician select one or more examples of sinus beats, which will be used for setting the ranges.

The feature extraction method is very quick, with some systems scanning at speeds of 480 times real time (a 24-hour tape scanned in 6 minutes). However, if the algorithm is too simplistic, errors will occur on all but the most "classic" (and noise-free) data. Therefore, manufacturers continue to improve the specificity and sensitivity of their algorithms.

CROSS-CORRELATION

Instead of feature extraction, some groups use a cross-correlation technique to classify the data. Cross-correlation mathematically compares two different data sets, or waveshapes, calculating how similar they are. The correlation coefficient is a number between -1 and 1 where 1 would mean the two waveshapes are identical. The waveshapes being compared include a defined window of time around the QRS complex (usually approximately 250 msec). The correlation analysis usually begins by labeling the first QRS complex as the representative waveshape. As each subsequent beat is detected, it is correlated and if it does not exceed a predefined threshold, the new beat is added to that group. If it is not included in any already present group, a new group is created.

Each system which uses the correlation technique must also establish a maximum number of groups, and techniques to merge groups to create space for new ones. Because the correlation technique often requires more calculation than feature extraction, analysis time is increased. For this reason, only a few large systems and research groups use the correlation technique (4,5). The correlation technique is thought to be superior to feature extraction because it analyzes waveshapes instead of derived measurements which are assumed to be distinctive between different morphologies. However, both techniques have their weaknesses and strengths and are only as good as the given implementation.

OTHER MEASUREMENTS

Other measurements may be made and stored as the data are being analyzed, either in real time or via a scanner. These measurements and episodes usually include heart rate, pauses, brady- and tachy-cardia and missed beats. Some systems also measure R-on-T

and ST segment changes. Pauses represent absence of ventricular activity for a certain period of time. Bradycardia or tachycardia is flagged when the heart rate exceeds a low or high limit respectively. A missed beat occurs when the time between two beats is twice as long as the normal interval. An R-on-T episode is flagged when the next QRS complex occurs during the T wave of the previous beat. Since T waves are not always easy to define in ambulatory monitoring recordings, most systems flag an R-on-T episode when the next "detected" ventricular beat is within a certain time period following the last QRS complex. This method is a simplistic view of a complex phenomena and all R-on-T episodes must be verified by the technician.

High quality signals having low noise content are important regardless of the system used for analysis. System response to common conditions of low signal and noise is also very important. If the system is over-sensitive, many false-positive episodes will be noted. In real-time systems, this may cause important episodes to go unstored due to lack of memory. In continuous sytems, the operator must spend time editing and validating more false events. As processors become smaller, more inexpensive, and faster, these situations will be improved.

## ST SEGMENT ANALYSIS

Measurement of ST segment changes has been a recent addition to systems. ST segment change is usually related to the occurrence of ischemia or coronary spasm. Ambulatory monitoring has shown that people may have periods of ST change that are asymptomatic. The significance of these changes is still being studied (6,7).

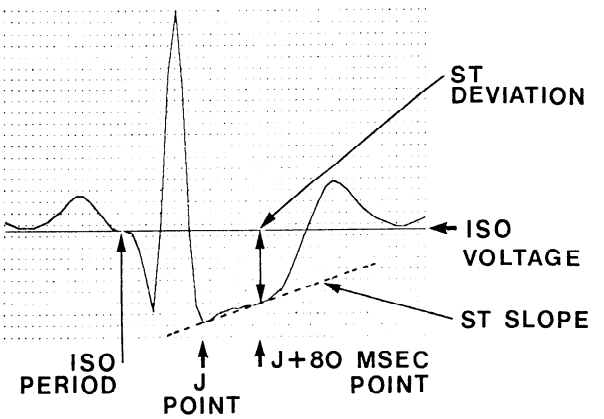


Figure 3

Certain timing and voltage references have been established in order to correctly measure ST segment change (Figure 3). These involve identification of the isoelectric level and J point. The isoelectric level (the level of the PQ interval) is used as the voltage reference to measure ST segment change. The J point, represents the end of the S wave and beginning of the ST segment. This inflection point is not always well-defined. ST changes are usually measured as the amount of deflection from the isoelectric level at the J + 60 msec or J + 80 msec point. These measurements are only valid on sinus beats. Another traditional measurement is the ST segment slope, a flat or downward slope, indicating a more critical patient condition.

In most commercial systems, the ST segment change is measured as the amount of deflection at a time within the ST segment. We know of no commercial system which also includes an ST slope calculation. In most systems, the timing and voltage references (isoelectric and J point) are detected automatically and cannot be validated by the operator. Also, the type and number of beats used in the measurement are difficult, if not impossible, to determine. Some systems may just measure the ST segment at a given offset of time from the R wave rather than from the J point.

If ST segment analysis is done, another factor to consider is the frequency response and ST segment reproducibility of these systems. We have tested several systems and found that they do not meet the AHA standards for frequency response (8). Although there was limited frequency response, some systems appeared to accurately reproduce the ST segment. It is not known exactly how limited frequency response affects the reproducibility of various ST segment waveforms. In essence, we feel that ST segment measurements done on most commercial ambulatory systems should be considered a rough quantitation of the changes and care needs to be taken when evaluating its clinical significance compared to exercise testing.

## CONCLUSIONS

This paper has discussed the currently available devices for ambulatory ECG monitoring. We have discussed principles of operation and types of algorithms that are used for analysis. With continued advances in technology more sophisticated devices will become available which will increase accuracy of analysis and decrease required technician and physician time.

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# CLINICAL APPLICATIONS OF BEDSIDE HEMODYNAMICS MONITORING USING THE SWAN-GANZ CATHETER

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## PHYSIOLOGIC BASIS FOR HEMODYNAMIC MONITORING

Hemodynamic monitoring is an important aspect of contemporary care of critically ill patients. The fundamental value of this technique is that it provides direct physiological measurements, the appropriate use of which is predicated by an understanding of normal cardiac physiology as well as its alterations in the critically ill patient. Derivation of primary parameters, such as cardiac output (CO), preload, afterload, and contractility allow for quantitative analysis of factors that affect cardiac performance and tissue perfusion. Once these factors are known, they can be thoughtfully manipulated to improve or optimize cardiac function in various clinical states.

### Determinants of Cardiac Output

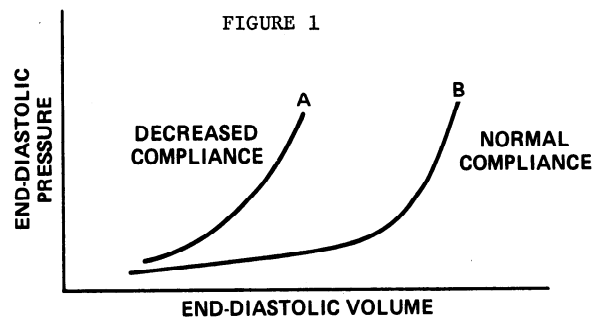
One of the important variables that can be measured by means of contemporary hemodynamic monitoring techniques is CO, volume of blood pumped by the heart per minute and stroke volume (SV), the amount of blood ejected from the ventricle during each systole. SV also represents the difference between ventricular end-diastolic volume (EDV) and the end-systolic volume (ESV) of the ventricle; when it is expressed as a percent of the EDV, it is referred to as the ejection fraction (EF). The performance of the heart as a pump, as reflected by the SV of the intact ventricle, has been shown to be determined by three main factors: (a) preload, the length of the muscle at the start of contraction, or the ventricular EDV; (b) afterload, the tension that the muscle is called upon to develop during contraction; and (c) contractility, the inotropic state of the muscle, expressed as the velocity of fibre shortening for any given preload or afterload.

### PRELOAD

Preload can be defined as the end-diastolic stretch of the muscle fibre which in the intact ventricle, is its EDV. Ventricular volume is related to intraventricular pressure by ventricular distensibility, or compliance. While fibre length or ventricular volume can be determined by angiographic or thermodilution techniques, or both, these measurements are more difficult to obtain than simple end-diastolic pressure (EDP). Therefore, it is common in clinical situations to measure left ventricular filling pressure (LVFP) and accept it as a measure of fibre length or EDV (though it is always kept in mind that certain pathophysiologic states may alter this pressure-volume relationship). Left ventricular EDP (LVEDP) is related to mean left atrial pressure (LAP) unless there is an obstruction at the level of the mitral valve - for example, mitral stenosis. Because of ease of measurements, pulmonary artery EDP (PAEDP) as well as mean pulmonary capillary wedge pressure (PCW) are used to approximate LAP. PCW is an important pressure obtained by hemodynamic monitoring and is commonly measured with the use of a balloon-tipped flotation catheter, such as that described by Swan and Ganz and their colleagues in 1970 (2).

An increase in EDV (diastolic fibre stretch) causes an increase in SV. By plotting the generated SV at increasing levels of EDV, one creates a ventricular function curve. The curve plateaus, indicating that the relationship is nonlinear and eventually SV does not continue to increase despite an increasing EDV. In a clinical setting SV is plotted against the PCW or the PAEDP because it is more convenient to use filling pressure to approximate end-diastolic fibre length than it is to measure filling volume.

FIGURE 1




RELATION BETWEEN VENTRICULAR EDV AND END-DIASTOLIC PRESSURE (EDP)

The ventricular diastolic volume is related to the ventricular diastolic pressure, as is seen in Fig. 1. The normal curve (A) shows that this relationship allows relatively large changes in the ventricular EDV to be accompanied by relatively small changes in ventricular EDP. This diastolic pressure-volume relationship refers to the distensibility of the relaxed ventricle and, in a general sense, is termed ventricular compliance. Certain disease states, such as healing myocardial infarction, may give rise to a decrease in ventri-

cular compliance, as is seen in curve B. As compared with curve A, curve B demonstrates a much greater increase in EDP for a smaller increase in EDV. Thus, the normal pressure-volume relationship is altered. Both curves indicate that at a higher EDV, ventricular compliance is decreased. From Fig. 1 it is obvious that changes in diastolic pressure may reflect alterations in ventricular volume or compliance or both.

Three factors influence preload: the circulating blood volume, the distribution of the blood volume, and atrial contraction. When the circulating blood volume is depleted, as in instances of hemorrhage, the venous return to the heart declines and EDV falls; consequently there is a decrease in CO. For a given total blood volume, EDV is influenced by the distribution of blood between the intrathoracic and extrathoracic compartments. This is influenced by body position - for example, the venous return is greater when the idividual is supine. An elevation of intrathoracic pressure, as occurs in tension pneumothorax, during the Valsalva maneuver or during prolonged bouts of coughing, tends to impede venous return to the heart, diminish intrathoracic blood volume, and reduce CO. The resting venous tone also affects EDV. The smooth muscle in venous walls responds to a variety of neural and humoral stimuli. Venoconstriction increases venous return to the heart, as does the pumping action of skeletal muscle during exercise, which squeezes blood out of the veins. A vigorous and appropirately timed atrial contraction augments ventricular filling and the EDV and EDP. The atrial kick is of particular importance in patients with ventricular hypertrophy or diminished left ventricular compliance, whose resistance to ventricular filling tends to be increased. Thus, the measurement of LVFP and the understanding of its determinants permit selection of the most appropriate LVFP for an optimal CO.

## AFTERLOAD

It has become increasingly apparent that cardiac function is critically dependent on the impedance against which the ventricle must empty. Impedance is determined by the pressure-volume relationship of the aorta (its compliance) and by the peripheral vascular resistance (the arteriolar radius and the viscosity of the blood. By measuring mean driving pressure (using a sphygmomanometer, Doppler ultrasonography, or intra-artieral cannulation) and mean flow, one can calculate the resistance to ejection (ratio of pressure to flow). If ventricular function is normal, a rise in outflow resistance produces little change in the SV. However, with moderate myocardial dysfunction a rise in outflow resistance results in a greater fall in SV. When there is severe myocardial dysfunction, a rise in outflow resistance results in a pronounced fall in SV. Thus, resistance to ejection affects SV and consequently CO. This has been dramatically emphasized with the introduction of vasodilator therapy in the management of cardiac failure. Vasodilator drugs that relax the peripheral arterioles - for example, sodium nitroprusside can cause an increase in SV by allowing the poorly functioning ventricle to empty more completely since the impedance to ejection is decreased.

## CONTRACTILITY

The third main mechanism by which myocardial performance is altered is a change in the inotropic state (contractility) of ventricular muscle without a change in fibre length (EDP or EDV). Contractility can be defined as the maximum velocity of muscle shortening at zero load. A change in contractility in the intact heart implies a change in function that is independent of alteration in preload or afterload. An increase in contractility is associated with an increase in SV without change in preload. A depression in contractility causes the opposite effect. Thus, an increase in contractility may be associated with an increase in CO. Heart failure is usually accompanied by a decrease in contractility and a lowering of CO.

Myocardial contractility is related to a number of factors, including the quantity of norepinephrine released by sympathetic nerve endings, the concentration of other circulating catecholamines, the presence of exogenous inotropic agents (cardiac glycosides, isoporterenol, caffeine, etc.) pharmacologic depressants (quinidine, procainamide, barbituates, etc.) or physiologic depressants (hypoxia, hypercapnia, acidosis, etc.), and a loss of ventricular substance, as occurs in myocardial infarction.

## CLINICAL APPLICATIONS OF HEMODYNAMIC MONITORING

A list of clinical situations where bedside hemodynamic monitoring may be useful is given in Table I and Table II and summarizes the value of bedside hemodynamic monitoring in the management of critically ill patients.

**TABLE I: INDICATIONS OF BEDSIDE HEMODYNAMIC MONITORING**

1) Acute Myocardial Infarction Complicated by
   a) Severe heart failure - low output syndrome
   b) Shock cardiogenic vs. hypovolemic
   c) Acute mitral regurgitation
   d) Ventricular septal rupture
   e) Right ventricular infarction
   f) Recurrent or continuing myocardial ischemia
   g) Patient requiring parenteral vasodilator and/or inotropic therapy

2) Perioperative State
   a) Before and during surgery in "high-risk" patients
   b) Postop low-output state
   c) Patients undergoing hypotensive anesthesia

3) Miscellaneous
   a) Patients with extensive trauma and burns
   b) Patients suspected of massive pulmonary embolism
   c) Patients suspected of acute cardiac tamponade
   d) Evaluation of intensive therapeutic strategies in patients with chronic refractory heart failure
   e) Patients with acute respirtory failure requiring PEEP
   f) As a research tool for clinical investigation

TABLE II: VALUE OF BEDSIDE HEMODYNAMIC MONITORING

1) Allows precise measurement of (a) cardiac function, (b) degree of dysfunction, (c) mechanism of dysfunction.
2) Aids in the diagnosis of specific clinical syndromes; i.e., hypovolemia, acute mitral regurgitation, ventricular septal rupture, cardiac tamponade, right ventricular infarction, septic shock, acute pulmonary embolism, etc.
3) Allows selection of appropriate therapeutic intervention based on the hemodynamic profile.
4) Allows rapid assessment of response to therapy.
5) Aids in predicting a prognosis in patients with acute myocardial infarction.

The ability to perform bedside monitoring has been enabled by the widespread use of balloon-tipped catheters. Such catheters may be placed by cutdown or needle puncture of an internal jugular, antecubital, subclavian or femoral vein.

FIGURE 2

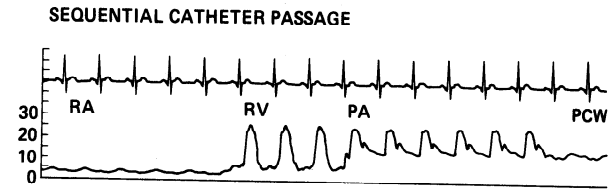



Figure 2 illustrates the waveforms of sequential catheter passage in a human subject. Advantages for use of the internal jugular vein as entry site are its size, constant anatomy, short direct route to the right side of the heart and ability to stabilize the catheter. It is the best approach for a subject on a ventilator. Disadvantages are possibilities for hemotoma, needle puncture of carotid artery and injury to thoracic duct or induction of a pneumothorax. An antecubital vein is safest and best for subjects on anticoagulants; the subject need not be supine at time of catheter insertion. Disadvantages are infection, phlebitis, venospasm and difficulties in entering thorax. The subclavian and femoral veins are also easy and ready access routes, but not as practical. With the femoral approach, flouroscopy is needed to enter the chest.

The following are guidelines for the save use of balloon-tipped catheters (8,9):

1. Keep "wedge" time to a minimum, especially in patients with pulmonary hypertension (preferably 10 to 15 sec.).

2. When the balloon is reinflated for recording wedge pressure, the inflation medium (carbon dioxide or air) must be added slowly under continuous monitoring of the pulmonary artery pressure waveform. Inflation must be stopped immediately when the pulmonary artery pressure tracing is seen to change to pulmonary wedge pressure.

3. If fluoroscopy is available (as in the cardiac catheterization laboratory), refloat the catheter tip from the central pulmonary artery for each wedge pressure measurement.

4. Careful note of the ballon inflation volume must be made. If wedge is recorded with a balloon volume significantly below that indicated on the catheter shaft, pull the catheter gradually into a position in which full or near full inflation volume produces a wedge tracing.

5. Anticipate spontaneous catheter tip migration toward the periphery of the pulmonary bed. To avoid possible damage to the pulmonary artery, monitor the presure tracing during every balloon inflation.

6. Spontaneous catheter tip migration into wedge position may also induce pulmonary infarction. Continuous frequent monitoring of the catheter tip pressure is therefore necessary.

7. Do not use liquids for balloon inflation; they may be irretrievable and may prevent balloon deflation.

8. Keep a syringe on the balloon lumen of the catheter to prevent accidental injection of liquids into the balloon.

Table III lists problems which occur during the course of hemodynamic monitoring and steps for their prevention and treatment (7-9).

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TABLE III

| TROUBLE-SHOOTING PROBLEMS IN HEMODYNAMIC MONITORING | | |
|---|---|---|
| **PROBLEM** | **CAUSE** | **PREVENTION AND TREATMENT** |
| Incorrect calibration or zero drift | Transducer membrane not level with patient's mid-chest | Relevel transducer and recalibrate. |
| Maintaining catheter patency | Lines under high back pressure | Use heparinized flush solution (normal saline) with 500 U of heparin per 500 ml. Mount flush solution in pressure bag at 200 to 300 mm Hg. Use intraflo® device in series with connecting tubing and flush. Do intermittent manual flushing with Intraflo® device. |
| Damped or lost pressure recording (inspect immediately) | Air in transducer or tubing | Aspirate catheter and flush system free of air bubbles. |
| | Leak in system | Tighten all connections and flush system. |
| | Blood clot at distal tip of catheter | Aspirate catheter and flush using 5 to 10 ml of solution in syringe. |
| | Kinked tubing or catheter | Inspect catheter and tubing for kinks or bends. Improve anchorage; splint where necessary. |
| | Fully clotted catheter (failure to flush after blood is withdrawn) | Attempt aspiration but do not flush; catheter usually must be replaced. |
| | Transducer not open to catheter | Open transducer by adjusting all stopcocks in system. |
| | Incorrect calibration or gain control | Recalibrate and ensure proper monitor settings. |
| Bleeding | | |
| From catheter or connecting tubing | Leak in system | Tighten all connections and flush system. |
| From insertion site | Improper fixation or vessel trauma | Inspect insertion site. Correct fixation and apply local pressure until bleeding stops. Advise doctor of this problem. |
| Catheter removed accidentally | Uncooperative or disoriented patient | Apply local pressure to insertion site and advise doctor. If catheter is reinserted, ensure adequate fixation. |
| Broken catheter | Usually due to trauma | Advise doctor to repair or replace[37] |
| Spontaneous "wedging" of Swan-Ganz catheter | Ballon left inflated | Staff must recognize difference between pulmonary artery and pulmonary capillary wedge pressure tracings. |
| | Distal migration of catheter | Deep breathing, coughing or positional change by patient may dislodge the catheter; if not, advise doctor to reposition catheter. Observe chest roentgenogram for pulmonary infiltrates. |
| Painful insertion site | Local inflammation or infection | Inspect insertion site and take swab for culture. Ensure insertion and removal by aseptic technique. Inspect insertion site daily and replace topical antibiotic. |
| | Excessive motion due to poor fixation | If pain is excessive advise doctor regarding changing insertion site. |
| Hematoma after catheter removal | Local bleeding from vessel | Apply local pressure until bleeding stops; if not successful advise doctor. |
| Cold, painful, ischemic hand (radial artery cannulation) | Radial arterial thrombosis | Advise doctor regarding anticoagulant therapy and catheter removal. |
| Balloon rupture (Swan-Ganz) | Air injection into balloon not recoverable; unable to obtain pulmonary capillary wedge pressure | Fill balloon with 1 ml of flush solution; if not recoverable, balloon is ruptured and should no longer be filled with air. |

# TELEMETRY METHODS: ANIMAL AND MAN

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## INTRODUCTION

Biotelemetry represents any remote means of measuring biologic information - by wire cable, mechanical means or wireless. By common useage, it has come to represent transmission by radiowave, although almost every portion of the electromagnetic spectrum has been used. Data may be transmitted over many miles, or for a few hundred feet to a few inches in the laboratory. By far the greatest activity has involved transmission from units worn external to the body using implanted or external sensors. With technologic advances in integrated circuit techniques and improved packaging and construction methods, systems are being developed that may be entirely implanted inside the body or swallowed (1,4). As a result of biotelemetry an increasing number of accurate measurements are being made in animals and man without restrictions from encumbering wires or interference with physiologic function. Recordings have been obtained in man during work, normal activity, sleep, exercise, monitoring of astronauts, sports and surveillance of critically ill patients. In animals a large number of parameters have been measured continuously or intermittently over long periods (days, months, years) to provide physiologic information or for ecologic (tracking) purposes (6).

Micro miniaturization and integrated circuit designs were initially applied to systems for the simple registration of ECG or deep body temperature, recently more sophisticated units have been developed to measure blood pressure, blood flow, flow velocity and/or profile, dimensions and gaseous or chemical content of tissues (4,5). Need for measurement of chemical or hormonal parameters has also led to back-pack systems allowing for periodic blood sampling and its preservation, with subsequent analysis for endocrine and biochemical factors on sample retrieval. Lastly, units may be used to relay or input data or substances to the body. Investigators have successfully demonstrated the efficacy of nerve stimulators and portable or totally implantable drug infusion-delivery systems in both animals and man.

Back-pack systems have the longest history. They became increasingly used following the pioneering work of Rushmer and co-workers which demonstrated marked differences in cardiovascular function between awake intact dogs and open-chested preparations. Some units have been directly connected (umbilical) to awake animals, others have included a vest or attachment by a head plug. To free the animal or subject a power source is included with the unit, which has usually been a battery. Location and method of monitoring has been dependent on the type of measurement, animal model and its temperament. The domestic nature of dogs makes the use of a vest quite simple, while specially designed vests and protected head-mounted plugs are more commonly used in primates. Vests are usually poorly tolerated by rodents. Head-mounted plugs for neurophysiological recordings (sensors, stimulators and/or transmitters) have been widely used with success.

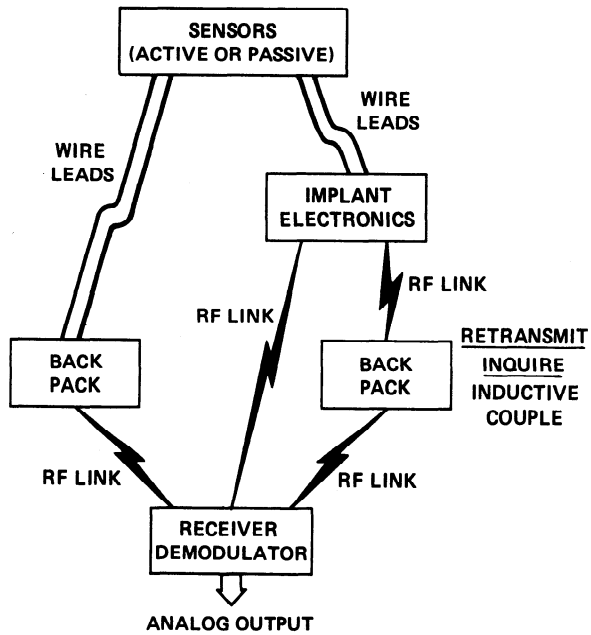


Figure 1. Schematic of Telemetry System Operation

The overall manner of system operation is shown in Fig. 1. Sensor leads (usually implanted inside the body) are attached to a transmitter where transduced signals are electrically converted, preprocessed (usually amplified) and manipulated for broadcast to a receiver-demodulator for subsequent information registration in analog or equivalent form. Accuracy and reliability of data transmission is maintained through use of a carrier which is either amplitude or frequency modulated (alone or in combination) by the primary signal.

Back-packs have the advantage of ready replacement of power source. This allows use of smaller batteries for long-term experiments or replacement in the case of premature battery failure. Additionally, a single transmitter pack can be rotated between animals. Back-packs have the disadvantage of leads that penetrate the skin with potential breakage and incidence of local or systemic infection.

Totally implanted units with data transmission through the intact skin have their greatest advantage with long-term experiments and have provided intermittent or continuous recordings of single or multiple variables. Certain systems, such as swallowable transmitters, provide data unavailable by any other means. Instrumented animals have total freedom and range of motion and require no post-implant attention. Physiology can be followed over the course of each day and during any significant event including eating, sleep, normal social interaction or change of environment.

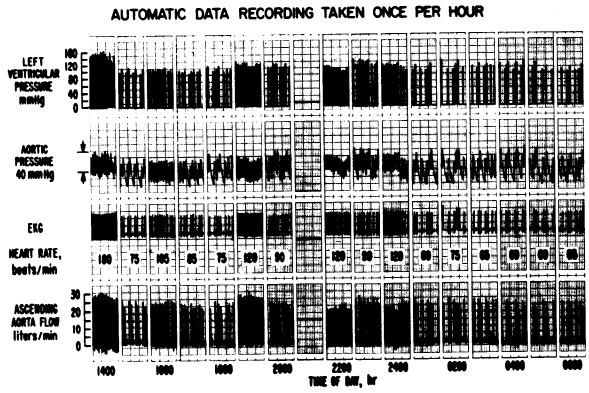


Figure 2. Automatic Data Recording

Figure 2 demonstrates the results of recording heart rate pressure and flow in a dog over a 24-hour period. Note changes during eating, normal activity and sleep. With continued improvements in design and construction they promise to become the primary means for following the courses of certain induced or naturally occurring disease processes such as hypertension or coronary artery disease, documenting drug physiology and pharmacology and evidencing the mechanisms of adaptation to various stresses, such as long-term (1+ year) space flight and the manner of subsequent recovery following any exposure. Disadvantages of implant systems are their high cost, need for careful circuit design to minimize power requirements, and concern for transducer and component reliability, since adjustments cannot be easily made after units are placed inside the body.

A number of frequency bands are normally used for wireless transmission. The very low frequencies, 500 kHz (AM band) to 10 MHz, do not propagate well with the small antennas feasible for use inside or outside the body. An exception is very short-range telemetry (few inches) using small laboratory animals such as rats. Fortunately the FCC has authorized the FM entertainment band (88-108 MHz) for lower-powered telemetry applications, markedly improving range and lowering cost since commercial equipment is readily available. Even with small 0.75 inch diameter implanted antennas, low-powered implanted transmitters have produced ranges up to 100 feet. In routine laboratory applications (ranges up to 5 to 15 feet) such transmitters provide strong signals to overcome all except the strongest FM stations, but become marginal beyond 50 feet due to station interference. Back-pack transmitters with larger replaceable batteries and containing effective antennas can have ranges of many miles. The 172-216 MHz VHF frequencies are authorized for such use, but have received only limited application since standard FM receivers are not readily available for such bands. FCC power limitations on the FM and TV bands limit their effective use to less than 500-600 feet. For greater range special frequency assignments in the mobile VHF band, such as those used for ECG transmission by ambulance and emergency vehicles, are required. In these cases implant or back-pack units have transmitted to a second or rebroadcast unit (transponder) which then relays the information at the required frequencies.

PARAMETERS:

The feasibility of using telemetry for physiologic monitoring is often dependent upon the type of measurement required (1). ECG is one measurement easily acquired since a complex transducer is not required. The signal necessary for amplification is obtained from a simple pair of electrodes, amplified and then coded for transmission. Very little power is needed, if only short-range monitoring is required. Several years of continuous transmission has been possible with a single small pacemaker battery cell. Highly miniaturized units have now been developed using integrated circuit (IC) techniques so that units without battery are no more than 1-2 $mm^3$ in volume. Measurements of electroencepholograms (EEG's) and electromyograms (EMG) can be similarly handled. With the advent of implantable pressure transducers in the mid 1960's, telemetry of vascular pressure has also become quite routine (4). The most widely used transducer has been a 2.5 to 7 mm in diameter X 1.2 mm thick titanium disk which uses four element strain gages sensors for electrical readout. Because of size they have been used primarily for cardiac and aortic pressure measurements in dogs and primates. Normally supplied cells with 350 or 500 Ω gages are replaced for implant use with 5000 Ω bridges to minimize current drain. Using a 1.35 V medium sized pacemaker battery, a typical system would use 1 mA of current to transmit 50 feet with 30% of the power used by the transducer. 500 hours of useful operation is available from a 500 ma-hour cell. Useful life can be improved by operating only on command through local (magnetic) or remotely controlled (RF) switches in the power supply. Depending on the program, several years or more of operation have occurred. As with pacemakers, batteries deteriorate (internal leakage) more rapidly at the elevated temperature of the body and this factor may limit the ultimate life of the system. This

problem has been markedly improved with the recent availability of lithium power cells which have long shelf lives of up to 10 years at body temperature. Of course, these cells cost considerably more. Other possibilities include use of rechargeable or nuclear batteries or powering through radio induction (1,3). Other types of pressure sensors have been constructed and tested. IC capacitance cells (1-7 mm in diameter) have long-term zero drift stability; IC strain gage transducers are inherently small and are available in sizes from 0.5 to 1 mm in diameter.

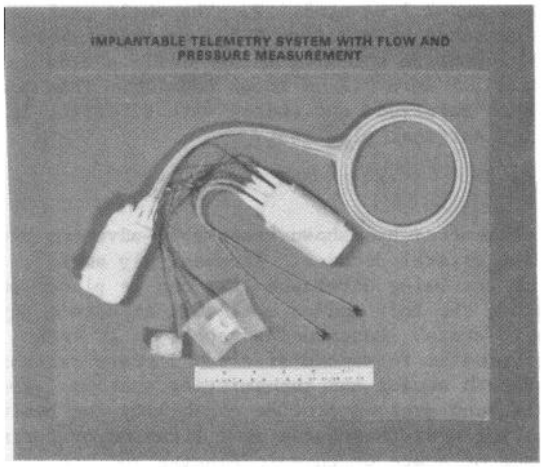


Figure 3. Implantable Telemetry System with Flow and Pressure Measurement

Both electromagnetic (EMF) and doppler flow systems have been used with telemetry (4). Figure 3 illustrates a multichannel implantable unit containing ECG, two pressure cells and an EMF probe. Results from its use two months post-op are shown in Figure 2. The large power consumption of electromagnetic probes (usually 2-4 A of probe current) has made their use difficult. This has been reduced to about 300 mA for back-pack or implant purposes, but still remains more than 10 times the amount used by ultrasonic flowmeters. High power consumption limits continuous use to only 4 to 8 hours and necessitates large batteries and frequent recharging. The system in Figure 3 uses rechargeable Ni-Cd batteries and the recharging coil which is placed subcutaneously is shown. Only a single EMF probe has been practical for use with implant systems, yet as many as four probes have been used with battery-operated back-pack units. The useful life of such latter systems is still only several hours without battery replacement or recharge.

Although transit time ultrasonic flowmeters have been built and tested, doppler systems have been the most widely applied. Both continuous wave (CW) and pulsed systems are available. CW units are the simplest in design and easiest to apply, providing accurate zero flow by simply turning off the supply voltage. They have been used hardwire, back-pack and more recently, in the implant mode. Pulsed systems are far more complicated, but provide important information on flow velocity profile. The latter system uses a single crystal and, therefore, need not entirely encircle the vessel with a cuff. Velocity profile is detected by range gating to accept the doppler signal from a particular zone, across the vessel lumen. Thermoammetry is the only other quantitative technique which approaches this method. Vessel diameter is determined from transit time information. The method is inherently limited by sensitivity of the transducer to change in angle between the ultrasonic beam and blood velocity vector and requires careful calibration before and/or after use. Most systems use frequencies between 8 to 10 Mhz and pulse durations of 0.3 to 0.5 μsec. The maximum measureable flow velocity (doppler frequency) is limited by the repetition rate of the pulse, measurable vessel diameter is also inversely proportional to this rate which is usually between 1 to 30 KHz. Gate delay and width are adjustable between 0 and 70 μsec. The transducer itself can be very small (1 $mm^2$) in surface area. Flow has been successfully measured in vessels 2 to 3 mm in diameter. Recently, pulsed flow systems attached to an 18 gauge needle have been used to measure blood flow in small cerebral blood vessels, hardwire systems have been used on the rat aorta and provided 6 months of useful data. Implant versions using IC technology have drawn less than 50 mW of power and provided over 5 months of useful intermittent information on portal vein blood flow in conscious dogs (5).

## POWER AND IC TECHNOLOGY:

Most physiological measurements require data on multiple parameters (1,4,5). For the cardiovascular system this represents measurement of ECG, pressure, dimensions, flow and oxygen utilization. Such systems are far more complex than single channel units, result in higher power consumption and are suited only for larger animals. Multiple individual transmitters and receivers can and have been used, but more than two transmitters and receivers add needless complexity and expense, since electronic multiplexing can be used. Usually only one transmitter and receiver is required with each data channel time shared (switched) on a single carrier. Two transmitters seem justified for studies measuring mutliple variables from the upper and lower parts of the body in order to decrease lead length, entanglement and possible lead breakages. As many as 5 to 7 channels of cardiovascular data have been simultaneously provided by a variety of multichannel systems including ECG, two to four pressures, flow (doppler or EMF) and/or dimensions (ultrasound or mutual inductance). A seven-channel system is shown in Figure 3. Other packages have transmitted data for ECG and several single or two three-axis accelerometers. Units have functioned well in large dogs and primates from several months to several years. IC circuitry, decreasing size and improving reliability have allowed for design and construction of these systems and even more complicated units, such as a totally implanted echocardiograph, providing M-mode data from an appropriate sensor sutured to the right or left ventricular epicardium or 10 channels of neurophysiologic data. These latter systems have operated successfully from head plugs on rats for weeks to months.

For smaller animals and implants IC design and switching of the battery power supply or battery elimination have been crucial. The most attractive energy saving devices have been transcutaneous on-off switches, varying from implanted magnets to circuits that turn battery power on with a short RF burst with automatic turn off after a prescribed time, or with an additional similar RF signal (1,5). Since data is taken at periodic intervals power is saved proportional to ratio of the on-off cycles. For long-term daily recordings it may be necessary to only collect data 30 seconds every 5 minutes or every hour (see Figure 2). In this manner 8-10 hours of useful battery life for a complex multichannel system can provide 3 to 7 weeks of data before recharging, for a low-powered system years of data can result. RF switches operate in a manner similar to model airplane controllers. Such units were used by Van Citter and Franklin for long distance control (up to 1 mile) to operate back-pack units for measuring blood pressure and flow in free ranging animals in Africa.

Another highly successful approach for powering units is through induction, since it eliminates the batteries which may be the largest component in a microminiaturized system. Power is radiated from an external coil which may be worn in a vest or incorporated in the cage walls or floor. Transmission of RF through the skin has not been difficult, although some energy is absorbed by body tissues and re-radiates to the receiver. Implanted coils as small as 7.5 mm in diameter have been successfully used in rats. Frequencies above 200 MHz are not usually used because of absorption and difficulty in building transmitters at this frequency and above. Since the pick up coil is very small compared to the energizing coil, energy transfer efficiency is low (falls off as the cube root of the distance) so that supplied power is only in the microwatt range for most cage-mounted systems. Such power is sufficient to energize a small ECG and/or temperature unit indefinitely. Similar systems have been used to power artificial hearts, but require very large energizing voltages. A concern in such cases are subtle physiological effects due to the extremely strong associated magnetic fields. In animals such as dogs or primates this has been overcome by using units worn in a vest and transmitting power only a few inches to subcutaneously placed coils.

Initially, units were constructed of discrete parts (cordwood or PC boards) and represented application of conventional technology and readily available components. Resulting systems were relatively inexpensive, but had very low component density and were often bulky, even for back-pack application. Use of IC circuit design has resulted in marked size reduction enabling implantation or multichannel operation. IC circuit designs have been either hybrid or monolithic (2,5). Hybrid IC's are not truly IC's, but a microminiature assembly of discrete electronic elements. For such application, resistors, capacitors, transitors are pholithographicaly defined as thick film or sputtered thin film devices which are individually associated or connected prior to encapsulation. Monolithic IC's are processed in total on a single silicon chip (custom IC) and provide the most miniature device. Hybrid techniques can be used to interconnect several custom IC's and increase their versatility. Production of the monolithic device entails a large initial capital investment, but is then very inexpensive when mass-produced as a standard item. Over the past 3-5 years, an increasing number of monolithic IC's have become available which can be assembled with required component parts to form almost any needed complete circuit. A typical implant doppler flowmeter now contains two custom IC's, each 3 mm X 3 mm (5). The first chip contains the timer/exciter position, has 154 integrated components and net power consumption of 2.8 mA at 2.7 V. The second IC, which is the receiver/multiplexer, has 152 integrated components and consumes 2.3 mA at 2.7 V. The whole package is interconnected on a 2.4 cm X 1.1 cm multilayered hybrid substrate which is hermetically sealed in a 3.2 cm x 1.5 cm x 0.7 cm kovar housing. This package, when paralyned and coated with silastic, is used for surgical placement.

## SUMMARY

Biotelemetry has shown remarkable advances over the past several decades. Increasingly small systems are being developed that can be placed on or within the body and/or swallowed to detect physiologic state. Continued advances in IC technology promise to reduce size and improve reliability of both sensor and transmitting systems. For animals such systems provide capability for health monitoring over the course of a lifetime or during presence of acute or chronic disease and its treatment. For man, small units are already finding application in monitoring intracranial pressure, peripheral or central nervous stimulation (including pacemakers) and drug or medication delivery, such as insulin.

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# Book Reviews

## *Normal Renal Function.* W. J. O'Connor

London: Croom Helm, 1982, 433 pp., illus., index, £15.95 (UK)

This volume represents a timely rewriting of a monograph entitled *Renal Function* and published in 1962. Much of the information is the same but is somewhat differently organized. The book has been produced from camera-ready copy. Having written several books, some of them published in this form, I am only too aware of the advantages and the problems. This type of text can be rather tiring for the reader and is best prepared on a typewriter giving proportional spacing or on a word processor allowing justification of both the right- and left-hand margins. Publishers should probably encourage and even help authors to prepare camera-ready manuscripts in this way. Choice of typeface is also important. That for *Normal Renal Function* is not sufficiently bold. The lettering on the figures is frequently very much smaller than that employed in the main text, so that with reduction and the broken typeface it is difficult to read. The summary sections in each chapter are useful, and there is a comprehensive reference list at the end of the book. In many ways, however, a reference list at the end of each chapter, as in the earlier volume, is preferable.

The emphasis in this book is very much on the "normal" of *Normal Renal Function.* The information is presented in two main sections: *1*) acute experiments on normal renal function and *2*) balance experiments. Certain chapters, such as Chapt. 11, "Release of antidiuretic hormone from the neurohypophysis," are difficult to place and do not fit well into either section. The work is obviously that of an enthusiastic experimental physiologist, someone who believes that if the needs of disciplines such as medicine, animal husbandry, and nutrition are to be served, then quantitative data on normal animals need to be produced. He has moreover put beliefs into practice, having overcome the problems associated with work on conscious animals to produce wide-ranging results on renal function in normal dogs. While experiments at a microscopic or cellular level are obviously necessary and have greatly advanced our knowledge, it is refreshing to read a review concerned with responses in the intact animal.

Not all experimenters have the facilities or the desire to work on conscious animals, and for certain topics covered in the book there is a limited amount of information available. Even allowing for this, rather too much emphasis is placed on work published prior to 1960. This is particularly noticeable in the chapter on experimental diabetes insipidus, where no mention is made of the Brattleboro rat with hereditary diabetes insipidus. Discovery of this strain of rat has allowed extensive observations to be made on conscious animals totally deficient in vasopressin.

Overall, the book gives considerable insight into experimental method in physiology and from this point of view would be of value to the student. For the specialist there is detailed consideration of the intake and excretion of urea and the ions sodium, potassium, chloride, bicarbonate, sulfate, and phosphate. In general, this volume would be a useful addition to the library of the renal physiologist and also be of value to the more general reader.

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## *Prostaglandins: Organ- and Tissue-Specific Actions.* S. Greenberg, P. J. Kadowitz, and T. F. Burks (Editors)

New York: Dekker, 1982, 454 pp., illus., index, $59.50

This monograph is the twenty-first in a modern pharmacology and toxicology series. An introductory section reviews cardiovascular medical physiology, including adrenergic neurotransmission and capillary filtration dynamics. A lengthy clinically relevant dissertation on hypertension, vascular smooth muscle, and prostaglandins precedes a review of prostaglandins and the renin-angiotension and kallekrein-kinin system. Pertinent questions of data interpretation are raised. A second section deals with prostaglandins and the circulation. Fatty acids as putative neurotransmitters and as modulators of myogenic vascular tone and adrenergic responses are discussed in a chapter on prostaglandins and the cutaneous vasculature. Arachidonic acid tissue perfusion results are emphasized, and the direction of future research is discussed. The direct and modulator actions of prostaglandins on uterine blood flow are also reviewed, to be followed in a later section by a concise summary of prostaglandin effects on uterine smooth muscle. Involvement of prostaglandins in hypertension is well represented in chapters on renal function and the renin-angiotension-aldosterone system with a thorough review of reninology. Chapters also discuss prostaglandins and cardiac muscle, platelets, erythropoiesis, and the pulmonary vascular bed. Format often differs widely among chapters, and this is especially apparent in comparing the historical review perspective of platelet prostanoids, with the methodologic manuscript data presentation of the pulmonary system. Prostaglandins and gastrointestinal smooth muscle activity are adequately treated, with graphic data comparing prostanoids with morphine and other pharmacological agents. Perhaps the most interesting section discusses prostaglandins and pathophysiological processes. Prostaglandin involvement in cerebral vasospasm is a novel addition and presents effectively the incongruency principle of cerebrovasospasm. The importance of cerebrospinal fluid in brain prostaglandin interaction is summarized. A healthy critique of the hypothesis of prostaglandin involvement in cerebrovasospasm is provided, along with an extensive discussion of future and needed research. Prostaglandins and central nervous system function discusses prostanoid release from the cerbral cortex, interaction with cyclic nucleotides, and role in pituitary hormone secretion. Generally, the text is quite readable, but many chapters lack complementary graphic illustration. Few chapters contain references as late as 1981. However, a pervasive spirit of criticism and query regarding the hypothesized role of prostaglandins in tissues prevails, much to the volume's credit.

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## *Cardiovascular Pharmacology of the Prostaglandins.*
A. G. Herman, P. M. Vanhoutte, H. Denolin, and A. Goosens (Editors)

New York: Raven, 1982, 472 pp., illus., index, $55.00

In a field as broad as prostaglandin physiology, it is imperative that new texts describe specialized and limited functions of these cellular autocoids. In *Cardiovascular Pharmacology*, discussion of basic prostaglandin biosynthetic pathway and regulation of synthesis by steroids and NSAIDs is minimized, although an interesting discussion of the prostaglandin reciprocal coupling factor hypothesis is included. Newer theories of the role of prostaglandins in nerve function are presented toward a view of reassessing $PGE_2$ and prostacyclin in vascular adrenergic neurotransmission. A synopsis of the hemostatic process and physiological agents affecting thrombotic events is also provided. Discussion of the pharmacological approach to occlusive vascular disease is included. Several summary presentations of the interrelationship between prostaglandins, platelets, and vascular endothelium adequately review the topic. Chapters on platelet activating factor and mechanisms responsible for the pathogenesis of atherosclerosis complement nicely the broad hemostatic overview. A short introduction to prostaglandins and blood pressure regulation precedes an extensive review of prostaglandins and renal, perinatal, and microcirculation and circulatory shock. The clinical aspect of prostaglandins in cardiovascular disease is admirably represented in chapters dealing with peripheral vascular disease, platelet modulating therapy in cerebrovascular disease, angina pectoris, and ischemic heart disease. The critical appraisal of studies, such as the persantine-aspirin reinfarction study, the anturane reinfarction trial, and aspirin and secondary mortality after myocardial infarction, complete the clinical discussion of prostaglandins and cardiovascular pharmacology.

The text is organized very well, possesses a modern bibliography, and allows the reader to readily grasp an understanding of any one of the various subject areas. The appreciated slant toward clinical awareness makes the book a valuable resource for clinicians and those involved in didactic training in pharmacologic science.

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## *Germ Cells and Fertilization* (2nd ed.).
C. R. Austin and R. V. Short (Editors)

New York: Cambridge Univ. Press, 1982, 177 pp., illus., index, $11.95.

Although this book is considered to be the second edition of the same title, the authors and the contents are different from the first edition. It brings our knowledge up to 1982 from the first edition published ten years ago. The authors are well-known experienced research workers in the field of their review. In dealing with primordial germ cells and regulation of meiosis, Byskov of Copenhagen gave a good account of the development, differentiation, and regulation of the germ cells as well as the life cycles of male and female germ cells before and after puberty. In the chapter on oogenesis and ovulation, Baker of West Yorkshire presented the periods of oogenesis and the times of ovulation in different animals. He also described the life history and the population of the female germ cells, their development involved with DNA and RNA, the enzymes in the follicles, the eggs at ovulation, and finally the atresia of follicles. The mammalian egg was reviewed by Austin of Cambridge, UK, who dealt with the size and structure of the egg, the possible molecular arrangement of its plasma membrane, and the fertile life, abnormality, and parthenogenesis of the egg. In the chapter of spermatogenesis and spermatozoa, Setchell of Australia discussed in detail the position of testis in different species, the Sertoli cells in relation to spermatogenesis, the composition of tubule fluid, the spermatogenic cycles (in a simplified system) and waves, and the synthesis of DNA and RNA during sperm formation. In the chapter on the sperm and egg transport, Harper of San Antonio reviewed the mechanism of sperm transport and the physiological changes of spermatozoa in the male and female tract. The number of sperm ejaculated and the site of deposition, the time between mating and the arrival of sperm in the oviducts, the fertile life of sperm and eggs, the movement of eggs in the oviducts, and the time of egg denudation and entry into the uterus were all presented in tables. The chapter on fertilization was written by Bedford of New York, who reviewed the final preparation of sperm for fertilization, capacitation and stimulation for acrosome reaction, then the interaction of sperm with the zona pellucida and the fusion of membrane between sperm and egg. The activation of the egg, such as block to polyspermy, the pronucleus formation, and syngamy, were also described. He also discussed the specificity of fertilization, errors of fertilization, and in vitro fertilization.

In general this is a very concise, outstanding, well-illustrated, and handsomely printed book. It is strongly recommended to students and research workers who are interested in reproductive biology. One misprinting noted by the reviewer is on page 160 concerning the longer survival of sperm in the female tract, it should be mares and hares.

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## *Membranes and Transport,* vol. 2
A. N. Martonosi (Editor)

New York: Plenum, 1982, 679 pp., illus., index, $75.00

*Membranes and Transport* is a two-volume collection of 182 short reviews by leading authorities who consider the current state of knowledge regarding structure, biosynthesis, and function of biological membranes in microorganisms, animal cells, and plants. Volume 2 contains 95 articles and is divided into sections devoted to the transport of metabolites and ions in microbial, animal, and plant cells; channels, pores, and intracellular communication; excitable membranes; structure and permeability of blood cell membranes; and properties and regulation of cell surfaces. The reviews are uniformly of high quality with adequate bibliographies.

The major problem with this volume relates to its ambitious scope, reflecting the diverse activity in this broad area of research. This limits prospective reader interest.

Graduate students who are beginning their research in a particular field or an experienced researcher coming to a specific field for the first time will find this volume most useful. On the other hand, because of the brevity of most reviews, experts and nonexperts alike will, of necessity, have to go to original sources for a more complete understanding of one or another of the many topics covered.

While the intention of the editor was to facilitate communication across disciplines of information related to membrane research, only the most indefatigable reader will be able to digest and assimilate the potpourri of topics, approaches, and research interests emanating from the more than 600 pages of volume 2. On the positive side, the volume should serve as a valuable reference source. Moreover, each paper is capable of standing on it own, so that it is not necessary to submerge oneself in other sections in order to comprehend a particular one. A certain amount of repetition in the content of some articles, particularly in the first section dealing with active transport across bacterial membranes, will be of value to those readers who find a reinforcing value in the redundancies.

In addition to its lack of focus and broadness in scope, this volume will not have enduring value, because this publication is only a status report that is expected to be superseded by subsequent volumes that will chronicle the inevitable expansion of our knowledge of membrane transport. Nevertheless, this volume serves a most useful purpose by undertaking the difficult task of highlighting a diverse and important area of research in which there is a crucial need for a free exchange of scientific information.

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## *The Clocks That Time Us: Physiology of the Circadian Timing System.* N. C. Moore-Ede, F. M. Sulzman, and C. A. Fuller

Cambridge, MA: Harvard Univ. Press, 1982, 448 pp., illus., index, $25.00

Although time is a parameter that appears in many of the relationships that describe the function of physiological systems, it is one that is commonly treated in only the most superficial of fashions. Particularly in teaching, we tend to view the responses of the organism as a sequence of essentially steady states, with little emphasis placed on the dynamic transients that get the system from one state to another. While we may distinquish between "fast" (regulation of mean arterial pressure) and "slow" processes (blood volume regulation), we teach very little about the dynamics of physiological systems.

There is another level at which time as a parameter is commonly ignored. It is usually assumed that if a normal physiological system is unperturbed over periods of time ranging from hours to weeks, that its outputs, whatever we choose to measure, will remain constant. In *The Clocks That Time Us*, Moore-Ede, Sulzman, and Fuller systematically present the accumulating evidence that this assumption is false and that, in fact, at all levels of organization and function there are cyclical variations driven by biological "clocks."

This is a book that should prove fascinating and profitable reading for physiologists, physicians, biologists, and students of behavior. In it the authors have presented the results of 100 years of work in a field that has seemingly remained arcane (and thus ignored or at least overlooked) for too long. While this is clearly a "technical" book, as opposed to a "popular" presentation, it really only asks of the reader a minimal level of familiarity with biology and perhaps a somewhat deeper background in physiology. Those at ease with physics and math (and thus not put off by references to oscillators and phase angles) will probably come away with the greatest insight into the field, but even if one skips the more quantitative arguments, there is plenty of "meat" left.

The book is organized in a very straightforward and useful manner. Chapters 1-3 describe the basic phenomenology of biological rhythms, provide definitions of the terminology used in the field (a potential stumbling block for the novice), describe the techniques used in such studies, and carefully and clearly explain the various ways in which data are usually presented in this field (another major difficulty for most of us). This material warrants careful reading and plenty of thought; it establishes the basic, and necessary, framework for the consideration of the "physiology" of circadian (and other) rhythms.

Chapter 4 deals with our growing knowledge about the neural basis for timing mechanisms. Although the amount of detail here may be excessive for the nonneurobiologist, the material is clearly important and can be skimmed for the essence of the message by the nonexpert. Chapter 5 summarizes our knowledge of the rhythmic activity of various organ systems in various organisms. Chapter 6 describes our more limited data about such functions in humans.

The final chapter will be for many the most interesting, as it deals with the application of our current knowledge about biological rhythms to medical and behavioral (functional) problems. Even in these days of dwindling travel money, the phenomenon of "jet lag" is a familiar one to almost all of us. While no "quick fix" for this malady is described, the basis for its occurrence is explained and a helpful suggestion or two is offered (immediately eat and sleep on a schedule normal for your destination). On a more disturbing note, the problems of flight crews subjected to frequent cross-timezone flights is discussed, and it is clear that neither the airlines nor the FAA seem very aware of the hazards with which they are flirting.

This is a book that should have a wide audience. Lecturers on physiological topics will gain an appreciation for a much neglected aspect of physiology, and even if the "curriculm crunch" prevents much discussion of circadian physiology, one may be able to squeeze a little of this message into the lecture sequence. Graduate students in physiology or the neurosciences will certainly benefit for a more in depth exposure to this field, if only for the "rounding" that will result. And physicians should certainly begin a careful consideration of how the existence of circadian rhythms, and all of the consequences that follow, should modify their practice of medicine.

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