THE PHYSIOLOGIST

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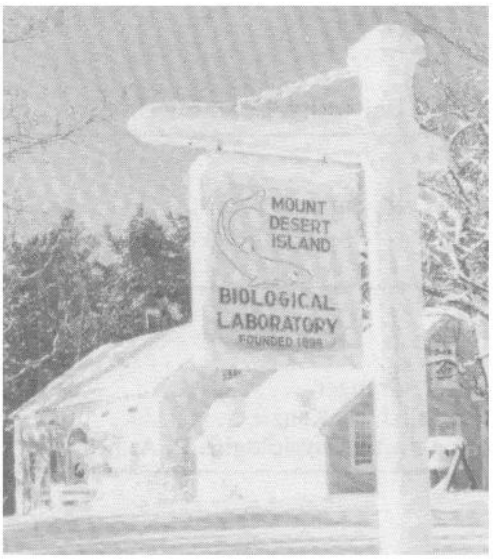
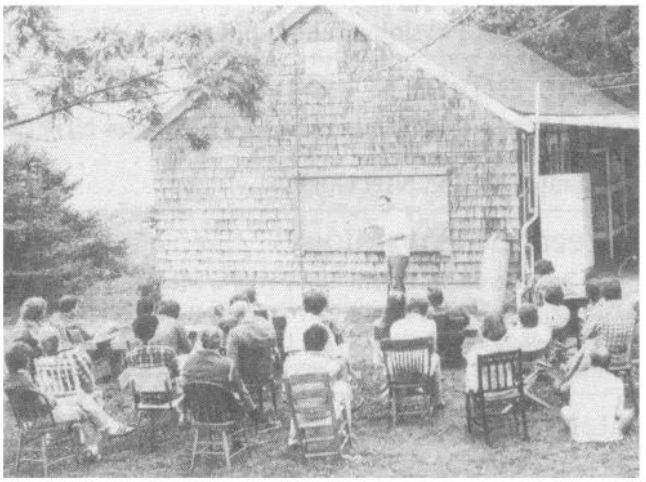
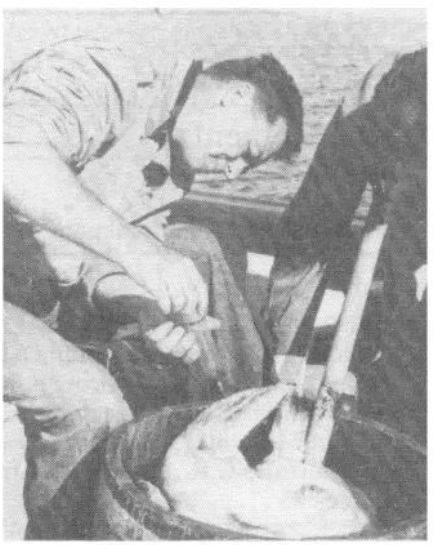
Cover: Longitudinal view of long-sarcomere, tonic-type muscle fiber from walking leg of crayfish (*Astacus fluviatilis*).
See *Skeletal Muscle*, p. 284.







Clockwise from upper left: kidney shed and Neal Laboratory [courtesy of R. P. Forster]; R. P. Forster and L. Goldstein working outside Neal Laboratory [photo by B. Schmidt-Neilsen]; R. Kinne lecturing to investigators on Laboratory Point [from MDIBL Archives]; R. P. Forster taking blood from a goosefish, about 1952 [courtesy of R. P. Forster]; Laboratory from the air [photo by R. Hylander]; Laboratory sign in the snow [from MDIBL Archives].

A History of Renal Physiology at The Mount Desert Island Biological Laboratory

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The history of renal physiology at Mount Desert Island Biological Laboratory (MDIBL) begins with a very colorful and interesting man, Dr. **Eli K. Marshall** (Figure 1). Before 1926, the investigators working at the small summer laboratory in Salsbury Cove were mostly naturalists engaged in ecological, zoological, and tissue culture studies. Since Marshall's arrival at the Laboratory, his work and insights have to a large degree shaped the field of renal physiology in general and at MDIBL in particular. This is quite surprising considering that Marshall's research in basic renal physiology lasted only 11-12 years (1920–1932). He had, as he himself said, solved the basic problems that had bothered him, and he was not interested in the second decimal!

In the summer of 1957, Marshall gave a lecture at MDIBL on "Historical development of modern concepts of renal physiology." Dr. Roy Forster introduced him as a genius. Quoting from Carlyle, who has said "Genius is a transcendent capacity of taking trouble," Forster added, "When one qualifies that statement with the corollary — genius is the transcendent capacity of making trouble — there are many in this room who will agree with me." And later Forster added, "Speaking of discovery in science, Pasteur has said 'chance favors the prepared mind.' Our speaker [Marshall] is adequately prepared, as results have shown. Amongst his equipment is a high order of native intelligence, physical drive, absolute honesty, lots of courage coupled with the utter refusal to be bluffed, Southern charm which has led many to emerge from an encounter with Dr. Marshall quite surprised to find a knife firmly implanted between their ribs."

Later in his introduction Forster said, "We at the laboratory hold Dr. Marshall in high regard for his personal services to us, his interest in problems being carried on here, and his willingness to give advice, frequently pointing out to us that what we are now doing he had already published 30 years ago, and what with his avowed lack of interest in the second decimal we frequently find on rereading his older works that they are provocative, wide open to plagiarism, and still rich veins well worth mining."

Three years before Marshall first came to MDIBL he and Dr. J. L. Vickers had published a paper entitled "The mechanism of the elimination of phenolsulphonephthalein by the kidney — a proof of secretion by the convoluted tubules" (14). In this paper, Marshall showed that the amount of phenol red found in the urine could not be accounted for by filtration alone. He also showed that phenol red accumulated in the dog renal cortex when injected intravascularly, even after the blood pressure had been lowered to the point of stopping all filtration. The first part of his proof for secretion was logical and convincing, but still circumstantial, because at that time no direct methods were available for measuring glomerular filtration rate. The second part was strong evidence. Marshall's conclusions were strongly opposed by the leaders in the field, notably A. R. Cushny and A. N. Richards. To understand this, we must recall that Cushney's book *The Secretion of Urine,* published in 1917, in which he presented his new hypothesis that urine is formed by filtration and reabsorption of an ideal solution (2), was considered the ultimate truth, particularly after Richards had brilliantly showed, by micropuncture, that the glomerular filtrate is identical in composition to the plasma minus the proteins.

In 1924, E. K. Marshall and M. M. Crane, in a paper on tubular secretion in the frog kidney, formulated the following questions, "Is the concentration (in the urine) of substances such as urea, phosphate or sulphate brought about entirely by the reabsorption of water, by secretion of these bodies, by certain parts of the tubule, or by a combination of both processes? Does the kidney secrete at all? What is the rate of glomerular filtration under any given set of conditions? To what extent does the kidney eliminate substances which are not performed in the blood (e.g., ammonia, hippuric acid)? These questions which are more or less intimately connected must be decided before much further advance in our knowledge of the mechanism of renal excretion can be made, and before the more difficult task of the localization of function in the different parts of the tubule can be attacked with much hope of success" (11). The conclusion of this same paper states, "The observations of Marshall and Vickers for secretion of phenol red by the mammal have been extended and found to hold for the frog's kidney. Phenol red is concentrated or stored in the cells of both the amphibian and mammalian kidneys. The efficiency of the kidneys of both classes of animals is much lower when the plasma concentrations are high than at lower ones. This is taken to mean saturation of the secreting cells. Urea is concentrated in the frog's kidney in a similar way as phenol red" (11). It should be added here that the method used by Marshall for quantitative urea determination was his own classical enzymatic method using urease which he derived from jack beans.

The opposition to Marshall's findings continued unabated. Then one day in the library Marshall came across two French papers (1902, 1910) in which the kidneys of *Lophius piscatorius* were described as having neither an arterial blood supply nor glomeruli. Marshall was astounded to find that no work had been done to confirm or extend these findings or to study the function of such a pure tubular kidney. Consequently, in the summer of 1926, Marshall together with A. L. Grafflin came to MDIBL to undertake a structural and functional study of the kidneys of the goosefish, *L. piscatorius*. The Laboratory, which was established in South Harpswell, Maine, had relocated to Mount Desert Island in 1921. It's research facilities consisted of a new frame building with eight research rooms with electricity and running freshwater and seawater; this is the present Neal laboratory. At that time Homer Smith, whom Marshall had first met during World War I, was working on sand dollar eggs at MDIBL. There followed some of the most productive years in the history of renal physiology. Marshall and Grafflin now showed that the kidneys of the goosefish obviously produced urine and that many substances thought to enter the urine by filtration were present in the urine (12). In 1928 Marshall presented these findings in Woods Hole. After his talk, Richards was heard to say, "Marshall has at last found one beast in the whole animal kingdom which fits with his theory."

Marshall now turned his attention toward comparative anatomy and physiology of the vertebrate kidney, studying the excretion in teleost fishes, reptiles, and frogs and comparing function and tubular structure. This led to his well-known comparison of tubular segments in vertebrate kidneys in 1934 (10, Figure 1). He showed that most fish can secrete magnesium ions and reabsorb chloride ions and that a number of organic molecules are secreted. He was very interested in the transport of water into the tubules (water secretion) and showed that fish with glomerular kidneys could be rendered functionally aglomerular by phlorizin poisoning; such kidneys continued to produce urine, indicating fluid transport into the renal tubules. It is rather amazing, but Richards' opposition to tubular secretion continued until 1931, when Marshall was able to show that 70% of phenol red entering the renal artery in the dog is not present in the renal vein but is excreted in the urine (9). This finding finally convinced Richards, and Marshall turned his interest away from kidney physiology, because as he said, he was not interested in the second decimal.

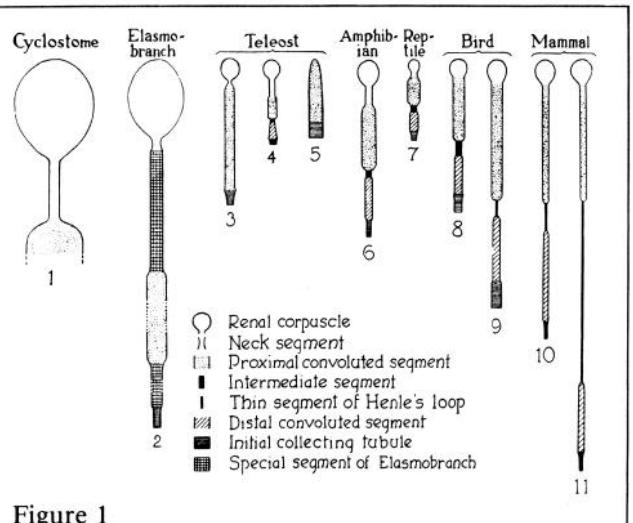

Figure 1
Schematic representation of vertebrate renal tubules from Marshall (9).

Another finding of the greatest significance for later developments in renal physiology was the observation that glucose was not present in goosefish urine, even after phlorizin poisoning of the reabsorptive mechanism. This find gave Marshall the idea that nonreabsorbed sugars, even glucose, following phlorizin treatment could be used in any animal to measure glomerular filtration rate. In 1923 Marshall visited my father's laboratory (August Krogh) in Copenhagen, where he had long discussions with P. Brandt Rehberg. Rehberg suggested using creatinine for measuring glomerular filtration rate because it, of all naturally occuring compounds, is found in the highest concentration in the urine (15). Marshall, however, found that creatinine occurs in goosefish urine and therefore is at least partially secreted by the tubules. Thus sugars promised to be more reliable than creatinine as markers for measuring glomerular filtration.

Homer Smith must have become intrigued by the new tools for studying renal function and for measuring urea quantitatively. His interest in sand dollar eggs apparently ceased, and he started to study the composition of body fluids and excretion through kidneys and gills of the elasmobranchs in Frenchman's Bay (24, 25). He was the first to show that the dogfish and other elasmobranchs maintain a very high (350) mM) plasma urea concentration and that their plasma osmolality is hyperosmotic to the surrounding seawater.

During the thirties several new investigators came to MDIBL. Some were already attracted to the new developments in renal physiology; others, including Ladd Prosser, William Doyle, J. Wendell Burger, and Robert Pitts, came to work on entirely different problems but gradually became excited by the problems in excretion. During the early part of this decade a major advance in renal physiology came about through the comparison of different markers for glomerular filtration. James A. Shannon, who worked at the Laboratory for six summers, systematically compared the excretion of nonmetabolized sugars and of creatinine in the dogfish (20, 22, 23). In 1934 he studied the excretion of inulin in the dogfish for the first time (21). As far as I can tell from the literature, the first experiments using inulin were made in Richards' laboratory that same year. Richards had, independently of Homer Smith's group, been looking for a larger nonsecreted nonreabsorbed molecule for estimating glomerular filtration rate. Using inulin, the investigators at MDIBL found that xylose is not a reliable marker for the glomerular filtrate except during phlorizin poisoning, because it is partly reabsorbed by the glucose reabsorptive mechanism.

Smith now synthesized the many new insights that had been gained in renal physiology in his first comprehensive book *The Physiology of the Kidney* pub-

lished in 1937 (26). This book, as well as Smith's later book (27), had an enormous impact because of the clarity of the concepts. Smith introduced the clearance concept and described methods for measuring not only glomerular filtration rate but also rate of renal blood flow and rates of secretion and reabsorption. Like Cushny (2), Smith presented the concepts in such a way that they could easily be put to experimental tests. The concept of tubular maximum was first understood by Marshall in 1924 (12), when he found a limiting uptake of phenol-red in renal cells with increasing plasma concentration. Smith presented the Tm concept and showed how Tm could be measured in vivo.

Following the publication of Smith's first book (26) a number of new investigators appeared at MDIBL between 1937 and 41. These include Willie Smith, Rudolf T. Kempton, J. Wendell Burger, Roy P. Forster, E. P. Hiatt, and Stanley E. Bradley. Tubular secretion of a number of organic substances were studied by Shannon, Willie Smith, and Pitts et al. **Forster** was able to verify and quantitate the intermittency of glomerular function in the frog by measuring the variations in glucose T_m (3). This intermittency had first been observed directly by Richards. Work which Homer Smith had started on the seal was continued by Hiatt, Bradley, and Hiatt. The interesting phenomenon that, in the seal, the glomerular filtration rate and renal blood flow more than doubles after feeding was shown by this group.

During World War II the customary activities were suspended. In fact the Laboratory was used for testing mustard gas. Following the war there was a sad state of affairs at MDIBL. The pier and dock had been washed away and the Laboratory had no money and no visiting investigators. In the MDIBL Bulletin it is simply stated, "In 1945 the director R. P. Forster was in residence and pursued a study on diuresis and antidiuresis in aglomerular fish." A valiant effort to save the Laboratory was undertaken by E. K. Marshall, Homer Smith, and Roy Forster.

In the summer of 1946 eleven investigators were in residence. Three of them were renal physiologists, R. P. Forster, W. P. Anslow, and L. G. Wesson. During the latter part of the forties activities at the Laboratory gradually picked up. W. P. Anslow and G. Schreiner worked on changes in renal function produced in the dog by dietary changes. Forster started working with cellular transport kinetics in isolated renal tubules. In 1948, he and J. V. Taggert introduced a very important new method "The use of isolated renal tubules for examination of metabolic processes underlying active cellular transport" (4, 29). Michael Ladd, who later introduced the concept of free water clearance (7), studied the relationship of filtration rate to maximal water diuresis in the seal, because of the highly variable filtration rate in this animal.

In the early 1950's Homer Smith, who was then president of the corporation, made a major effort to recruit renal physiologists to MDIBL. I first met Smith in Cincinnati in 1951, when he came to give a lecture at the Medical College. He gave a fascinating lecture on recent developments in renal physiology, and I had the opportunity to meet him in my laboratory. At that time I was working on the renal function in kangaroo rats. My interest in this had started with work on water metabolism of desert rodents in the Arizona desert. When we found that kangaroo rats can excrete an extremely concentrated urine (6,000–7,000 mosM), and that especially urea may be concentrated to more than 3,000 mM, I wished to study their renal function. I had read Homer Smith's book of 1937 from cover to cover and had started clearance studies on the kangaroo rat. When Smith saw what a devoted student of his I was, he invited me to spend a summer at MDIBL, and because of my specific interest in urea secretion, he said, "You can work with Roy Forster." Due to Smith's recruiting efforts, the population of renal physiologists at the Laboratory grew dramatically.

At this point I should like to relate some of the details of the daily life at the Laboratory. Going to the Laboratory in 1952, I packed two boxes containing all of the equipment and chemicals I needed for the summer's work. Life was simpler then. Now many investigators bring enough equipment to fill a moving van! Roy Forster and I worked in two laboratories. Wendell Burger was in the room next to me and Stan Bradley's group worked down the hall on seals. As Roy and I worked on renal function and urea secretion in bullfrogs, we needed frogs in good health. Frogs that were shipped were in bad condition, so we went out on the most exciting frog-hunting expedition. Ray Rappaport, who was far superior to us in catching them, went along. He would sneak up on a frog in the pond, scoop it up in a net, and throw himself on the ground on top of the frog. That summer Homer Smith was writing his book *From Fish to Philosopher* (28) in his cottage. Whenever he came upon an interesting new idea, he would come down to the Laboratory and talk to Roy and me. That was quite exciting! Marshall, who was retired, also came around at regular intervals.

During that summer Wendell Burger, in a very casual way, or so it seemed to me, was working on the renal function of the lobster. He did not do any of the analyses himself but asked his various friends at the Laboratory to include them with their own analyses. I was therefore quite surprised when a few years later he published an excellent paper on excretion in the lobster (1).

During the decade 1951–1960, some very important discoveries were made at MDIBL. Forster continued with Taggart and others to study cellular transport kinetics in kidney slices and in isolated flounder tubules. Groups of other investigators also started using the technique. Forster and his collaborators were able to show the different properties of luminal and contraluminal plasma membranes in the transport of dyes across the tubular epithelium. He showed, as Marshall had 20 years earlier, that many secreted or transported substances accumulate within the tubular cells during the process. I see Forster's work as the beginning of the discipline of membrane transport at MDIBL. Hans Ussing visited the laboratory in 1954. Adrian Hogben started to work on transport across swim bladder and gastric mucosa.

Meanwhile, some investigators (A. P. Fishman, H. Heineman, J. E. Hodler, E. L. Becker, and T. Maren) were using carbonic anhydrase inhibitor to investigate the mechanism of urinary acidification in fishes (Figure 2). Maren, who had come to the Laboratory in 1954, increasingly concentrated his efforts on carbonic anhydrase (Figure 3). He also worked on the Marshall gland (8), an appendage of the genitourinary system of the male skate which contains a fluid of very high alkalinity. Marshall had one day come down to the laboratory and said to Maren, "Why don't you work on my gland?"

Figure 2
Work on the laboratory dock. *Left to right:* Al Fishman, Henry Heineman and Homer W. Smith [from *Bull. MDIBL,* vol. 4].

Figure 3
Tom Maren working on the dock with a dogfish [from MDIBL Archives].

Figure 4
Working on nasal salt gland in a gull are (*left to right*) Maryanne Robinson, Humio Osaki, and Knu Schmidt-Nielsen, summer of 1957 [from MDIBL Archives].

Maybe the most significant development in this period was the discovery by Knut Schmidt-Nielsen and his collaborators of the salt-secreting gland in birds. Knut had earlier spent a summer on a small island off the coast of Norway working on urine composition in gulls following ingestion of seawater. The question had been raised in August Krogh's laboratory how oceanic birds without access to freshwater can survive if they cannot concentrate the urine. Knut found, to his astonishment, that when he gave the gulls a load of seawater by stomach tube the urine chloride concentration decreased to very low values. Rehberg, learning about it, thought Knut's chloride analyses had gone wrong. Then in the summer of 1956, repeating the experiments on cormorants, Knut saw that a fluid started dripping from the beak of the bird following the salt load. Further physiological (Figure 4) and morphological experiments showed a well-developed salt-excreting mechanism by a highly specialized gland (19).

My own work toward the end of this decade involved the countercurrent system in mammals. On Mount Desert Island, I was able to catch beavers *(Castor canadensis)* and to show that these water-loving animals, which lack an inner medulla of the kidney, are unable to concentrate the urine above 700 mosM. This observation, together with observations made on various desert rodents and other mammals, was the basis for the comparison between length of the inner medulla and urinary concentrating ability (17).

Marshall would have judged the work in the decade 1950–1960 as sometimes dealing with the first decimal (e.g., the salt gland studies) and at other times dealing with the second decimal (e.g., the membrane transport work). He was deeply impressed with the work by Forster and his colleagues but not much impressed with the countercurrent hypothesis. When I, in the summer of 1957, showed him my manuscript for the review article "Urea excretion in mammals" (16), Marshall said he liked it except for the part dealing with the countercurrent mechanism (Figure 5).

As we enter the decade of the sixties, it becomes increasingly difficult to summarize the research, since the Laboratory by this time had become a very popular place for many outstanding scientists. I shall not try to

Figure 5
Bodil Schmidt-Nielsen consulting with E. K. Marshall on urea data, winter 1957 [photo by K. Schmidt-Nielsen].

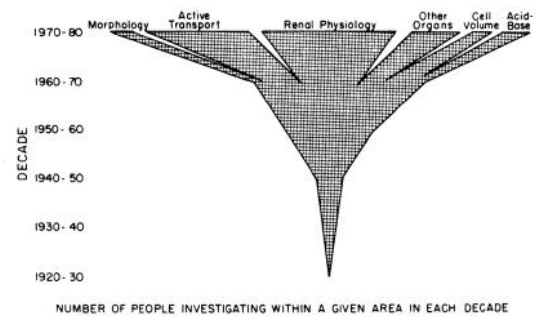

Figure 7
Graph indicating number of investigators working in renal physiology and closely related fields during each decade. As specialization occurs, there is great overlap between fields; therefore this graph is only an approximation. [The author thanks Heather McDuffie for her great help in compiling this material from the Bulletins of MDIBL].

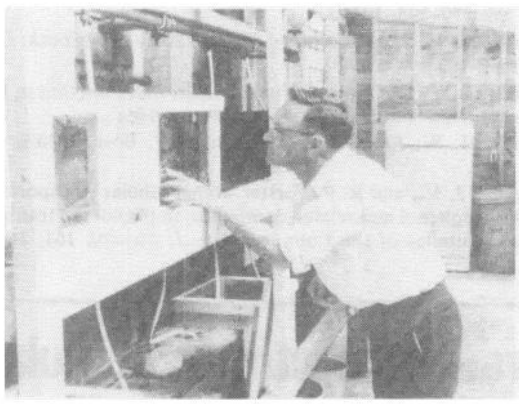

Figure 6
Wendell Burger looking at his fish outside the Halsey laboratory at MDIBL [from MDIBL Archives].

Figure 8
William B. Kinter with one of his Canada geese after he became a year-round investigator at MDIBL. [Courtesy of H. Church].

single out specific contributions during this time, except for one. This is Burger's discovery in 1961 of the function of the rectal gland in the dogfish. Burger (Figure 6), who had catheterized the bile duct of the dogfish the year before, became curious about the rectal gland. In his first abstract he wrote, "The conspicuous rectal or digitiform gland of dogfish and of other elasmobranchs has been observed by thousands of students, but its function seems unknown. Surgical catheterization of the duct of the gland resulted in fluid for analysis and data on rate of flow." He now found the excreted fluid to be watery, colorless, nearly neutral, and isosmotic with the plasma. But this fluid was an almost pure NaCl solution, with few other ions and little urea. Thus he had discovered, in the elasmobranchs, another salt gland which helps them maintain salt balance. Burger himself proceeded in the coming years to characterize the excreted fluid and to determine the chemical stimulations which cause the gland to excrete. This discovery by Burger has had a profound effect on the work at the laboratory, not only because of the biological importance of the salt-excreting mechanism but also because the gland has served as a tool for many investigators at the laboratory for the study of epithelial chloride transport. L. E. Hokin and collaborators in 1971 used a large number of rectal glands in an attempt to purify Na^+-K^+-ATPase. This attempt may have decreased the dogfish population in Frenchman's Bay for years.

During the decade of the sixties, specialization had become increasingly more apparent. This trend continued into the decade of the seventies (see Figure 7). In 1971 something happened at MDIBL which changed its character in a dramatic way, much to the dismay of some of the seasonal investigators: the laboratory went into year-round operation. This development was precipitated by Dr. William Kinter's (Figure 8) and my desire to work year-round at the Laboratory. Fortunately for us, it was possible to work out the details both with the Laboratory and with the National Institute of Health (I am very grateful to the officials of NIH for the help they have given us over the years).

Thus two groups of renal physiologists became the first investigators to use the facilities all year. Again some of the problems that we and our collaborators worked on can be traced directly back to Marshall and Smith: tubular fluid secretion in the eel (18), confirming Marshall's old finding that glomerular teleosts also have the ability to secrete water (13); and tubular secretion and reabsorption of organic compounds (5, 6). This was a problem Marshall called attention to in his talk of 1957, when he cautioned that the equations presented by Smith for calculating tubular secretion or reabsorption would lead to erroneous results if a given substance could move both ways. Before Kinter died in 1979 he

had started collaborating with Rolf Kinne using membrane vesicles for determining transport across apical and basolateral plasma membranes. Kinne now comes to the Laboratory regularly and has many collaborators among the MDIBL scientists. Obviously, the third or fourth decimal is now the target. My own current work deals with the effect of the renal pelvic contractions on the renal papilla as well as the regulation of the urea clearance in the mammalian kidney. I would consider that still the first decimal. Maybe this is why I have such a great affection for Dr. Marshall.

Since it is obviously impossible to mention all of the outstanding individuals or their work I am referring the readers to the MDIBL Bulletins, which are available in most University Libraries.

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To prepare this manuscript *the Bulletin of the Mount Desert Island Biological Laboratory* has been used extensively. The *Bulletin* abstracts mentioned in this paper are not referred to individually, since they can readily be located in the *Bulletin of MDIBL* (from 1930 to date). Dr. Forster's introduction to Dr. Marshall's talk has not appeared in print, but Dr. Forster has kindly lent me a copy. Dr. Marshall's talk of 1957 was preserved on tape. I have used a copy given to me by Dr. Howard Haines.

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Distinguished American Physiologists

Samuel Robert Means Reynolds (1903-1982)

When Sam Reynolds died in September 1982 there ended an extraordinary career in biological research which spanned the major portion of what many agree to be the golden era of American Science. Some knew Sam as an anatomist and some as an endocrinologist, and obstetricians and gynecologists thought of him as one of their own. I knew him as a physiologist, which was what he really was and wanted to be known as. True he followed a somewhat unorthodox pathway to physiological fame but let his accomplishments alone praise him.

As a medical student in the late 1930s at the old Long Island College of Medicine (now SUNY Downstate) in Brooklyn I first met Sam, who was then Associate Professor of Physiology. Because of tuberculosis I had to take a year off from school and George B. Ray the Department Chairman offered me an assistantship in Physiology. Sam was then working out the responses of the uterus in rabbits to pitocin, acetylcholine, and estrogens. He had devised a method of exteriorizing the rabbit uterus to the abdominal wall and recording its contractions in the unanesthetized state (2). Obviously he was intensely interested in estrogens and progestogens, which were then quite novel. Since I was more interested in the circulation, Sam challenged me to devise some simple method of measuring the microcirculation in human skin. I came up with some methods of grading the responses of the smallest skin vessels based on Sir Thomas Lewis's observations. Sam encouraged me to go on in this work, and some dozen papers were eventually published on reactive hyperemia in human skin (1). He sent me to my first meeting of the American Physiological Society (1941) in Chicago to present some of this work. This was an experience I have never forgotten.

Born in Swarthmore, Pennsylvania, Sam also attended Swarthmore College. There he received the A.B. in Biology and later his M.A., with Detlev W. Bronk as his advisor and with whom he later served an assistantship in physiology and zoology. Next he qualified for his Ph.D. in Physiology under H.C. Bazett at the University of Pennsylvania. Here he worked with M. H. Friedman and M. H. Jacobs, and undoubtedly they greatly stimulated his interest in the then new field of endocrinology.

Next we find Sam at the Western Reserve School of Medicine as an instructor under the famous C. J. Wiggers working on coronary artery perfusion. However, the circulation did not interest him, and he joined the newly organized Department of Physiology at the Long Island College of Medicine in Brooklyn. Besides he was now married to Mary Elizabeth Curtis, herself a Ph.D. from Yale, and he wanted to step up his financial situation. Sam stayed in Brooklyn for 8 years rising to a rank of Associate Professor. It was here in the venerable Hoagland Laboratory that he did his fundamental work on the physiology of the uterus which led later to the publication of his classic book on that subject in 1939 (3). While in Brooklyn he made many important friendships with obstetricians and gynecologists, thus gaining first-hand clinical experience. He also found time to be Research Director of the Kate Lubin Research Foundation of the Cumberland Hospital in Brooklyn. A Guggenheim Fellowship allowed him to spend time at the University of Rochester with George W. Corner. This was an important contact, for he was to join Corner in 1941 as a member of the Carnegie Institution of Washington. I remember visiting Sam during this period. The Carnegie Institution Department of Embryology headed by Corner was actually in Baltimore, and Sam enjoyed the closeness to the clinical facilities of John Hopkins. He was working at the time with what was then a revolutionary method of measuring uterine contractions directly from the abdomen of women in labor. He was also in the midst of anatomical-physiological demonstrations of the change in structure of uterine arteries with the growth and development of the uterus in pregnancy (7). In 1950 Sam again as a Guggenheim Fellow spent time at the Nuffield Institute for Medical Research at Oxford University in England. Here he worked with M. M. L. Prichard, Gordan Ardran, and Geoffrey Dawes making fundamental studies on the fetal circulation, the changes occurring at birth, and the placental venous system (6).

After 15 years at the Carnegie Sam became in 1956 Professor and Chairman of the Department of Anatomy at the University of Illinois in Chicago. As a department chairman Sam had more administrative duties than he cared for, but he performed these very well. He was active in the Association of Anatomists and the Association of Department Chairmen of Anatomy. However, he managed to continue to conduct a continuous volume of research despite heavy teaching duties (8).

Sam had hypertension, which he successfully combatted for many years. However, a severe coronary attack convinced him to retire in 1969. He returned to Pennsylvania to live in the rolling hills of the country he loved so well. Active to the last he continued to teach and write (4, 5) and to be a Lecturer in Obstetrics at the Hershey Medical School of Pennsylvania State University.

Of the many honors that came to Sam during his productive career I believe that the honorary D.Sc. from Swarthmore and the Doctorate of Humane Letters from Loyola University meant the most to him. He was also very proud of his recognition by South American countries, including Chile, Uruguay, Peru, and Brazil. Naturally he was most recognized by obstetricians and gynecologists and as a consequence was an honorary

member of the constituent societies of Switzerland, France, and most south American countries. In 1979 he was honored by the Distinguished Service Award of the American College of Obstetricians and Gynecologists.

Sam is survived by his wife Mary-Lib, his true and staunch supporter in the years of privation of a career devoted strictly to research. Two daughters Nancy and Harriet graced this union, and they were a joy and delight to Sam.

Because he had over 200 original articles, numerous reviews, and four books to his credit, there is little chance that many physiologists would equal or surpass Sam's record for original research. Yet his many students and fellows are his greatest achievement, and I am especially proud to have been one of them. His unique contribution was the ability to rework a field that appeared to be exhausted and to devise ingenious approaches which led to significant advances. Surely, something of this attribute in addition to his good humor and boundless optimism was passed on to those of us who were privileged to work with him.

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Joseph R. Di Palma

John Field (1902–1983)

John Field, born in Philadelphia in 1902 and raised there, left in 1919 to attend Stanford University, and from then on, except for government service in Washington, DC, 1948–52, remained in California. After

attaining his academic degrees in chemistry at Stanford (B.A., 1923; M.A., 1924; Ph.D., 1928), he became a member of Stanford's Department of Physiology, rising through the ranks to become Professor in 1942. His research interests followed a continuous line from the biochemistry and physiology of muscle, through many aspects of oxidative and glycolytic metabolism, to general thermal regulatory mechanisms. His work inspired many colleagues and students who since then have made their contributions to these and related fields.

1948 saw the beginning of several years' service in government when, on leave from Stanford, Dr. Field became Acting Director of the Arctic Research Laboratory of the office of Naval Research, in which organization he then became Head of the Biology Branch from 1949–1951. The following year he assumed the post of Assistant Director of the newly founded National Science Foundation.

Meanwhile, in 1951 Dr. Field was appointed first chairman of the Department of Physiology at the new UCLA School of Medicine and took over this position actively in 1952 at the end of his year with NSF. He led the development of the department as chairman until 1963, while also serving as Associate Dean of the School of Medicine from 1958 until his retirement in 1969.

In addition to his scientific and administrative endeavors, Dr. Field became increasingly active in the areas of medical education and medical history. He served the American Physiological Society as chairman of symposia on both these topics, as well as of numerous scientific sessions at APS meetings. He was, moreover, Editor-in-Chief of the first section of the *Handbook of Physiology* (Neurophysiology) published by the APS in 1959.

Retirement in 1969 saw no let-up in Dr. Field's activities, which were directed increasingly to study of and publication on the history of medical education in the United States. He was slowed only by illness which led to his death in May 1983. American Physiology and the APS were strengthened and advanced by John Field's contributions, and his many students, friends, and colleagues were enriched by their contact with this remarkable man.

Ralph R. Sonnenschein

[Donations in memory of Dr. Field may be made to UCLA Foundation — John Field Fund and sent to Ms. Nancy Donahue, Room 12-139 CHS, UCLA, Los Angeles, CA 90024.]

Departmental History

Department of Physiology and Biophysics School of Dentistry Oregon Health Sciences University Portland, Oregon 97201

The Dental School of the Oregon Health Sciences University is one of the few dental schools in the nation whose basic science departments are independent of those of a medical school. This autonomy has existed from the school's beginning. In 1899 the six-year-old Tacoma College of Dental Surgery moved from Tacoma, Washington, to new quarters in Portland, Oregon, at the corner of (NW) Fifteenth and Couch Streets. That same year the Oregon College of Dentistry opened at (SW) Second and Morrison Streets in Portland, and the two schools soon merged as the North Pacific College of Dentistry, operating at the Fifteenth and Couch location. Rapid growth and the need for more space brought about a move to a new building at East (NE) Sixth and Oregon Streets before the start of the 1911-12 academic year. In 1945, the North Pacific College was offered as a gift to the State of Oregon. It was accepted by the legislature and incorporated as a school of the University of Oregon, but it was not until 1956 that it moved west across the Willamette River to proximity with the University's medical school.

In November, 1974, the University of Oregon Medical, Dental, and Nursing Schools, all located on Portland's Marquam Hill, were established as an independent unit of the Oregon State System of Higher Education under the name University of Oregon Health Sciences Center. The name was changed again in 1981 to Oregon Health Sciences University.

An initial 50 years as a proprietary institution before going public, as well as an even longer period of physical separation from a medical school, produced a tradition of independence that remains strong today. The result of this independence from the Medical School, and the Dental School's long-standing almost exclusive devotion to the vocational goal of its students, has been small basic science departments. For example, many of the physiology faculty, including department heads, have served only part time. Some staff members have been shared with other departments; others have divided their time between academic physiology and the practice of dentistry or medicine.

In the school's early years, the attention of physiology was focused on the organ system that included the teeth. The catalog description of the physiology course offered by the Tacoma College of Dental Surgery in 1897-98 stated that its purpose was "to make students thoroughly acquainted with modern physiology, particular stress being laid upon the physiology of the alimentary canal." Two years later, the revised physiology course description indicated that "the purpose of this course is to impart a general knowledge of human physiology, with special reference at the same time to important odontological requirements." This dual concentration continues today.

Until the Dental School became part of the University of Oregon in 1946, the professor of physiology and head of the department was always an M.D., usually actively practicing medicine. Two interesting physicians who held the post were Robert G. Yenney and J. Allen Gilbert. Yenney, who headed physiology at the North Pacific College of Dentistry from 1899 to 1918, was a popular physician, a bacteriologist, and also Head of the Department of Medicine at the University of Oregon Medical School. He was organizer and commander of the University of Oregon Base Hospital Unit of World War I. Gilbert, Yenney's successor, displayed a psychological bent. During his tenure (1919-32 and 1941-46), the physiology course, according to the catalog description, included a "brief review of physiological psychology in an attempt to expose the so-called higher psychic powers of man." Although he was very interested in psychic phenomena, Gilbert stopped short of the popular belief in spiritual communication with the dead advanced by others, among them Sir Arthur Conan Doyle. Gilbert proposed a test for mystics and offered $500 for an authenticated message from his wife, who had died late in 1917. The reward was never collected.

Since the Dental School's merger with the University of Oregon in 1946, the heads of the Physiology Department have regularly held the Ph.D. degree. From 1946 to 1957, Nilkanth M. Phatak, a pharmacologist and Head of the Pharmacology Department, was Acting Head of the Physiology Department. During this period, there was some discussion of combining the two departments, but the idea was eventually abandoned. Declan J. Anderson, an Englishman from Guys' Hospital in London who possessed both a dental degree and a Ph.D. in physiology, was named Department Chair in 1958, but he returned to England after only one year. He remained on the roster of the Dental School as Adjunct Professor of Physiology for a few years, an arrangement that allowed students to spend a year studying in England while receiving credit toward an M.S.D. at the University of Oregon Dental School.

In January 1958, Leonard H. Elwell became Department Chair. He came from the University of Michigan and remained at the Dental School until his retirement in 1977. His successor, Arthur C. Brown, came from the University of Washington and remains as incumbent.

In 1980, the Department name was changed to Department of Physiology and Biophysics, to reflect its increasing involvement with biophysics in teaching and research.

Leonard H. Elwell

Animal Issues Take Backseat as House Debates NIH Proposals

The issues of laboratory animal reforms have become somewhat secondary now in the US House of Representatives as a political battle has developed over what is good for the management of the National Institutes of Health (NIH).

Up until the eve of the Congressional summer recess in early August the House appeared to be moving toward enactment of its NIH authorization renewal bill (HR. 2350), which would place much of the decision making and research management of NIH into the hands of the Congress. In addition to the renewal of existing NIH authorities the bill has nearly three dozen amendments that would regulate federally supported research, including two amendments which concern the use of laboratory animals.

Rep. Henry A. Waxman (D-CA), the prime sponsor of HR. 2350, won support early for his bill and its amendments in the Subcommittee on Health and the Environment, which he serves as chairman, and later in the full Committee on Energy and Commerce. But when the bill was introduced on the House floor it was met by a substitute from Rep. James T. Broyhill (R-NC) and Rep. Edward R. Madigan (R-IL), the ranking minority members of the Committee on Energy and Commerce.

The substitute bill only calls for the renewal of all existing NIH authorities at the increased funding levels proposed in HR. 2350 and for the establishment of a separate institute for arthritis and musculoskeletal diseases. All of the other amendments in HR. 2350 are deleted in the substitute bill, including both laboratory animal amendments.

In offering the substitute bill to the House members Madigan said that the Waxman bill emphasizes the management details, which Madigan described as "a prime example to a wrong approach." Broyhill added, "Those who have the responsibilities for administering NIH are better qualified than those of us on the House floor, operating in a political environment like this, to make the determination as to where the dollars go."

Waxman claims that his bill is vital to the future of NIH and added that he has the support of voluntary health agencies such as the American Cancer Society and the American Lung Association as well as the backing of specialized health groups such as the American Academy of Orthopaedic Surgeons, the Gluten Intolerance Group, the International Association of Enterostomal Therapy, and the Association of Schools of Public Health. Broyhill responded that this is "a political pork barrel which guarantees NIH's downfall."

Madigan questioned why Waxman's bill is opposed by those who broadly represent the nation's biomedical research institutions, asking, "Why is it that the Association of American Medical Colleges, the Federation of American Societies for Experimental Biology, the National Society for Medical Research, the American Physiological Society, the Association for Academic Health Centers, the National Institutes of health, and the American Medical Association all oppose the gentleman's bill?"

The outcome of this political battle over the philosophical question as to how scientific decisions at NIH should be made could end in a stalemate unless some compromises are achieved in both houses of the Congress.

Even if Waxman's bill prevails in a House vote, there has been little display of support for it in the Senate. The Senate's version of the NIH renewal authorization (S. 773), introduced by Sen. Orrin G. Hatch (R-UT) as chairman of the Committee on Labor and Human Resources, contains only a few of the provisions found in the Waxman bill. Furthermore, Sen. Robert Packwood (R-OR) has placed a "hold" on the Senate bill because of his opposition to the provisions concerning fetal research. As long as Packwood maintains his hold the bill cannot be forwarded from the committee to the Senate floor.

Should both houses move ahead with their respective versions of the NIH renewal authorization, further compromises will have to be achieved in the House-Senate conference committee, an area where the Congress has failed before to agree on NIH legislation. Madigan cited such differences of the past, saying, "A NIH reauthorization bill has not been signed into law since December 1980 when the House and the other body reached a stalemate and threw out both (House and Senate) bills, replacing them with a simple reauthorization."

APS Provides Testimony On Sen. Dole's Animal Bill

The American Physiological Society was one of seven organizations invited by the Senate Committee on Agriculture, Nutrition, and Forestry to give testimony at the public hearing in July on Sen. Robert J. Dole's (R-KS) bill, "Improved Standards For Laboratory Animals Act" (S. 657).

Also invited to comment on the bill to amend provisions of the Animal Welfare Act were the US Department of Agriculture's Animal and Plant Health Inspection Service, the National Institutes of Health, the American Farm Bureau Federation, the Association of American Medical Colleges, the American Institute of Biological Sciences, and two physicians representing a coalition of animal rights organizations.

The Society's statement was presented by APS Immediate Past President, Dr. Walter C. Randall. The complete text of the APS statement appears in this section of *The Physiologist*.

Sen. Dole has said that he plans to make some changes in the bill before it is given to the committee for its markup. No date for a committee markup has been scheduled at this time.

Animal Cruelty Conviction Reversed by Maryland Court

The Maryland Court of Appeals has reversed an animal scientists' conviction for mistreatment of a laboratory monkey on the grounds that the state's animal cruelty laws do not apply to federally funded research.

The unanimous decision by the seven members of the state's highest court ended a two-year ordeal for Dr. Edward Taub, who was first charged in September 1981 with 117 counts of animal cruelty stemming from his work at the Institute for Behavioral Research in Silver Spring, MD. His research with 17 monkeys was sponsored by a grant from NIH.

In October 1981 Taub was convicted on 6 of the 117 counts and was later acquitted on 5 of those convictions in his first appeal in 1982. The Appeals Court's actions was on the one remaining conviction.

The original charges were brought by Montgomery County police after Alex Pacheco, a volunteer worker in Taub's laboratory, presented evidence and photographs to the police alleging cruel treatment of the 17 monkeys. Taub was using deafferented monkeys in his study of treatment for stroke victims. Pacheco is the co-founder of the animal rights group known as People for the Ethical Treatment of Animals (PETA).

The 93-year-old Maryland animal cruelty law covers failure to provide proper food, water, veterinary care, protection from extremes in weather and temperature, shelter, inhumane treatment, and torture. All of Taub's convictions were for failure to provide adequate veterinary medical care.

In its decision the court said that it had analyzed the state's statute and that it is clear that the legislature did not intend to apply the animal cruelty law to research activity under a Federal program. The court also said that the Federal Animal Welfare Act was passed to make sure that research animals would be well cared for and that the Federal laws and the standards of NIH apply to Taub and his work.

Dr. Taub, no longer employed by the Silver Spring institute, has been awarded a Guggenheim fellowship grant to write about his research. He also is appealing to NIH to restore the remainder of his grant which was rescinded after his initial convictions.

Animal Rights Groups Halts Military Wound Lab Program

A Washington-based animal rights group was successful in halting the Uniformed Services University of the Health Sciences (USUHS) wound laboratory program, which is designed to train future military physicians how to treat combat wounds.

The program at the Bethesda, MD, campus called for shooting 80 dogs with high-velocity weapons. The mongrel dogs were from dealers who purchased them from animal pounds where the dogs were scheduled for euthanasia. All of the dogs were to be totally anesthetized before they were shot. Surgeons and medical students would treat the wounds, and then the dogs would be killed.

Alex Pacheco, founder of PETA, brought the wound laboratory program to the attention of The Washington Post, which printed the story on the front page. Within hours of publication of the story, Secretary of the US Department of Defense, Caspar Weinberger, halted the practice at the wound lab and said, "There will be no shooting of dogs as long as I am the Secretary."

PETA now is working to have the Congress cut off funding for the laboratory and said that it also intends to work through the courts to close down the laboratory.

William M. Samuels, CAE

APS Testimony on S.657

"Improved Standards For Laboratory Animals Act"

Presented by Walter C. Randall, before the US Senate Committee on Agriculture, Nutrition, and Forestry, July 20, 1983. (See Public Affairs, *Physiologist* 26: 112-113, 1983.)

"My name is **Walter Randall** and I am the immediate Past President of the American Physiological Society which represents more than 6,000 physiologists actively engaged in the use of laboratory animals for the purposes of biomedical research and teaching.

"Physiology is the study of how living beings function, and it is understandable that physiologists are the largest users of live-animal models for research. More than half of the total number of animals required are used for cardiovascular, neurophysiological, endocrinological, and respiratory research. My work for the last 29 years at Chicago's Stritch School of Medicine, where I served 21 years as Chairman of Physiology, is in the area of cardiovascular research. Also, I am a living beneficiary of this area of research, as last year I underwent quadruple aorta coronary bypass surgery. I am here in the conviction that 80% of the diagnosis and treatment I received was not known to medicine 5 or 15 years ago. The advances in bypass surgery are based entirely on animal-oriented cardiovascular surgery.

"The APS recognizes that the use of laboratory animals for biomedical research and teaching will continue to be required if we are to advance in knowledge and if we are to continue to train tomorrow's physicians and scientists. We need to conserve and use our animal resources.

"The need for animal models will never be eliminated for the purposes of research and teaching. But it should be noted that the numbers of animal species used for these purposes are declining through the voluntary efforts by the scientists and educators. A recent survey by the Society reveals that only 66% of the departments of physiology used dogs, cats, and frogs in 1982 for classical teaching experiments, compared with 90% in 1979. There was no particular law enacted or external influence that caused this 27% reduction in the number of animals used, but rather a voluntary desire by responsible physiologists to conserve a vital resource.

"It is unfortunate that there now is a preconceived notion that restrictive Federal legislation is needed despite verified trends which display marked reductions in the numbers of animals being used in both research and teaching. There is conclusive evidence from Federal agency records that both the guidelines of the National Institutes of Health and the standards of the Animal Welfare Act are accepted and followed by responsible researchers and scientists using living-animal models.

"By and large, statements of malicious laboratory animal abuse by those who oppose animal research and scientific inquiry are anecdotal and are largely without verification. Such statements are designed, in my opinion, to sow seeds of mistrust about science and research in the minds of those unfamiliar with the standards and regulations that govern all research practices involving the use of laboratory animals.

"It is because of such anecdotal testimony that the Society maintains its position that restrictive legislation is not needed. The Congress already has provided the mechanism for the assurances of proper care and treatment of laboratory animals with the enactment and subsequent amendments to the Animal Welfare Act. In addition to this Act the National Institutes of Health has established guidelines for the care of laboratory animals, and the American Physiological Society as well as several other national scientific societies have had standards for animal care and treatment which predate all such Federal initiatives. It is a matter of record that the American Physiological Society's guidelines for laboratory animal care (see box) were the original basis for both the NIH guidelines and the Animal Welfare Act.

"However, if the Congress honestly believes that further legislation is needed for animal research, then the Society supports the concept of S. 657, the 'Improved Standards for Laboratory Animals Act.'

The purpose of S. 657 is to amend the Animal Welfare Act, currently the only legislative authority governing the use of animals. It is for this reason that the Society opposes proposals that would place similar legislative authorities in other departments of the Federal Government, since such action would lead to a divergence of standards and regulations, thus causing much confusion to the researchers and increasing both the institutional and Federal costs in monitoring the nation's biomedical research programs.

"The concept of amending the animal Welfare Act has the merit of encompassing all facets of animal use in research and testing unlike other proposals which are limited to those awarded grants and contracts from the US Department of Health and Human Services.

"Thus, it is the judgment of the American Physiological Society that S. 657 provides a logical approach to ensuring continued standards for the care and treatment of laboratory animals, and it is within this framework that the Society would give its qualified support. But it must be noted that there are areas within the currently proposed bill that are of major concern to all physiologists and other scientists who are involved with animal experimentation.

"One such major concern is the proposal to involve the Secretary of Agriculture in the promulgation of standards for research facilities, including requirements for methodologies in experimental procedures (page 4, lines 13-16 of S. 657). Support from the research community for the enactment of the Animal Welfare Act came from the fact that Congress at that time saw fit to prohibit any interference of research protocols by the Secretary. That prohibition is still paramount in importance to the researcher today as it was when the Animal Welfare Act was enacted. Without this prohibition continuance in the law, biomedical research will become more restrictive in its scope than any law that could be enacted by Congress. To involve the Secretary of Agriculture in setting standards for research methodologies and procedures would stifle individuals now engaged in research. It also would distract the brightest of young minds from careers in biomedical research.

"If legislative measures are needed at this time, the American Physiological Society encourages the concept of making amendments to the Animal Welfare Act. However, the Society encourages this Committee to give serious consideration of the *facts* of the concern cited before acting on passage of this legislation. A study of these issues and questions involving the use of laboratory animals in research and teaching is vital before putting any new restrictions into place that may soon prove to be undesirable and could have a long-term effect on the health and well-being of this nation's citizens. You risk serious curtailment in the spectacular development of new knowledge which contributes to the control of disease.

"Many of the answers to your questions could come from a study proposed by Senators Orrin Hatch and Edward Kennedy. It is the Society's belief that this study would be complimentary to S. 657. The society also believes an objective study would show that restrictive legislation is unnecessary and potentially dangerous.

"The Society is grateful for this opportunity to express the views of its constituency and appreciate the efforts of Senator Robert Dole for permitting the Society to review and comment on this proposal when it was in its formative stages.

"It would be my pleasure to respond to the members of the Committee who may have questions about the Society and its position on S. 657."

APS Statements on NIH Guide Revisions

Presented by David J. Ramsay at a Public Meeting convened by the National Research Council in San Francisco, July 11, 1983. (See Public Affairs, *Physiologist* 26: 113–114, 1983.)

"At these meetings, I am representing the American Physiological Society. I am Dr. **David J. Ramsay**, D. M., D. Phil., Professor of Physiology in the School of Medicine, and Academic Vice Chancellor at the University of California, San Francisco. I have had a long-time interest in the promotion of humane care of animals used in research and have been heavily involved in these issues, both in England and in the United States.

"In my view, a major dilemma in the design of regulations to ensure the humane treatment of laboratory animals used in research is to achieve an appropriate balance between central and local control. In the design of regulations, it is obviously appropriate that guidelines on animal husbandry, physical plant, use of anesthetic and analgesic agents, euthanasia, and standards of postoperative care should be generally applicable and thus controlled centrally. Government and funding agencies should be able to assure themselves that such guidelines are observed. However, it is equally apparent that the conduct of experiments and the design of protocols to ensure humane treatment of animals is better done at the local level. With the best of intentions, there is no way that a central agency can have adequate knowledge and control over an animal experiment which is taking place some 2,000 miles away! Furthermore, local conditions may vary widely from institution to institution, such that a protocol may be appropriate in one institution and quite inappropriate in another.

"The fact that control at the local level is recognized by both government and the National Institutes of Health is shown by present practice. For example, under the Animal Welfare Acts, the local committee has jurisdiction over anesthesia, postoperative care, and the general conduct of experiments. Again, when either administrative staff or peer review committees are concerned about an animal-related issue, the Animal Care Committee of the institution is requested to check into the situation and make recommendations to correct. No grant can be awarded unless NIH is satisfied with animal welfare issues.

"Over the past few years, a number of institutions, including my own, have instituted review of research protocols for animal welfare issues. Thus the scope of activity of the institutional committee increased to include a detailed screening of protocols, particularly those involving survival surgery and experiments on conscious animals.

"The question of membership of the committee is an important and sensitive one. Those in the animal welfare movement often dismiss the validity of a committee containing a majority of animal researchers. They question whether a group of animal users will, or can, regulate the conduct of research by their colleagues. In fact, in my experience, and those of others I have consulted, nothing could be further from the truth. The peer review system works just as critically in the review of protocols for humane treatment of animals as it does in the review of grants for scientific merit in NIH. I think this is because the animal researchers have detailed knowledge, and often experience, in the research being reviewed. Often, better ways to carry out the experiments are suggested, and important modifications to improve the humane care of the animals, and thus the quality of the science, are made.

"Although the major input to the institutional review committee should come from animal researchers, it is important that the makeup of the animal care committee is broadly based. In my own institution, we have found the contributions of students, staff, and those not directly involved in animal experimentation to provide important insights and points of view.

"The animal care committee is taking on an important new role. It is viewed by many members of the public as a way in which they can be assured that humane treatment of laboratory animals is taking place within the walls of an institution. To increase their confidence in the process and to bring additional and important points of view to the animal care committee, it is recommended that membership of the committee should include community representation not associated with the research facility. Additional important inputs could also come from nonanimal users, for example, an ethicist from within the institution.

"Thus the system of local control, further refined by the expansion of membership and duties of the institutional committee, where researchers play an important role in regulating research, should be strengthened. If the local committee can heighten the sensitivities of all those involved in research to animal welfare issues, this can only improve the humane care of laboratory animals."

Presented by Walter C. Randall at a Public Meeting convened by the National Research Council in Rosemont, Illinois, July 17, 1983. (See Public Affairs, *Physiologist* 26: 113–114, 1983.)

"I **[Walter C. Randall]** am a cardiovascular physiologist representing the American Physiological Society which, as a group of research and education professionals, fully supports the concept and the efforts of the Institute of Laboratory Animal Resources (ILAR). We in medical schools are, of course, primarily concerned with how the human body functions normally as a necessary prelude to recognition of abnormal or pathological performance. For each and every medical student, this is a uniquely new and necessary experience. He cannot truly learn physiology from textbooks. He must personally *experience* direct contact with normally behaving living tissues before he can fully appreciate dysfunction. For more than 40 years I have closely observed this acquisition of understanding as a medical student personally senses the actual beating of the heart in situ, in concert with the waxing and waning in lung volume. The student has already taken many biology courses; often he holds a major in Biology; he has already read a massive textbook on physiology; and he has dissected the heart and the lungs in the anatomy laboratory. But he does not really *understand* the functional mechanisms of cardiac performance until he *sees* and *feels* the heart beating within a living context.

"To illustrate, consider ventricular fibrillation. The student has read in his textbook that this represents a catastrophic desynchronization of excitation and con-

traction within multiple isolated portions of the ventricular musculature. He has already read that this is the fundamental cause of death in most cardiac dysrhythmias. He knows that is is an important phenomenon and that he will encounter it early and repeatedly in his practice of medicine. He knows that if he cannot control it within a few seconds of its onset, his patient will die. Thus, before he comes to the laboratory he has studied fibrillation and he is acquainted with its ominous connotation. But he does not *understand* it; he *cannot* until he has personally *experienced* what happens to the heart during fibrillation; after he has held the heart in his hands at its very onset.

"In the laboratory, the student realizes that the anesthetized dog's life will be sacrificed exclusively and explicitly for his opportunity to experience and to learn. The student observes, he palpates, he listens, and he makes quantitative measurements of functional details which he can study later. He holds the heart in his hand. Then he comprehends fully, generally for the first time, the differences between systole and diastole, the regularity in rhythm of contraction, the importance of atrial and ventricular synchrony, the sequence of excitation and contraction. All of these have been adequately described in his textbook, he cannot *really* appreciate them until he personally experiences the *qualities* of performance that can only be transmitted to him by this individual, personal, "hands-on" communication with the living system. He must not acquire this initial learning in human subjects. Yet he must bring to the bedside absolute confidence in his understanding of normal function, not only of the heart, but every system within the body. This learning is the responsibility of the physiology laboratory, and we *must* have access to living animals to accomplish it. Not only must they remain available to us, but they must also remain within our budgetary ability to pay for them.

"Another absolutely essential use of living whole animals is in research. If the body of physiological knowledge were truly complete, perhaps there would be no legitimate reason to use living animals in research. But the body of knowledge is *not* complete. Far from it. And animals must be substituted for human beings in the acquisition of new knowledge. Virtually every major advance in medicine has been based on new knowledge gained through research on living animals. I recently sustained an acute need for medical help. After angiography, I was informed that my coronary arteries were almost totally occluded and that I required bypass surgery, which I achieved, and I stand before you delighted with the additional years of life that have been given me. At least 80% of the diagnosis and treatment I received was simply not known to medicine only 5–10 years ago. **All because of research involving living animals.** I speak for several hundred thousand people each year who receive bypass operations and at least an equal number who have coronary disease but come under medical treatment. What applies to us as cardiovascular patients, applies equally to all of you who have or will have, respiratory, endocrine, renal-urinary tract, gastrointestinal, neural diseases, etc. The ability of today's experienced physician to treat our ailments is totally dependent on research — a vast majority of it based on animal experimentation.

"Let us go back to the illustration of ventricular fibrillation which I used earlier. I was taught (in one of the premier laboratories of the world) that ventricular fibrillation is always fatal. And at the time it was. Hearts of large mammals and humans do not spontaneously recover from ventricular fibrillation, and once it starts, blood pressure promptly falls to zero. So 30–40 years ago, the mechanism of fibrillation, and certainly the way to counteract it, were not understood. Since it was invariably fatal, it could not be induced in human subject in order to study it. But employing anesthetized dogs, my teacher gradually learned its cause, how to induce it, and knowing this, other scientists learned how to stop it. These animal experiments furnished the bases for today's routine defibrillation in every modern hospital and for the induction of therapeutic quiescence during cardiac surgery. The procedure is frequently lifesaving in CPR (cardiopulmonary resuscitation), and automatic defibrillators are now being implanted in patients with instantaneous recognition and treatment of the dysrhythmia.

"Thus the essential and intimate relationship between use of animal models in research and progress in treating human disease can easily be documented. The latter is simply not possible without the former. Much remains to be done. You at the National Research Council must add your influence and prestige to the efforts of APS and the biomedical community as a whole in preserving accessibility to animals for these purposes.

"The APS is fully supportive of ILAR's insistence on clean and comfortable quarters for animals in research and teaching institutions. We endorse requirements for properly trained and equipped personnel for the humane care of animals. The American Physiological Society's Animal Care and Experimentation Committee recently reviewed the current NIH Guidelines and found them to be carefully formulated and effective. It will soon forward its recommendations for your consideration. We consider ourselves to be in a crucially important partnership with you and NIH in achieving the best possible health and compassionate care of experimental animals. The aggressive pursuit of these objectives is of critical concern to ILAR, to APS, to all of the biomedical sciences, and most of all to the public at large, which is perhaps unknowingly but totally dependent on them for continuing progress in achieving better diagnosis and treatment of disease. We covet your total commitment to the rational handling of arguments which would deny their ready availability to properly qualified scientists.

Career Opportunities in Physiology

Basic Science Department in a Private Medical School

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The major differences between a private and state medical school for a young physiologist are historically in the areas of internal funding for research, teaching loads, graduate training, and availability of major centralized support facilities such as machine or electronic shops. In this presentation, I would like to focus on the environment and responsibilities of a new faculty member at a private medical school. Although some of the distinctions between private and public institutions have been eroded by the recent financial problems at the federal and state levels, differences between the two types of schools will probably remain. As recently described (1), the responsibilities of a faculty member in a basic science department are research, teaching, and service. These responsibilities are common to both private and public schools. However, the emphasis placed upon each responsibility, especially for a new faculty member, may differ between the two types of schools. While teaching and service are important, research is probably the most important task for a new faculty member in a private school. A large amount of time and effort is required to establish an independent research program with continuous funding from outside the school. Both institutional and departmental funds for research and salary support are limited in a private school. Thus research funding must be obtained from competitive sources outside the institution. While salaries for an Assistant Professor of Physiology may be similar for the two types of institutions, in a private school, obtaining salary support from outside sources will help both the department and institution conserve the limited funds for other programs.

In developing a research program in a private medical school, one will be required to do "bench" research and obtain preliminary data for grant applications. Most, if not all, the research will be initially performed by yourself, since there are limited funds for technical support. Additional time is required for writing manuscripts and grant applications. Thus a large amount of time is required to start your research program, and your chairman can help in keeping your teaching and committee assignments small. This emphasis on research will change as your research program becomes more developed. An advantage to working in many private medical schools is the absence of a large number of allied health programs that require an extensive teaching load. The departmental teaching load is thus often smaller at a private school than a large public school, and the chairman can be more flexible with the teaching assignments. With a small teaching load, you will be better able to concentrate on developing your research program. However, you must also be prepared to assume teaching responsibilities outside your area of research interest. Often someone else already teaches in that area, and you will be needed to teach some other area of physiology.

As outlined in Table 1, there are a few important considerations in starting a research program at a private school. Since initial funds will be very limited, the project should be small and well defined. Most of the work will be done by yourself, so that a large project requiring additional technical support would not be appropriate at this point in your career. One of the primary goals during your first year as a faculty member at a private school is to use the small, initial funds provided by the institution to generate data for grant applications and your first publications as a principal investigator. In addition, the project should not require sophisticated and unusual pieces of equipment not already available in the department, since funds to purchase them will probably not be available and the facilities to design and construct them will be limited. As your research funding becomes greater and more stable, the project can become more complex and larger. This may mean that you will have to initially use major pieces of equipment, such as gamma counters, spectrophotometers, or balances, located in other laboratories. While this may be inconvenient at times, it will permit you to conserve the limited funds to purchase animals and supplies.

The third consideration is that there are other, more senior, members of the department interested in your research area and that they are willing to help you establish your program. Many times your ideas can become more focused and clear by presenting them to other people. In addition, the more senior investigators can help in the preparation of grants because they have had experience with the review process and know how to prepare a strong application. The ability to collaborate with more senior investigators should be an important consideration in choosing a position at a private school. There is less diversity of research interests in a small private school than in a large state school. Often there are a few concentrated areas of interest within the department. Thus it is important to make sure that there are other faculty members interested in your research area at the school and that they are willing to take the time to help you.

The fourth consideration in starting your own research program is that the initial project you select be directly related to your postdoctoral work. Your previous experience with the field will help give you the needed confidence in writing grant applications and manuscripts. Your familiarity with the literature will

Table 1
Considerations for Starting a Research Program at a Small Private Medical School

1. Project is small and well defined
2. Essential equipment for the project is already available for your use
3. Collaboration with other faculty interested in your research area is available
4. Project is an extension of your postdoctoral work

help in interpreting experimental results and providing direction for your program. This consideration emphasizes the importance of choosing a good postdoctoral fellowship. Your long-term goal should be to become an internationally recognized scholar and expert in your field. It is during your postdoctoral years that you start the long process toward this goal and obtain the needed experience to start your own research program.

One of the most important initial tasks as a new faculty member in a private medical school is obtaining outside research funds, since generally the department will not have adequate funds to support your research on a long-term basis. Table 2 lists a sequence of sources to obtain research funding. There are usually institutional grants, such as Biomedical Research Support Grants, which can be used for initial support. This source of funding provides a small amount of "seed" money that can be used to start a program and requires the preparation of a small simple application. Initially, additional funding can be obtained through collaboration with other investigators who already have large, well-funded, research programs. However, one must keep in mind that the goal is to develop your own research program with independent support. Thus collaboration can be very helpful in starting your research but should not be your main avenue for obtaining funds. The next step is submission of a small grant to a local Heart Association, Kidney Association, or American Lung Association. These agencies are very willing to support young investigators, and the applications, although more complex than institutional ones, are still relatively simple to prepare. While the amount of support may be small and only for a few years, these grants will help in obtaining more extensive data for larger grant applications to other agencies. The next step is submission of a larger application to the National Institutes of Health. These applications are more complex and require considerable amount of preliminary data. When writing one of these applications, you should keep in mind that you are competing with senior investigators with considerably greater experience. Thus you should take enough time to prepare a well-documented proposal. Since the review process for outside funding requires 9–10 months, it is important to submit grant applications as soon as possible. Generally, you should expect to submit an application to one of the smaller agencies within the first few months after starting a faculty position. This means that during your last postdoctoral year, you should start planning the experiments.

As your research funds become larger, your laboratory will increase in the number of people and the complexity of the projects. Both graduate students and postdoctoral fellows supported by training grants within the department may join your research projects so that you, as a member of the graduate faculty, provide a greater educational resource for the department and the institution. As your research program develops, it will gain its own momentum and you will have more time for teaching and service. Medical students will come to you for not only your knowledge of physiology but also for your knowledge of the biomedical community.

Table 2
Sequential List of Sources for Research Funding

1. Institutional
2. Collaboration with other faculty
3. Local Heart Association, etc
4. National Institutes of Health

Thus the main initial emphasis at a private medical school is to develop an independent research program with outside funding. This emphasis is due to the limited resources within the institution and the need to obtain funds from competitive sources outside the institution. Because of the smaller number of teaching programs at a private school, there is enough time to do the research and develop an established program. With the help of colleagues and departmental chairman, you can build your own research program based on your own ideas. As your research program develops, you will have the time necessary to increase your participation in teaching and become a well-rounded scholar. However, one of the main prerequisites for a faculty position in a private medical school is a solid training in research. During your years as a graduate student, you should choose an area of physiology which excites you. While doing your thesis research, you should become familiar with the literature and techniques related to that field and produce your first publications in the field. During your years as a postdoctoral fellow, you will gain additional experience and become more familiar with other investigators within your research field. With a solid background you should be able to then develop your own program. As your research program gains momentum, you will have time to increase your participation in teaching and service. Moreover, you will find that these three responsibilities, teaching, research, and service, are interrelated. Your participation in any one of the tasks will promote your confidence in the others.

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Basic Science Department in a State-Funded Medical School

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I was somewhat reluctant to accept Dr. Saba's invitation to advise Ph.D. students and fellows on the important aspects of career development with reference to attaining employment in a basic science department in a state medical school. My reluctance stemmed from the fact that this would involve describing a "formula" for success for what is generally perceived as the most common and desirable position for employment of physiologists. I was also concerned about how representative my working environment is of state medical schools in general. In spite of these concerns I accepted the invitation because it gives me the opportunity to describe what I consider to be the major priorities for

the development of a successful career as a physiologist. I hope that by doing so Ph.D. students and fellows will gain insight into the various criteria for selecting the most appropriate setting for developing their careers as physiologists.

Before describing my current position and responsibilities, I have been asked to provide you with a brief description of my academic background and employment history. In May of 1977 I was awarded the Ph.D. degree in Physiology at the University of Mississippi Medical Center. My research advisor was Dr. Aubrey E. Taylor. Within a few months after I received the Ph.D. degree, Dr. Taylor accepted the position of Chairman at the University of South Alabama. I was asked to take a junior faculty position in his department and became an Assistant Professor 4 months after receiving the Ph.D. degree. So, as a result of this move, I did not receive any formal postdoctoral training. Three years after taking a position at South Alabama I was promoted to an Associate Professorship, which is my current rank. My current funding status involves support from the NIH in the form of a Research Career Development Award and two research grants.

Now I would like to focus your attention on the factors which are generally perceived as significant ingredients for developing a successful career as a basic medical scientist. Clearly, the most important ingredient is achievement in research. The generally accepted measure of research achievement used by your employers and colleagues is the quality and quantity of research publications. If indeed these are the criteria used to measure success, then what are the factors that determine the level of success one achieves as a basic medical scientist.

Table 1 presents what I believe are the six major priorities for developing a successful career as a physiologist in a basic science department. These priorities are generally consistent with those put forward by the Career Opportunities Committee in a recent report (1). The omission of factors such as teaching from this list is not intended to deemphasize their importance within the basic science department but reflects the relevance of such factors in achieving success on an extramural basis.

Obviously, an important prerequisite for a successful ful career as a scientist is adequate training. This applies to both graduate and postdoctoral training. The quality of graduate training one receives is frequently the limiting factor that determines the number and quality of opportunities available for postgraduate training and support. The selection of a research advisor is perhaps the most critical decision in this regard. The decision regarding the selection of an advisor should be based on the same factors listed in Table 1, i.e., Is the potential advisor well trained? Is his research specialty conducive to developing your career and funding? Is he productive and funded by a national agency? Has he trained other Ph.D. students and postdoctoral fellows?

Although I did not obtain formal postdoctoral training, I do consider this important and encourage my graduate students to obtain a 2- to 3-year fellowship at another institution. Selection of a laboratory for a fellowship should, in my opinion, be based on the opportunities available to expand one's research skills. All too often selections are made based primarily on personal rather than career considerations, i.e., factors

Table 1
Priorities for Development of a Successful Career as a Physiologist

1. Adequate training (pre- and postdoctoral)
2. Research specialty
3. Selection of department/institution
4. Productivity
5. Research grant support
6. Training Ph.D. students and fellows

such as climate, proximity to parents or in-laws, cultural richness, and/or salary take precedence over the training potential of the laboratory. The short-term conveniences afforded by such decisions cannot outweigh the impact that excellent postdoctoral training has in developing a successful career as a scientist.

Another important priority for developing a successful career is the selection of a research specialty. Interest in specific areas of research varies with time. Ideally, one should select research topics in new and rapidly expanding areas rather than in areas that have become relatively stagnant or saturated. It is often difficult for the Ph.D. student or young scientist to judge which areas of research are conducive to developing a successful career; however, the level of funding by national agencies as well as the number of publications in an area during the past 2-3 years should serve as useful indicators.

I consider the selection of an institution and department to be the rate-limiting step regarding one's ability to develop a successful career as a basic medical scientist. In my setting, as in most institutions, there is considerable support for research at the institutional and departmental levels. The commitment of the administration toward research is an important consideration in selecting an institution. An administration which supports and encourages research is particularly advantageous for developing a successful career. I expect that this type of commitment exists in most medical schools, and it is not entirely altruistic because of the dependence of many institutions on indirect costs generated by funding agencies such as the NIH.

One type of support offered by my institution is intramural funding for research. For junior faculty members this support is in the form of seed money for setting up a laboratory and small grants to fund preliminary research projects. This type of support is available in other state-funded institutions; however, because of growing financial problems, this type of support may become quite rare in the future.

Perhaps the most important form of support necessary for career development is that afforded by your colleagues. This type of support has been particularly significant in the development of my career. My department is entirely comprised of cardiovascular physiologists, most of whom are primarily interested in the microcirculation (my area of research interest). This, coupled with a department chairman who is very supportive, makes for an excellent environment for collaborative research. The importance of colleague support cannot be overemphasized because all too often I hear from colleagues in other settings who feel that their research efforts are limited by having no one with similar interests to talk to on a day-to-day basis.

Another important consideration in selecting an institution and department is the time commitment to teaching and administrative duties. Clearly, the most important function of a basic scientist in a state-funded medical school is teaching medical students. However, the time and effort a physiologist must devote to this endeavor varies considerably from one institution to another. If you intend to develop a career as a researcher then the time spent on nonresearch endeavors becomes critical, particularly at the early stages of development. The same consideration should be given to administrative responsibilities such as committees. A policy at many institutions is that junior faculty members are not assigned heavy teaching loads or too many committees in order to minimize interference with the development of their research programs.

The final issue I wish to address regarding the selection of an institution and department is opportunities for advancement. This is something that one should consider prior to accepting a position. If you intend to develop a career as a researcher, then you should determine the importance placed by the administration on research productivity in gaining promotions. In addition, if one is committed to the tenure track system, then you should inquire about the institutional policy regarding this, particularly since the merits of the tenure track system are being reevaluated in many institutions. Finally, one should determine whether the institution and department have well-defined criteria for promotion and tenure. After evaluating these criteria then one must decide whether they are appropriate for the development of his or her career.

A major priority for developing a successful career as a physiologist in a state medical school is productivity. As discussed above the measure of productivity used by your employers and colleagues is the quality and quantity of research publications. Since the supply of basic scientists now appears to exceed the demand, competition for "good" positions have increased. As a result, research productivity has become an even more important factor in gaining employment in state medical schools. Without a reasonable degree of productivity one cannot expect to attain recognition at his/her institution or at the national level. Furthermore, lack of research productivity is perhaps the most frequent factor limiting one's ability to gain promotion and tenure.

An essential requirement for continued productivity in a state-funded medical school is extramural grant support. With the general decline in institutional and extramural funds for research support, the quest for funds at the national level is becoming more competitive. Therefore, now more than ever, it is essential that the young scientist master the art of grantsmanship and be willing to accept failure and try again on nonfunded grant proposals. As with productivity, the ability to secure research funds is becoming the most important ingredient for gaining employment in state medical schools.

Another important factor that determines the level of success one achieves as a basic medical scientist is the opportunity to train graduate students and postdoctorals. While this should not be of immediate concern to Ph.D. students and postdoctoral fellows, it is a factor that one should consider when selecting an institution and department for employment. Opportunities to train graduate students are not always available. I consider this factor to be particularly important for developing a career because it provides for a source of continuous intellectual stimulation by bright and enthusiastic young individuals.

To conclude I emphasize that there are no easy and clearly defined formulas for developing a successful career as a physiologist. However, as with any other profession, lots of hard work will go a long way in meeting this end.

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Basic Science Department in a Government-Funded Medical School

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The speakers at this symposium have been asked to discuss their background, training, and experience with regard to seeking a career in physiology and to describe the responsibilities they have in their unique environment. My topic relates to preparation for the responsibilities of a young assistant professor in a basic science department in a government-funded medical school. Not only are there unique aspects of a basic science department in a government-funded medical school but the school itself is also unique. The Uniformed Services University of the Health Sciences is the only government-funded medical school in the United States. Using military jargon, "The mission of the Uniformed Services University is to train physicians for the Army, Navy, and Air Force in order to maintain medical readiness in case of war and to provide peacetime health maintenance and care to active duty personnel." This mission in itself provides unique opportunities for the physiologist, in that a great deal of the emphasis in military medicine is placed on applied physiology. For example, studies are ongoing in the effects of hypoxia on performance in altitude chambers, work performance at high temperature and humidity, diving physiology, physiology of wound ballistics, and physiology under weightless conditions of space flight. In addition to these opportunities, we also enjoy the challenge of basic research such as control of coronary and skeletal muscle blood flow, basic mechanisms of hypertension, neuroendocrine interactions, and myocardial metabolism to name a few. The equipment and methods used in applied physiology research can also be used as powerful tools to examine basic science questions. The interactions between the two approaches and the involvement of the clinical staff make this a very exciting area. Preparation for a career here at the Uniformed Services University does not differ significantly from any other basic science department. However, we feel that an emphasis on the total physiologist is important here, so that interactions with applied

Table 1
Important Considerations when Developing a Graduate Program

1. Broad educational background
2. Comprehensive understanding of selected area of interest
3. Careful selection of advisor
4. Interaction and involvement with other graduate students and projects
5. Development of writing skills

physiology is enhanced. Therefore, beginning with graduate study and continuing through postdoctoral training, I will give my impression of the desired preparation to a career in physiology.

Presented in Table 1 are the considerations that I feel are important when organizing your graduate education. The foundation of your scientific career is laid in graduate school. A broad educational background is essential in these days of rapidly expanding scientific knowledge. You may be asked to teach or do collaborative research outside your particular area of interest; therefore, you will need not only to be well versed in your research field but also to have a broad knowledge of physiology. Your graduate years are excellent times to gain knowledge in wide areas. There will be plenty of time to focus on a finite problem as you proceed in postdoctoral training. A comprehensive understanding of your area of interest is also important. You may be the only person in your department in a particular area, and you will therefore be called upon as the "expert" for specific problems. For example, you may be the only endocrinologist in a department; not only would all the teaching in endocrinology come your way but also any consulting questions relative to endocrinology would be addressed to you. A careful selection of your major advisor is very important. As in most educational experiences, part of the process involves mimicry, or "academic imprinting." One tends to learn by watching and imitating, and a good advisor can subtly develop your abilities in research, teaching, and dealing with the academic environment simply by being a good example. The ability to formulate a hypothesis, design the appropriate experiment, perform data analyses, and draw plausible conclusions are all directed and nutured by your major advisor. During your graduate career there is the opportunity to learn the skills of collaboration and interaction with your peers. Interaction and involvement with other graduate students and other research projects help to develop communication skills that will be of importance in later faculty interactions. Another important communication skill which should be nurtured at this stage of your training is writing. Approximately 50% of your time will be spent writing: grants, manuscripts, letters, and memos. You have the time now to develop these skills. As responsibilities increase, the extra time for skill development is lost. Any extra time you can spend in group workshops, additional courses, or one-on-one writing and evaluation will be paid back at later time. You started your graduate training as a rough diamond; the graduate experience has cut and shaped you; but to be a quality diamond you need that final polishing. Postdoctoral training is designed to add that last finishing touch.

Table 2
Considerations when Selecting a Postdoctoral Training Experience

1. Learn new techniques
2. Work with a prominent person
3. Select an environment with good resources

The considerations that I have found important in a postdoctoral fellowship are noted in Table 2. Most people see a postdoctoral experience as 2–4 years of transition from a graduate student to a faculty position. I view this time not only as a training ground for faculty status but also a time to allow free thought, to learn new techniques, to experience new methods of problem solving, and to explore questions which may not be related to your focused hypothesis. These experiences may open new doors or trigger new ideas that will pay off at a later date. It is, of course, extremely important to be productive at this stage of development. Future employers will examine your curriculum vitae for significant publications during your postdoctoral years. It is often good to join a successful project in progress to ensure publications while also developing projects on your own. In this manner you can learn experimental design and development of ideas while ensuring yourself good publications in prominent journals. I think that it is very important to train where new techniques are available and where the state of the art research is ongoing. By selecting this environment, you will add new techniques to your list of previously learned techniques and will therefore increase your research flexibility. When you apply for your first job you will have a large bag of techniques with which to approach the problem you have decided to study. Some postdoctoral fellows choose an additional technique to measure a specific parameter which they are currently measuring to give them flexibility, while others choose an in vivo technique to compliment an in vitro technique or visa versa. Whatever you choose, by adding techniques, you increase your versatility. This added versatility will maximize your equipment and facilities and make you a more marketable individual. Your postdoctoral selection may or may not include work with a prominent physiologist. Someone who is well known in his/her field can give you a foot up when finding a faculty position. The prominent well-established investigators have lines of communication with those department chairmen who may have positions in your area of interest. To be productive and to have the opportunity to explore new areas, good financial, physical, and personnel resources are very important. Without adequate funding your research will be limited by lack of supplies and equipment. The physical layout must be conducive to your proposed research ideas. For example, if your model calls for chronic experimentation and those facilities are not available, this would not be an appropriate environment for your work. An additional consideration is the personnel available for consultation and collaboration. This is a rich and important source for increasing your curriculum vitae and repertoire of new techniques. The postdoctoral experience is one of the best times of your career; not encumbered by committees, teaching, grant writing, and other faculty duties, you can take the cut and shaped diamond and polish each facet in preparation for your first faculty position.

How will these graduate and postdoctoral experiences relate to your new faculty job description? Five important areas that you will need to consider are listed in Table 3. At the Uniformed Services University our primary job is teaching medical physiology to the first-year medical and graduate students. Other teaching responsibilities are advanced graduate courses, applied physiology, and special courses to medical residents. A broad base of knowledge and a comprehensive understanding of my particular area make it much easier to deal with these obligations. University and departmental committee obligations are another important part of our job. Committees such as promotion, biohazards, graduate, human use, radiation safety, and laboratory animal review are necessary for running this university. Once again a diverse background and multiple graduate experiences make completion of committee responsibilities more efficient. In the area of physiology, collaboration and consultation play a large role in university responsibilities. The Departments of Surgery, Medicine, and Anesthesiology promote active interactions with the Physiology Department. At the Uniformed Services University we participate in many areas of applied physiology with the close interactions with military medicine. An additional large block of your time will be spent with graduate students and postdoctoral fellows at most universities; our university is no exception. The combination of advising students and participating on their committees means that a great deal of time is spent working with graduate students. Those items discussed in Table 1 now become even more important because you have to draw from all of them to be a good advisor. The remainder of our time is dedicated to research. The equipment and facilities are conducive to active basic research, and the environment, as previously mentioned, is supportive of applied physiological research and collaborative clinical studies.

In my opinion the key to successfully competing for a job in physiology, regardless of the department or university, is to be a highly motived enthusiastc individual with comprehensive training and background. At this time physiology is a buyer's market. We are, economically speaking, "products." To be marketable, we must be the best product available. The laws of supply and demand pertain to you as physiologists just as they do any marketable product. There are many physiologists out there looking for jobs and the number of jobs are few. How do you get one? You must be the best product a department can find. You must be competitive in today's job market. Look around at your peers. What must you do to be competitive? Your preparation begins now in your graduate training. Give it the best you've got. There are jobs there for those who are willing to give it their best.

Table 3
A Typical Job Description
for a New Faculty Member

1. Teaching
2. Committee obligations
3. Consultant responsibilities
4. Advising graduate students
5. Research

Initiation of an Academic Career in a Clinical Department in a Private Medical School as a Ph.D. Physiologist

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There is no longer any doubt that there are many outstanding career opportunities for physiologists in departments of clinical medicine (1, 2, 4). Important demographic data to support this conclusion have been recently reported in *The Physiologist* (2). But how does an individual trained as a basic scientist in a physiology department find a position in a clinical department? How does one evaluate a potential job opportunity in a clinical department? What are the responsibilities of a basic scientist once that position has been accepted? Are there unique advantages or disadvantages for a basic scientist in a clinical environment? And finally, how does one ensure career development as a physiologist in this setting? Drawing on my own experiences, I'll attempt to address each of these issues in turn.

Of course, the most important prerequisite for landing any faculty-level position, whether it be in a basic science or clinical department, industry or government, is outstanding training as a physiologist (3). There are two phases in the continuum of the training process. First, graduate student training should provide a foundation for the development of both analytical skills and powers of scientific reasoning. The postdoctoral fellowship should extend these basic skills and in addition offer an environment that is conducive to tangible, demonstrable productivity (e.g., published manuscripts, small grants from local funding agencies, presentations at national meetings). Choosing the right postdoctoral fellowship is exceedingly important, because the productivity of that period becomes a passport to future job opportunities. In addition, despite the fact that most positions are formally advertised (e.g., *Science, Clinical Research, Federation Proceedings*), it is important to choose a mentor who is part of the grapevine, because a great majority of faculty positions are filled by word-of-mouth. To optimize one's chances of finding an acceptable position, it is important to become part of the infrastructure.

How does one evaluate a potential job opportunity in a clinical department? There are definitely positions in some clinical departments that can only result in frustration and unhappiness for a basic scientist. However, there are several features which can serve as strong positive indicators to obviate these problems. Perhaps most important is the existence of a research division within the clinical department (4). Ideally, the research division should be a distinct bureaucratic entity with its own budget and directed by an individual who can be clearly identified as a scientist. If run judiciously, the research division can function as a small physiology department within the larger clinical department. The research division can help overcome many of the poten-

tial problems that face a scientist in a clinical department. For example, it guarantees a critical mass of scientists to interact with on a daily basis. It is very difficult for most of us to grow as scientists without interacting with other scientists. Alternatively, this need may be fulfilled by a joint appointment in a basic science department, although I am somewhat skeptical about the practicality of this type of arrangement because typically there are logistical problems. Another positive indicator is a close, stable relationship between the director of the research division and the clinical chairman. During the job interview one should try to get the chairman's point of view concerning the relative standing of the research division director within the department, because the director should serve as a critical interface between the realistic needs of the scientists in his division, and the resources provided by the department. If any animosity or lack of respect between the chairman and the director is detectable during the job interview, this is a serious negative indicator.

Of course, it is absolutely essential that, as a scientist, you are viewed as a unique resource to the department and not simply as a support person with technical skills. One way to evaluate this is to ascertain how rigidly the chairman wants you to allocate your time. Assuming that there is a reasonable overlap between your research interests and the goals of the department, my view is that the department will benefit the most if you are allowed to pursue your own research interests without any time constraints. It is also important that there is a clear-cut understanding about the time frame for generating extramural funds. If there is too much of a rush, or no rush at all, then these are negative features. The department must be willing to provide sufficient funds for the scientist to become productive over the shortest period of time. However, the scientist must then be free to apply for extramural funds to support the laboratory and establish credibility as an independent investigator. The scientist must also determine the source of salary support. If the position is not funded with "hard money," then it should arouse suspicions about the sincerity of the department to truly support a basic scientist. And finally, the department should make full academic advancement available to the basic scientist, just as it would to clinical members of the department. This certainly is not an all-inclusive list, but if the clinical department offers most of the features described above, then a scientist can at least begin to consider this as a viable job opportunity.

What are the responsibilities of a basic scientist in a clinical department once a position has been accepted? Far and away the most important responsibility is to develop a productive, independent research laboratory. Once the laboratory is fully operational, then the scientist should start to train clinicians to do laboratory research. This does not mean that the scientist physically conducts experiments suggested by the clinician. On the contrary, the scientist has a responsibility to develop projects that are enticing and relevant enough to stimulate the clinician to be an active participant in the laboratory study. Ideally, a symbiotic relationship between the scientist and clinician should develop, because an additional responsibility of the scientist is to collaborate with the clinician on clinical research projects. I view this as an opportunity to expand my research interests. The scientist also shares in the responsibility of generating an academic atmosphere within the clinical department. The scientist should attend and actively contribute to both basic science and clinical conferences. In particular, the scientist should apply organizational and quantitative skills to the large body of data collected by clinicians, who often use this information solely to make qualitative decisions about patient therapy. The scientist also has the responsibility of representing the department at national meetings of importance to the department. This means that some laboratory time must be devoted to studies that are directly applicable to the department's clinical academic interests.

Are there any unique advantages or disadvantages for a basic scientist in a clinical department? Certainly, one important advantage is the availability of funds through the clinical income of the department. This stable source of support is especially advantageous in this era of shrinking federal support for basic research. However, as I mentioned previously, the scientist should continue to pursue extramural sources of support. Another distinct advantage is that daily interactions with clinicians greatly increase one's awareness of pathophysiology. Clinicians often make exceedingly interesting observations when treating patients. These observations stimulate many basic questions about pathophysiological mechanisms. As mentioned previously, clinical research opportunities are generally more available for a scientist in a clinical department. Finally, it is my impression that a clinical department provides an environment for more interdisciplinary research, as contrasted to the very focused research interests that are common to many basic scientists.

There can be disadvantages for the basic scientist in a clinical department. Although the salary for a scientist in a clinical department can often exceed that of a basic science department, the scientist will generally receive much less than his clinical counterpart. The fact that the strong emphasis is on research rather than formal teaching may be a drawback for some (or an advantage for others). However, there is a great deal of personal instruction of clinical faculty and residents in the laboratory to satisfy some of these needs. I personally feel that the many advantages far outweigh the disadvantages.

Finally, how does one ensure career development as a physiologist? The physiologist in a clinical or basic science department must be able to generate extramural funds, present research results at national meetings, and publish in critically refereed journals. But in addition, the real challenge for a physiologist in a clinical department is to serve as a unique, indispensable resource to the department.

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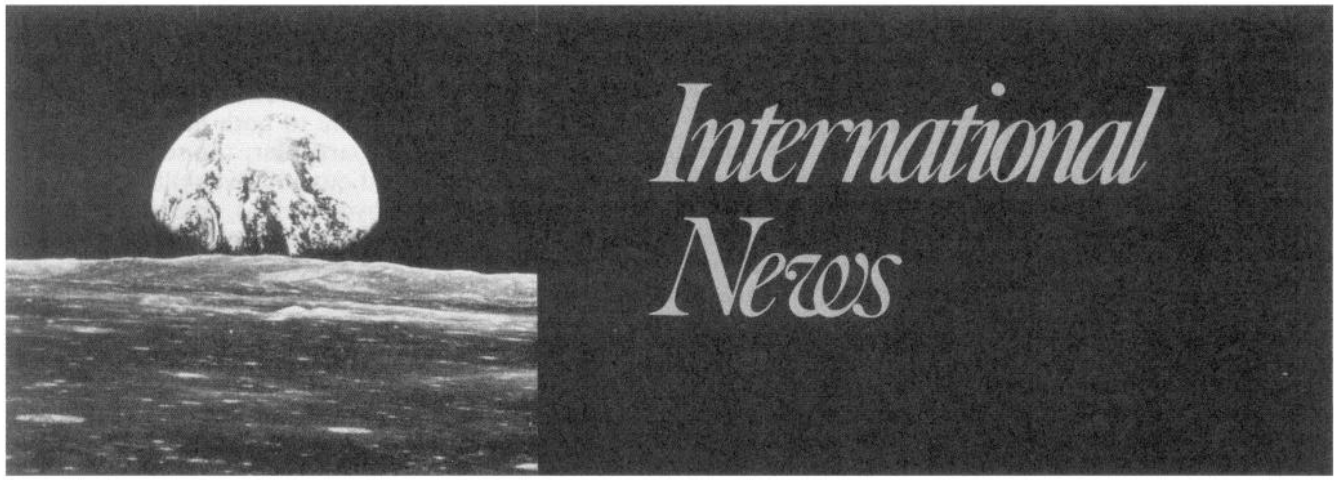
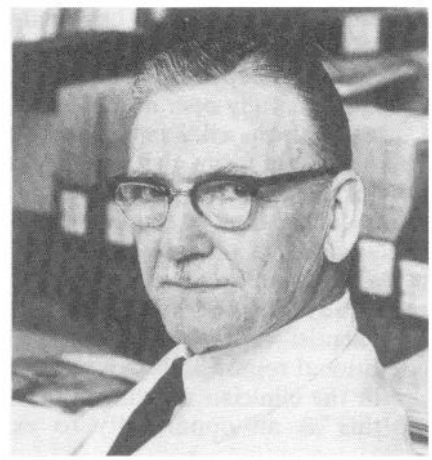


Ulf von Euler

Professor Emeritus Ulf von Euler-Chelpin, Nobel Laureate in Physiology or Medicine 1970, died in Stockholm on March 10, 1983, at the age of 78, from complications following open heart surgery. During his whole life he had been devoted to promotion of medical research, and he remained intensely so until the very end.

Ulf von Euler was born in 1905. His background was highly academic, with strong personal links to a Central European cultural tradition. His Swedish heritage was on the side of his mother, Astrid Cleve, professor in botany and geology, and daughter of the chemist, Professor P. T. Cleve, discoverer of the elements erbium, holmium, and tulium. His father, Hans von Euler-Chelpin, professor in chemistry in Stockholm, and Nobel Laureate in Chemistry 1929, was of German origin and distantly related to the famous Swiss mathematician Leonhard Euler, active in Petersburg during the eighteenth century. No wonder that Ulf von Euler was to become a scientist! He started early, publishing his first scientific paper, together with his father, at the age of 17. He defended his thesis at 25 and became professor and chairman of the Department of Physiology at Karolinska Institutet in 1939, at the age of 34. In this capacity he remained for more than three decades, contributing greatly toward building up Swedish basic medical research to its present internationally recognized standing. His integrity, broad knowledge, and sound judgment made him a highly esteemed member of the Swedish Academy of Sciences and the Swedish State Medical Board and Medical Research Council, a member since 1959 and Vice-President since 1965 of the Council of the International Union of Physiological Sciences (IUPS) and secretary and since 1965, President of the Nobel Foundation. His honors and distinctions are many and include the Nobel Prize in Physiology or Medicine 1970. He also made an important contribution as Chief Editor of *Acta Physiologica Scandinavica* for many years, until the end of his life.

Ulf von Euler's productivity was amazing. Altogether he published 465 scientific papers, over a period of six decades — a breathtaking pace that was kept even after his retirement; the list has 65 entries during that period of about 12 years. His production was not only vast but also covered many different and intriguing aspects. Still his leitmotif can be easily discerned: Throughout his scientific life, he remained dedicated to the search for the **chemical signal** that mediates control of a physiological event and for a **chemically** based explanation of its derangement under pathological conditions. Along this line he was to make a number of discoveries that have turned out, in retrospect, to be of the most fundamental biological importance. Already at 25, when working as a postgraduate in the laboratory of H. H. Dale in London, he discovered, in collaboration with J. H. Gaddum, that extracts of brain and intestine contained an atropine-resistant principle that contracted the gut in an "organ bath" and lowered the blood pressure of the anesthetized rabbit. With remarkable discipline and determination, driven by intuitive appreciation of the potential biological importance of the novel active principle, that essentially by accident became known as substance P, young von Euler patiently followed up his discovery, describing during the next few years its polypeptide nature, methods for its purification and assay, its general distribution in the body, and using the still relatively crude preparations of substance P available at the time, many aspects of its biological actions. In many ways he catalyzed progress in substance P research, the breakthrough of which was to come once its chemical nature became fully elucidated by Chang and Leeman, and as pure substance P became



J. Collsiö

available, some 40 years after Ulf von Euler's original discovery. He had repeatedly emphasized that substance P has a "neurotropic" effect, a highly significant observation, as today this agent is regarded as a member of the "neuropeptide" family, the first to be discovered. Its physiological functions remain to be finally established, but it seems very likely that it acts as a neurotransmitter and/or neuro modulator in many areas of both the central and the peripheral nervous system, for example, in transmission of signals from primary afferent pain fibers.

Three years after he had discovered substance P, von Euler found another atropine-resistant depressor principle, that he named "prostaglandin." Again he patiently and systematically followed up his original finding, defining during the 30s prostaglandin as an unsaturated, lipid-soluble, nitrogen-free organic acid, describing tissue sources, methods of extraction, and purification of the compound and its basic pharmacological properties. He also stimulated the biochemist Sune Bergström to proceed further with the chemical analysis, leading to the discovery that prostaglandin is not a single substance but a family of biologically highly active compounds. Out of the continued work of Bergström, his younger colleague Bengt Samuelsson at Karolinska Institutet, and John Vane in London, there merged a fascinating picture — that of prostaglandins and the closely related leukotrienes as members of an arachidonic acid-based biological control system that is of the highest importance for many physiological functions and also plays a key role under a number of pathophysiological conditions, such as fever, asthma, and vascular thrombosis. For these findings Bergström, Samuelsson, and Vane were awarded the Nobel Prize in Physiology or Medicine 1982.

Ulf von Euler's search for depressor principles had thus been abundantly successful. But it was for his equally successful search for pressor principles in various tissues and body fluids, leading to the discovery of the identity of the sympathetic neurotransmitter, that he himself would be most widely recognized. He was born only months after Elliott had introduced the novel concept of chemical neurotransmission, proposing that sympathetic nerve impulses are mediated by release of "adrenaline," and biological functions of adrenaline had been the subject of several of Ulf von Euler's earliest research papers, in the mid-20s. After settling down as professor of physiology at Karlinska Institutet in 1939, he started out to search for pressor principles that might be involved for example in clinical hypertension. One active compound in his extracts of sympathetically innervated tissues was apparently a catecholamine. Being a pupil of Dale, he was of course aware of the conclusion already reached by Barger and Dale in 1910, that the effects of sympathetic nerve stimulation are much more closely mimicked by noradrenaline, the unmethylated homologue, than by adrenaline. Applying a whole battery of tests he was able to prove that the active principle he had found was indeed noradrenaline, which he therefore proposed to be the sympathetic neurotransmitter. But this discovery, that he made at 40, was not easily accepted. Particularly over the next decade he played a decisive role in the work to overcome the lingering resistance of adherents to the "sympathin E-sympathin I" model and to conclusively establish the validity of his "noradrenaline hypothesis" as well as in working out its physiological, pharmacological, and clinical implications. Later together with N. A. Hillarp he made the important discovery of the mode of storage of neurotransmitter, in subcellular organelles, "nerve granules," about the properties of which he also made the pioneering studies. To the very end he continued to play a leading role in the development of the explosively growing catecholamine field. As recognition of the fundamental importance of his discoveries in this area, that have also been of decisive importance for the development of other fields and contributed greatly, for example, to our deepened understanding of many aspects of brain function in health and disease or of mechanisms of clinical hypertension. Ulf von Euler was awarded the Nobel Prize in Physiology or Medicine 1970.

Toward the end of his life he could look back on a uniquely successful research career. Each of the three major discoveries, that he had had the genius, and the good fortune, to make as a young scientist had grown (although in two cases only after an incubation period of nearly half a century) to become one of the hottest fields of the life sciences. But those who had the privilege of receiving their scientific training from Ulf von Euler also remember him as a great teacher. As such he was old-fashioned, individualistic, practicing a mixture of Socratic maieutic and Darwinian selectionism. He was not an empire-builder or a founder of schools of dogmatic adherents to his own views, but a believer in freedom in research. New, and sometimes outrageous, ideas in young colleagues were never flatly rejected but encouraged with a degree of enthusiasm adapted to his own intuitive faith in their soundness. Whenever disbelieving, his comment might be, "It would be most interesting if you turn out to be right . . ." His openness of mind and genuine scientific curiosity and his knack for finding the right experimental approach to test the validity of a new hypothesis made it a very educating experience to work close to him. A witty and instructive Editorial in *Circulation* (24: 1233, 1962) reveals some aspects of his philosophical outlook on various aspects of science, such as the art of recognizing a "discovery" from an "observation." It concludes by a maxim that he truly lived up to, "We must always guard the liberties of the mind and remember that some degree of heresy is often a sign of health in spiritual life."

As a person, Ulf von Euler was the opposite of a petty chauvinist — he was the aristocrat and the cosmopolitan, carrying on with dignity and style the intellectual and cultural tradition that he had inherited. His sphere of interest was wide: with him one could discuss literally any subject, from science to the arts to politics to philosophical problems. His dry humorous comments and mild sarcasms made his company always stimulating and sometimes delightful. He was not spared problems with his physical health during his last few years, but this did not prevent him from taking part intensely in various scientific activities, and he kept his full intellectual vitality to the very end. Ulf von Euler had the privilege to live to see an amazing growth and development of his scientific discoveries, and to rightly enjoy international recognition as a Grand Old Man of chemical information transfer. His many friends inside and outside the international scientific community miss him greatly.

L. Stjärne

New APS Publications

Two new Handbooks will be completed in 1983. The first *Skeletal Muscle* (Editor, Lee D. Peachey; Associate Editor, Richard H. Adrian) is a new Section in the series and *Peripheral Circulation and Organ Blood Flow* (Editors, John T. Shepherd and Francois M. Abboud) is the third volume in the revised and enlarged *The Cardiovascular System.*

Skeletal Muscle

Like earlier books in the *Handbook of Physiology* series, *Skeletal Muscle* has as its central purpose the presentation of an integrated view of the history, recent research, present state, and possible future of several aspects of its central topic. The chapters have been prepared by eminent authorities in the field and are directed at an audience of professional physiologists, including graduate or research students, who desire a working knowledge of the field, perhaps as a preface to planning and executing a research project in muscle or in a related area. The material provides a precise statement of the present state of the field and helps to bring into focus the next generation of experiments. The book should also prove useful as an authoritative and up-to-date review for teachers and students in advanced courses. The articles are more comprehensive and integrative than a typical annual review but no less authoritative and critical. The chapters are not intended as substitutes for journal articles or for presentations at scientific meetings and differ from most textbook chapters by being more analytical, more current, more authoritative, and less simplified, especially in the treatment of difficult and controversial issues. The first group of chapters starts with structural studies and leads to the mechanics of force generation and biochemistry of the contractile proteins. Chapters on the basic electrical properties of muscle fibers then discuss excitation-contraction coupling and the biochemistry of the sarcoplasmic reticulum. Finally, discussions of specialized insect muscles, development, adaptation, and muscle diseases round out this *Handbook.*

Peripheral Circulation and Organ Blood Flow

"Since 1963, when the prior *Handbook* volume dealing with the regulation of the circulation to the lungs and the systemic vascular beds was published, there have been remarkable advances in knowledge. In fact, so much has been accomplished that it is necessary to publish this volume entitled *Peripheral Circulation and Organ Blood Flow,* in two parts. Part 1 deals with the regulation of blood flow to individual vascular beds; part 2 covers the cardiovascular reflexes and circulatory integration. This *Handbook* volume complements the two already published on the heart and on vascular smooth muscle, and the series will be completed by one on the microcirculations.

"Part 1 starts with the historical perspectives of key concepts of the regulation of the peripheral circulation. Subsequent chapters describe the use of indicators for its study, the viscoelastic properties of the blood vessels, the control of the pulmonary circulation, and methods for the study of the cerebral circulation and its neural, chemical, and metabolic regulation. There follow chapters on the regulation of the renal circulation, including methods of measuring glomerular capillary pressure and peritubular capillary resistance; the contribution of the liver, spleen, and intestines to changes in total splanchnic blood flow and volume; and the dual function of blood flow to the female reproductive organs, serving both homeostatic and reproductive aims. Part 1 concludes with chapters on the unique feature of the circulation of the male reproductive system; the control of the circulation to skin, adipose tissue, skeletal muscle, and bone; and the role of the capacitance system in circulatory control.

"Part 2 provides a treatise on the prime role of the cardiovascular reflexes in harmonizing the components of the circulatory system. It commences with the arterial baroreflexes, including their static and dynamic performance, and continues with the reflex originating from receptors in the heart and lungs, the role of the chemoreceptors and the mechanisms responsible for their excitation, the function of receptors in the skeletal muscles, the reflex control of the circulation during dynamic and static exercise, and the peripheral and central receptors concerned with thermoregulation. The later chapters describe the central neural mechanisms for integrating the cardiovascular reflexes, the techniques for the study of the arterial and cardiopulmonary baroreflexes in humans, and the information gained, in both health and disease. The vascular effects of the peptides on the circulation are discussed, and the features of the fetal circulation, which depend on the combination of placental respiration, vascular shunts, and a high pulmonary vascular resistance, are described. The role of intravascular volume receptors in modulating renal salt and water excretion in humans and in nonhuman primates is reviewed, and the complex circulatory responses to diving that allow utilization of the oxygen stores for high-priority areas are described. The mechanisms leading to the remarkable increase in arterial blood pressure with isometric exercise are reviewed, and the effects of gravity on the cardiovascular system, and their relevance to space flight are outlined.

"All those interested in the cardiovascular system, whether their primary interests are in practice, education, or research, will find enrichment in the contents."

Animal Pain: Perception and Alleviation

Animal Pain: Perception and Alleviation will also be completed this year. Ralph L. Kitchell and Howard H. Erickson served as Editors and E. Carstens and Lloyd E. Davis as Associate Editors for this timely book.

"The book is divided into two sections. Pain perception in animals focuses on peripheral and supraspinal mechanisms involved in pain, segmental neurophysiological mechanisms, spinal cord pathways and control systems, stimulation analgesia and endorphins,

behavioral mechanisms for assessment of pain, assessment of pain during surgical procedures, and phylogenetic evolution of pain expression in animals.

Alleviation of pain in animals covers drug-disposition factors and species variation, evaluation of analgesic drugs in horses, and control of pain in dogs and cats. There is a significant variation among species in the absorption and biotransformation of drugs used to alleviate pain in animals.

"This book is intended as a source of basic information about the perception and alleviation of pain in animals for scientific investigators working in this area; for veterinarians interested in the health and welfare of animals, the assessment of pain during surgery, and the alleviation of pain; and for individuals involved in federal, state, and local regulation of the use of animals in research, education, and quality control of human and animal health products."

Look for promotional material on these important publications. Members of the American Physiological Society may order them at special prices from the Subscription Department of the Society at 9650 Rockville Pike, Bethesda, MD 20814.

Howard E. Morgan

The Steven M. Horvath International Jubilee

On June 19, 1983, Dr. and Mrs. Steven M. Horvath were invited by the Chancellor of his campus, the University of California, Santa Barbara, to attend a "no-excuses-accepted" reception. However, when they arrived, they were greeted not by the Chancellor, but by a majority of Steve's former students and fellows. They had come, without his prior knowledge, to honor their teacher by means of a symposium which was two years in the planning and successfully kept secret from him, despite the large number of people eventually involved. Indeed, Steve's surprise was complete, but he evidently was pleased (see picture). C. M. Blatteis and E. R. Nadel were the conspirators, aided and abetted by Mrs. Horvath and Mrs. Mary Lynn Freling, Steve's secretary; without their help, the meeting could not have taken place.

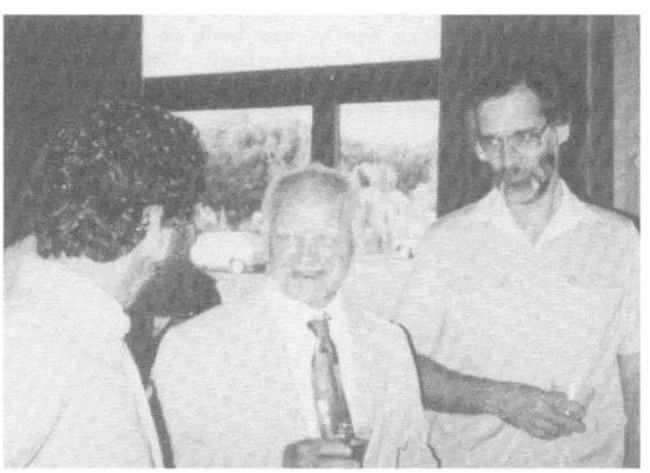
The occasion was organized to celebrate Steve's remarkable success in training 31 Ph.D. candidates and 58 postdoctoral fellows over the past 30 years. Wishing to demonstrate their deep admiration and affection for their mentor and to thank him for teaching them always to be curious and enthusiastic about physiology, over 50 of his pupils returned from literally around the world to present papers during a 2-day meeting entitled the "Steven M. Horvath International Jubilee." Their papers reflected Steve's own broad range of interests and attested to the success of his teaching — to form well-prepared generalists capable of going in depth on their own into any area.

Dr. Horvath currently is "Professor emeritus recalled," a title uniquely his: when he reached retirement age in 1980, he mandatorily became emeritus but was never allowed to leave his post — he was "recalled" immediately! Steve was born on September 15, 1911, in Cleveland, OH. He earned his B.A. and M.Sc. at Miami of Ohio and Ph.D. at Harvard (1942, under D.B. Dill, at the Fatigue Laboratory). Upon graduation, he was drafted and spent the war years at the US Army Armored Medical Research Laboratory, in Ft. Knox, KY, where he participated in the pioneering studies on man's responses to thermal stress. After the war, he accepted positions at Pennsylvania, Iowa (where he became professor), Lankenau Hospital Division of Research, and finally in 1962, at UCSB (where he is Professor and Director, Institute of Environmental Stress). But clearly his wisest move was in 1940, when he married Betty Dill, who has sustained him through high and low all these many years. She has deservedly built a reputation all her own in the physiology community, based on her warmth and understanding, her charm, and her soundness. They have three children, Aletha, Michael, and Peter, all grown now and off on their own successful, scientific, albeit not in physiology, careers.

Steve's research contributions are well known not only because they have been numerous (433 papers, presented to him in 5 bound volumes by his current students and fellows during the Jubilee Banquet), but mostly because they have been important. In addition to his papers, Steve has co-written or co-edited several books, including one co-authored with Betty on the history of the Fatigue Lab. His work has been recognized by consultantships to the National Institutes of Health, the US Army Research and Development Command, and sundry other federal and state agencies, as well as by many lectureships here and abroad. He also has served on the editorial boards of the *American Journal of Physiology,* the *Journal of Applied Physiology,* and other journals.

Steve's program has generated to date 89 physiologists, an impressive total by any standard, but the more remarkable in that most of his students are committed full-time academicians. He always has known just how to balance praise and criticism to motivte his students. But best of all, he has set the example and given them the standards by which they could guide their own careers. For this, his students and fellows are grateful. They were happy, therefore, to have had the opportunity to dedicate their small token of love and appreciation to their extraordinary teacher, Steven M. Horvath.

C. M. Blatteis



S. M. Horvath (*center*) in animated conversation with E. R. Nadel (*left*) and J. F. O'Hanlon (*right*).

THE BOOK PUBLISHING PROGRAM OF THE AMERICAN PHYSIOLOGICAL SOCIETY

Howard E. Morgan, M.D.

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Abstract: The book publishing program of The American Physiological Society is designed to foster the Societies' missions of supporting research and teaching and of providing a historical record of the discipline. Publications include multivolume scientific series (The Handbook of Physiology and The Clinical Physiology Series) historical volumes, and books oriented toward current day issues, such as animal welfare. The Society believes that book publishing is an important means by which it achieves its goals.

The mission of scientific societies, such as the American Physiological Society, are 1) to support research in its discipline and the application of this knowledge to the diagnosis and treatment of disease, 2) to foster training of physiologists and of those such as physicians, dentists, nurses, and veterinarians who will apply their knowledge of physiology to clinical care, and 3) to provide a historical record of the development of ideas that have led to new knowledge within the discipline. Each of these missions can be served by an innovative and aggressive book publishing program.

The primary means by which a Society can foster research within its discipline is by publishing high-quality journals that provide an outlet for the whole range of topics that are under study by its members. The volume of this material is, as a result, diverse and of a magnitude that it cannot be read by all Society members. An even larger problem is faced by the young person who is entering the field and is faced with decades of published material with which some familiarity must be gained. A solution to this problem is the publishing of books that provide a critical and comprehensive description of the current state of knowledge and direct both the trained physiologist and the student to the important papers in the original literature.

The American Physiological Society has met this need during the past 25 years by publication of a large series of volumes, now numbering 33, known as the HANDBOOK OF PHYSIOLOGY (Table 1). The purposes of this series are both to foster research and teaching of physiology. The first volume of this series contained a preface which stated, "the editors have planned a book which would differ from textbooks in being more complete, more analytical, and more authoritative.[1] It would differ from a series of monographs in being organized on a consistent plan without important gaps between topics and with as nearly as possible the same intensity of coverage to importance of topic throughout. It would differ from publications emphasizing new developments in that the background of currently accepted or classical concepts would be set forth, new ideas receiving not more than their due proportion of emphasis relative to the whole body of knowledge in the field. Finally, it would differ from a collection of original papers on a series of topics in that it would provide an integrated condensation and evaluation of the material contained therein. Moreover, the overall plan provides that key experimental evidence be described and discussed in sufficient detail to make clear their nature, validity, and significance for the fundamental concepts of the field. The success of the endeavor must be left to the reader's judgement".

By the criterion of acceptance and use by the scientific community, the Handbooks have been a great success. The topics that have been covered to date are neurophysiology, circulation, respiration, adipose tissue, endocrinology, renal, environmental physiology and the alimentary canal. Handbooks dealing with muscle and cellular physiology are in preparation and a second series of books covering the original subject areas either have appeared or are in preparation. A learned society such as the American Physiological Society, is an especially appropriate sponsor for a Handbooks-type project. Most of the potential authors are Society members, the members have a

TABLE 1. ESTABLISHED BOOK SERIES OF THE AMERICAN PHYSIOLOGICAL SOCIETY

	HANDBOOK OF PHYSIOLOGY	CLINICAL PHYSIOLOGY SERIES
SCOPE	BASIC SCIENCE	CLINICAL/BASIC SCIENCE
INITIATED	1959	1977
ORIGIN	INVITED CHAPTERS	SYMPOSIUM
WRITING TIME	LONG	SHORT
EDITING TIME	LONG	SHORT
LIFE OF BOOK	LONG	SHORT
NUMBER/YEAR	0-3	0-2
PAGE SIZE	8½ x 11	7 x 10
PAGES/VOLUME	500-1500	250-300
SALES	3000-12000	2000-3000
COST & PRICE	X $	X $/10

TABLE 2. NEW BOOKS OF THE AMERICAN PHYSIOLOGICAL SOCIETY.

	PEOPLE AND IDEAS SERIES	ANIMAL PAIN	EXCITATION AND NEURAL CONTROL OF THE HEART
SCOPE	HISTORY	GENERAL	SPECIALIZED
INITIATED	1984-85	1983	1981
ORIGIN	INVITED CHAPTERS	SYMPOSIUM	UPDATED REVIEWS
WRITING TIME	MEDIUM-LONG	SHORT	SHORT
EDITING TIME	MEDIUM	SHORT	SHORT
LIFE OF BOOK	LONG	MEDIUM	SHORT
NUMBER/YEAR	1	1	1
PAGE SIZE	6-3/4 x 10	6 x 9	7 x 10
PAGES/VOLUME	~500	~300	300
SALES	SMALL	UNKNOWN	SMALL
COST & PRICE	$/5	$/10	$/10

personal interest in fostering research within their own subfield and in physiology in general, and the Society can sustain the publication of such a series on a non-profit basis. In contrast, a commercial publisher must seek authors from a discipline, may not have the purpose of promoting research within that particular field, and may not be able to sustain publication of the series over many years. The Handbook concept, however, has been broadened by commercial publishers in an effective manner by providing multidisciplinary books within a clinical discipline, such as gastroenterology, that contributes significantly to progress in those areas.

One next could ask why an author would choose to publish a critical and comprehensive assessment of his field within books of a learned society rather than through commercial firms. As a result of non-profit operation, the author must forego a modest royalty for his work, but he has more freedom to develop his topic in the manner that he wishes and the assurance that his works will be included within a set of reference books that will provide a cornerstone for research in his discipline. Special care in the copyediting is given to provide a book that has a unity and is more than a collection of articles. To ensure against any inadvertent changes in meaning, the author is given two opportunities to examine the text before it is published, one before the manuscript is sent to the printer to be set in type and a second time in the galley proof stage. The books are published on 8½ x 11 inch pages; high quality reproduction of half-tones and figures is assured.

Thus far, the Handbooks have been discussed primarily in the context of fostering research within the discipline. It is clear, however, that such books have an important role in the training mission of the Society. Teachers of physiology use these volumes to prepare lectures for a wide range of health-profession students as well as for graduate students within physiology and related disciplines. The books are not generally used as texts even for graduate courses because they are more comprehensive than course time can accommodate. Reading assignments are common, however, and portions of the books may be covered in detail. From this description of the Handbook project, it is clear that the Society has been pleased with the projects contributions to the Societies research and training missions.

To summarize the Handbook of Physiology series, the books are oriented toward basic science and consist of invited chapters that are written over a period of 1-2 years and are carefully edited. The life of the series has proved to be long. The Society has published up to 3 volumes per year on 8½ x 11 pages. The volumes have contained 500 to 1500 pages and sales have ranged from 3,000 to 12,000 copies.

Another important mission of the American Physiological Society is the application of basic physiological knowledge and research techniques to the diagnosis and treatment of disease. Ultimately, this goal can be accomplished only if those involved in clinical care become firmly grounded in physiological research, but interest in such a career can be promoted by publications designed to bridge the gap between basic and applied research. Publication of the JOURNAL OF APPLIED PHYSIOLOGY has been the primary mechanism used by the Society since 1948 to bridge this gap, but in addition, a series of books in Clinical Physiology has been ongoing for the past 6 years (Table 1). These books are focussed on important clinical topics and extend from basic studies to clinical research. The books are derived from symposia that are organized by the Subcommittee on Clinical Science of the Publications Committee and presented at the meetings of the Society. In this way, the book publishing program also contributes to the Society's missions by enhancing the quality and scope of the presentations at its meetings. Since the books are derived from Symposia, the writing and editing time are short as is the life of the book. The Society has published as many as 2 volumes in the Clinical Series per year on 7 x 10 pages. The volumes contain 250 to 300 pages and sales have ranged from 2,000 to 3,000. The cost and price of these volumes is about 1/10 that of a Handbook of Physiology. Publications in this series have dealt with topics such as Pulmonary Edema, Secretory Diarrhea, Neurogenic Control of the Circulation and Calcium Antagonists. A symposium "Man at High Altitude" sponsored by the Subcommittee was held at San Diego last October and will appear as a book in the Clinical Physiology Series in 1983. This symposium reported on a

medical expedition to Mount Everest. These symposia and the books derived from them have been popular with authors whose research is in basic and clinical disciplines because their work is made known to a broader group of biomedical scientists than normally would be the case.

Another mission of the Society is to provide a historical record of the development of ideas that have led to new knowledge and can best be served by a book publishing program in this area. Since the American Physiological Society will celebrate its Centennial in 1987, the Publications Committee has launched a new "People and Ideas Series" (Table 2). The initial publication in this series has been the reprinting of the elegant book, "Circulation of the Blood: Men and Ideas", edited by A. P. Fishman and D. W. Richards and originally published in 1964 by the Oxford University Press.[2] The purpose of this book, and others in the series to follow, was summarized in the Forward to the original volume. "The primary objective in its design has been to provide a study of the origins, discovery, and progress of certain of the great ideas of this branch of science, and to bring to life, insofar as possible, the great men who made these discoveries and achieved this progress." The authors have made these chapters much more than a historical record. Each is a critical review in depth of the whole physiology of the subject, based on the developments of the past, considering the knowledge and theory of the present, and in some instances even looking toward the future. They are written for the physiologist as much as for the historian."

Currently, three additional volumes in the "People and Ideas Series" are being developed. These areas include endocrinology, membranes and transport, and renal physiology. The current period is a particularly good one for the preparation of such volumes because many scientists who contributed great ideas to these fields are nearing the end of their careers. We expect the invited chapters to be prepared over a period of about 1 year, and for the book to have a long life. We intend to publish 1 book per year consisting of about 500 pages measuring 6-3/4 x 10". The sales will probably be small and the cost will be about 1/5 that of a Handbook.

Finally, a book publishing program allows the Society to address topics of current interest and importance to its members. Animal welfare and the use of animals in research is a topic that is attracting public interest and is of concern to all physiologists. To provide the general scientific community with authoratative information on this topic, a book entitled "Animal Pain" will appear this year (Table 2). The book is based on a symposium on pain perception by animals that was held in 1982. The articles were prepared over a few months and editing of the book is nearing completion. We anticipate the life of the book to be fairly long because of the breadth of interest in these topics and the small number of publications in this area. The book will contain about 300 pages measuring 6 x 9 and will cost about 1/10 that of a Handbook. Frankly, we have no firm basis for predicting sales, but have decided to proceed because of the importance of this topic to the Society. A second book entitled "Animal Stress" is being planned and will be based on a symposium to be held this summer. A quite different topic of current interest also has been dealt with by the book publishing program. The book entitled "Excitation and Neural Control of the Heart", published in 1981, consists of a series of updated review articles that appeared in the Heart and Circulatory Physiology Section of the AMERICAN JOURNAL OF PHYSIOLOGY (Table 2). As a result, writing and editing time were short. Since the book deals with current research topics, its life will be short. The sales have been small and the cost low. Publication of such volumes was undertaken as an aid to those interested in this subfield of Physiology.

Overall, the American Physiological Society has looked upon its book publishing enterprise as an important mechanism to achieve its missions of support fundamental research, application of physiological knowledge to clinical problem, training of physiologists and other health-professionals, in providing a historical record of the field and in addressing topics of current importance. Although the Society is relatively small, approximately 6000 members, the output of books has been steady and has been accomplished without a permanent loss of Society funds. The Society is firmly committed to continuing its book publishing program and looks forward to even greater contributions to the Society's programs.

References

1. Field, J. In: Handbook of Physiology, Section 1: Neurophysiology, Vol. I. Washington, D.C., American Physiological Society, pp. vii-ix.

2. Fishman, A. P. and D. W. Richards. Circulation of the Blood, Men and Ideas. New York, Oxford University Press.

Presented at a session, "Should a Society Publish Books?" during the meeting of the Council of Biology Editors, International Federation of Scientific Editors' Association, and Society for Scholarly Publishing in Philadelphia, Pennsylvania, May 16, 1983.

Mayo Appointments

APS Council member, **Franklin G. Knox,** professor of physiology and internal medicine, was appointed director for Education, Mayo Foundation, and dean, Mayo Medical School. He succeeds chairman of APS Public Affairs Committee, **John T. Shepherd,** dean since 1976 and now chairman of the Mayo Board of Development. Knox has been chairman of the Department of Physiology and Biophysics since 1974. He is also associate director, Research Training and Degree Programs, in the Division of Education.

Election to the National Academy of Science

APS member **Dominick P. Purpura,** a noted neuroscientist and dean of the Stanford University School of Medicine, has been elected to the National Academy of Sciences. He became dean in 1982, coming from the Albert Einstein College of Medicine, and is the holder of the Carol and Elizabeth Naumann endowed chair as well as professor in the departments of Neurobiology and Neurology. Purpura is noted for research in human cortical development using basic data and techniques of neuroscience. He was among the first to observe that the brains of children who are mentally retarded with no known chromosomal aberrations had structural abnormalities in their nerve cells.

Rachmiel Levine, an international authority on diabetes, APS member, and a former section editor of the *American Journal of Physiology,* has been elected to membership in the National Academy of Sciences. He now serves as deputy director for research emeritus at the City of Hope after having been medical director of the institution from 1971 to 1978. Levine is noted for being the first to describe the way insulin acts, thus paving the way for better understanding of the nature and methods of treating diabetes. He is the editor of the journal *Advances in Metabolic Disorders* and serves on the editorial board of *Hormone and Metabolic Research.* He is the author of more than 200 publications in the fields of diabetes, hormone action, gout, adrenal function, and the metabolism of carbohydrates. Educated at McGill University, Montreal, Levine held hospital and teaching posts at Michael Reese Hospital, Chicago, and was professor and chairman of the department of medicine at New York Medical College for 10 years before joining the City of Hope in 1971. He became deputy director for research in 1978 and served in that capacity until last year when he became emeritus.

Wellcome Visiting Professorships Awarded

Announcement is made by the Federation of American Societies for Experimental Biology (FASEB) and The Burroughs Wellcome Fund that 18 awards of Wellcome Visiting Professorships in the Basic Medical Sciences have been made for the academic year 1983/84. Designed to stimulate interest in the basic sciences and to recognize eminent scientists in Physiology, Biological Chemistry, Pharmacology, Pathology, Nutrition and Immunology, the Visiting Professorships are offered annually.

The six constituent societies and the Executive Committee of FASEB chose the following from a large number of applicants:

Joseph S. DiSalvo, Henry Binder, Gerald D. Fischbach, Bruce M. Alberts, Robert H. Abeles, Arthur Pardee, Sydney Spector, Donald Jenden, James A. Ferrendelli, Ronald A. DeLellis, Geoffrey M. Cooper, Charles G. Wilber, J. C. Waterlow, D. M. Watkin, Werner G. Bergen, Jan Klein, Leroy Hood, and **Thomas A. Waldmann.**

As a Wellcome Visiting Professor, each of these distinguished scientists will visit a host institution for several days to engage in teaching and discussion with students and faculty and will deliver a Wellcome Lecture in the Basic Medical Sciences. Each professorship provides an award of $1,500 plus the travel expenses of the professor and accompanying spouse.

New Chief of Medicine at St. Luke's-Roosevelt Hospital Center

Gerard M. Turino, APS member, is the new Director of Medicine at St. Luke's-Roosevelt Hospital Center. An internationally recognized authority on cardiopulmonary diseases, Turino is Professor of Medicine at Columbia University's College of Physicians & Surgeons, with which St. Luke's-Roosevelt is affiliated. He is principal investigator of an interdisciplinary program, sponsored by the National Heart, Lung, and Blood Institute of the National Institutes of Health, which is examining chemical, cellular, and structural predisposition to diseases of the lung. Prior to his appointment at St. Luke's-Roosevelt, he held appointments as attending physician in Medicine at Presbyterian Hospital and Harlem Hospital.

Donald S. Fredrickson Elected to Avon Board of Directors

Donald S. Fredrickson, chairman of the APS Publications Committee (1969–71), has been elected to the Board of Directors of Avon Products, Inc. He was the former Director of the National Institutes of Health and the President of the Institute of Medicine, National Academy of Sciences. He is currently Vice President of the Howard Hughes Medical Institute.

News from Senior Physiologists

Carl Pfaffmann to Edward Adolph:

Thank you for your letter to all members born in 1913. I have just had the pleasure of celebrating my 70th birthday with a gathering of some of my students, former post docs and colleagues, at Sarasota, FL, at the fifth annual meeting of one of the newest societies, the Association for Chemoreception Sciences.

This newer US organization is made up of physiologists, psychologists, animal behaviorists, food chemists, flavor scientists, odor control engineers, some medical specialists, etc., so that it is a wide interdisciplinary group of workers in the chemical senses. It was organized by our second and third generations of younger people, some of whom were my students. Chemosensory science has been considerably behind the other special senses but has been growing and prospering with each successive year as the field has attracted more investigators and research support. In years gone by I had been personally involved in organizing the International Symposia on Olfaction and Taste (ISOT), originally with my cophysiologists Dr. Lloyd Beidler and the late Professor Yngve Zotgterman. ISOT has continued to meet triennially as a satellite of the International Congresses of Physiology, and I shall be attending ISOT VIII this August in Melbourne just prior to the International Congress in Sydney.

For the future I will be continuing at Rockefeller as a professor emeritus, keeping my office, a small laboratory, and a continuing NSF grant with a fine young Research Associate plus lab assistant. We're onto a reexamination in a more modern biophysical vein of the age-old phenomenon of electric taste, first properly characterized by Volta almost two centuries ago. We think that this somewhat exotic phenomenon deserves more attention and has the potential of providing new insights on the transduction process in chemoreceptor membranes.

Next year I plan to be at the university fewer days a week with more time to enjoy my country house in Connecticut. Fortunately my health remains good and I am still able to pursue my hobbies of sailing on Long Island sound in the summer and skiing in the mountains of Vermont in the winter. Thank you very much for your letter. As my wife says, as far as she can make out, my impending retirement has been somewhat exaggerated.

The Rockefeller University
1230 York Ave.
New York, NY 10021-6399

Future Meetings

1984	
FASEB Annual Meeting	Apr 1-6, St Louis
*APS "Fall" Meeting	Jul 29-Aug 3, Lexington
1985	
FASEB Annual Meeting	Apr 21-26, Anaheim
*APS "Fall" Meeting	Aug 4-9, Buffalo
1986	
FASEB Annual Meeting	Apr 13-18, St. Louis
IUPS Congress	July 12-20, Vancouver, Canada

*Campus meeting

Aurin M. Chase to Arthur B. Otis:

Having been retired for some time now, I've gotten quite used to it and really enjoy it. I have a nice office in the Moffett Lab, a newly renovated wing of Guyot Hall, and receive notices of the regular staff meetings, attending a few each year. With undergradute laboratories going full blast off the corridor outside my office, and with busy research programs of my former colleagues running nearby, there is no feeling of being out of things. All-in-all, it's an ideal setup! I've not done any experimental laboratory work in some time but do quite a little reading and a bit of writing. I *have* been doing some field work involving a flock of turkey vultures, at least some of which stay year round in Princeton. I'm especially interested in their soaring ability and in some of their adaptations and in how they communicate with each other. This is more animal behavior than physiology, but the "experimental work" is good exercise and doesn't (at least the way I do it) require research grants to get expensive apparatus.

My wife and I continue to enjoy good health and usually spend at least a month each summer at a 150-year-old family farm in New Hampshire. It's heavily populated with Chases and their wives, husbands, children, and grandchildren.

Dept. of Biology, Princeton University
Princeton, NJ 08544

Hubert R. Catchpole to Arthur:

While my membership in the APS (1938) begins to qualify me as one of the older members, I have not been formally connected with Physiology since January 1943, when I departed an Assistant Professorship in John Fulton's Department at Yale to take up an Apprentice Seamanship (second class) in the US Navy. When I terminated my career as Research Professor of Pathology at the University of Illinois College of Medicine in Chicago, in 1975, I resumed, in a way, my physiological bent as a teacher in the Department of Histology at the same University. Physiological? But of course.

In the Physiological Laboratory at Cambridge, England, in 1925, J. N. Langley, discoverer of the autonomic system, was Professor of Physiology, and Tripos (Honours) student in Physiology were issued very wet tissue sections cut, I imagine, on the original microtome. Then, through good offices of such youngsters as Hartridge, Adrian, and Roughton we were initiated into the mysteries of teasing and staining same. Sometime I shall have to find out if they still do it this way.

110 W. Oak St., Chicago, IL 60610

R. M. Melampy to Arthur:

Thank you for the birthday greetings from the Committee on Senior Physiologists. My teaching and research at Iowa State University have been in the area of physiology of reproduction of farm animals. I am most grateful for the excellent support provided over the years by the National Institutes of Health, the US Department of Agriculture, and the University.

Dept. of Animal Science
Iowa State University
Ames, IA 50011

David Nachmansohn to Arthur:

Thank you for your recent note. Not long ago I finished my autobiography entitled "Molecular Aspects of Bioelectricity. Challenge of a Concept," which will be published by the Springer-Verlag. In 1979 my book "German-Jewish Pioneers in Science 1900–1933. Highlights in Atom Physics, Chemistry, and Biochemistry" (Springer-Verlag, Heidelberg-New York, 388 pp) appeared and is now in the process of being translated into German. I am at present recuperating from a stroke suffered early last year.

Dept. of Neurology
College of Physicians & Surgeons
of Columbia University
New York, NY 10032

Carl F. Schmidt to Bob Alexander:

Let me thank you for your letter of July 5th. Being about to celebrate my ninetieth birthday, I hasten to reply. After my wife died of a massive coronary attack last November, I was left rattling around in the apartment alone. Early this month I responded to the urgings of my son and his wife to join them in their home in Bryn Mawr. I have discontinued all work in the laboratory as well as attendance at meetings. I try to walk about five miles a day and am in good physical condition. I am now engaged in reading the diaries that I have kept practically all the time since 1914 and have begun a series of accounts of the ensuing years beginning with my two years in China in 1922–1924. In addition I have the letters that we sent to my mother from China. It is amazing how much the situation out there has changed since then, if one can trust the descriptions of recent travelers.

My activities in the future will depend on how this account is received. My life has covered some very interesting times, and I have some unusual records, but my experience in writing has been in the sciences. The age of ninety is scarcely the time to begin a new enterprise.

Emil Bozler to Bob:

Thank you for your inquiry about my activity. Some of my time is spent in some of the favorite hobbies of the aged, such as gardening, music, but I am also working full time in the laboratory. My interest has been caught by the problem of the effects of movement on mechanics and energetics of contraction in various types of muscles. After 10 years of work I reached the conclusion that movement modifies activity by positive feedback and thereby largely determines the time course of normal contraction and that this modification is due to a distinct mechanism which does not involve a change in ionized Ca. Such notions have not found favor by most referees. However, my NIH research grant has been renewed recently and runs past my 83rd birthday; an invited review of my work is in press in a prominent Japanese journal. Being able to continue productive work is due to lucky circumstances, having the support of the administration and stumbling on an important but neglected problem which can be studied with simple techniques and without technical assistance.

Dept. of Physiology
The Ohio State University
Columbus, OH 43210

William W. Scott to Roy O. Greep:

This year I reached the age of 70, and at present I am David Hall McConnell Professor of Urology, Emeritus, at Johns Hopkins. In June I relinquished the editorship of *The Journal of Urology,* which is the official publication of The American Urological Association. Late in 1981, I succeeded in arranging consolidation of *Investigative Urology,* which I founded in 1963, and *Urologic Survey,* founded in 1951 by Hugh Jewett, with *The Journal of Urology.* This is in its third volume and appears to be a success from all standpoints. I continue to see patients in the clinic, mostly people with prostatic cancer, and to participate in the chemotherapeutic efforts of the National Prostatic Cancer Project. From a research standpoint, I continue to participate in programmatical studies on benign prostatic enlargement in dogs and men. As one who has helped to train some 65 urologists, 21 of whom head a division or a department in this specialty, I'm convinced that part of one's resident training in a clinical specialty should be in basic research. Familiarity with "the scientific method" is as important to the clinician as it is to the basic scientist.

James Buchanan Brady Urological Institute
Johns Hopkins Hospital
Baltimore, MD 21205

Anna M. Baetjer to Louise Marshall:

I was delighted to receive your note from APS and to learn of your work at UCLA. I did write of my activities for *The Physiologist* some time ago, but since I continue to teach a class and do a little research work here at Hopkins, I have nothing new to report. However, I always read with interest the notes which other retirees write. I was, of course, very interested in the Michigan Supplement which arrived a few days ago. In fact, I sent a copy of the chapter on Dr. Howell to our Archive office in case they did not receive it. I note that you swim for exercise. My only strenuous exercise is in the summer, when I spend two weeks at a small lodge in the glacier section of the Canadian rockies and climb the trails each day.

School of Hygiene and Public Health
The Johns Hopkins University
Baltimore, MD 21205

Herbert Chasis to Louise:

Thank you for the birthday greeting. If it does not interfere with more important demands made on your time, I should certainly appreciate receiving future greetings from the APS. I continue to spend full time in the Dept. of Medicine at New York University School of Medicine as Professor of Medicine. I spend most of the week at my desk in the Homer W. Smith Laboratory for the Study of Hyptertensive and Renal Diseases. I also continue to see patients, for which I set aside one day a week. My intership at Bellevue Hospital started in 1930, so that I have had the opportunity to witness the changing pattern of diseases and their therapies over the last half-century. A real revolution has taken place, and we have a better understanding of the multiple etiologic and pathogenetic factors responsible for these changes.

New York University Medical Center
550 First Ave.
New York, NY 10016

Irwin J. Pincus to Louise:

I was delighted to receive your letter from the Committee on Senior Physiologists. I did, in fact, retire this year but have continued with some interesting activities. Thus I teach a group of six first-year medical students. We meet on the ward, and they talk to people who happen to be patients. They find out who they are and discuss the relevance of the preclinical sciences to the patient's problem. This course called "Introduction to Clinical Medicine" is the most exciting teaching I have ever done — for almost 15 years. Since I was a gastroenterologist, I still enjoy making rounds at Harbor General-UCLA Hospital and attending the basic science clinical conferences.

610 North Roxbury Drive
Beverly Hills, CA 90210

Jessamine Hilliard to Louise:

I take piano lessons hoping to improve the dexterity of my left hand, part of which was lost to a stroke in 1975. In addition, I do part-time volunteer work at St. Joseph Hospital in Orange, where I work in the library researching projects for the hospital staff. Other than that, I mostly just sit, practice, read, and wash dishes.

[Addendum: Dr. Hilliard has just completed a manuscript that describes her work in the early 1950s when she and a co-worker conducted an exhaustive biochemical search for abnormal substances in the urine of sex offenders. The study was financed by the State of California and constituted the first research project conducted at the newly formed School of Medicine at the University of California, Los Angeles. Dr Hilliard continued work in endocrinology there until her retirement.]

1511 Clear View Lane
Santa Ana, CA 92705

Richard Bernard to Louise:

Yes, please [send future birthday greetings]. No scientific activity. Will visit California (as tourist) next September. Reading regularly *The Physiologist.*

1105 Avenue des Laurentides, App. 4
Quebec, Quebec
G1S 3C2, Canada

Falconer Smith to Louise:

I retired in 1972 from chairmanship of the Biology Department of American University and since then have lived in real retirement taking interest in civic projects. Then in January 1981 I experienced what they called a "Small Stroke" left side — two large capital S's flashed in my mind at that point. Since that event I have been reviewing all that I learned about the neuromusculature. PT is helping, since I can get about with a cane and much labor. We see Paul and Katherine Altland from time to time. We have a lovely hilltop home with all the Blue Ridge to look at daily, 3 miles from Harpers Ferry National Park. We love Charlestown and all its friendly people! It is only 60 miles from Bethesda, so we see our kids a lot.

Box 536
Charlestown, WV 25414

Announcements

1984 Lita Annenberg Hazen Awards

Nomination material is now available for the 1984 Lita Annenberg Hazen Awards for Excellence in Clinical Research. The purpose of the awards is to encourage increased participation in clinical research by physicians. Prizes amounting to $100,000 are awarded: $50,000 (tax free) to an outstanding physician investigator and $50,000 for the support of a research fellow or fellows. *For further information contact:* Thomas C. Chalmers, Chairman, The Lita Annenberg Hazen Awards, Mount Sinai School of Medicine, 1 Gustave L. Levy Place, Annenberg 24-64, New York, NY 10029. Phone: (212) 650-8832.

Clarence Merskey M.D. Memorial Fund

Clarence Merskey, distinguished hematologist, world-renowned expert on disorders of blood coagulation, and Professor of Medicine and Laboratory Medicine at the Albert Einstein College of Medicine where he served for nearly a quarter of a century, died in his sleep on 10 November 1982. He was respected, admired, and loved by the entire hematologic community. We would like to perpetuate his memory at the institution where he spent so much of his life in teaching, research, and patient care. While no specific plans for this memorial can be made until the magnitude of the fund is better defined, it is hoped that an endowment for a senior or junior faculty position in hematology, a postdoctoral trainee post in hematology, or a program for medical students interested in blood research and blood diseases can be established. Send *contributions (tax deductible) payable to Albert Einstein College of Medicine to:* Ernst R. Jaffé, Albert Einstein College of Medicine, 1300 Morris Park Ave., Bronx, NY 10461.

IV International Congress on Prolactin

The IV International Congress on Prolactin will convene in Charlottesville, VA, 27-29, June 1984. In addition to invited lectures, ample time will be allotted for verbal and poster presentations chosen on the basis of submitted abstracts.

For more information contact: Robert M. MacLeod, Chairman, IV International Congress on Prolactin, University of Virginia School of Medicine, Charlottesville, VA 22908.

International Symposium on Stress and Heart Disease

International Symposium on Stress and Heart Disease, will be held in Winnipeg, Canada, 27-29, June 1984. The scientific program will include invited speakers, selected discussants, and free communications in the area of stress, hormones, hypertension, arrhythmias, coronary spasm, sudden death, and cardiomyopathies. *For abstract forms and other information contact:* Robert E. Beamish, Experimental Cardiology Section, Dept. of Physiology, Faculty of Medicine, University of Manitoba, Winnipeg R3E OW3, Canada.

INSTRUCTIONS FOR APPLYING FOR APS MEMBERSHIP

CURRENT APPLICATION FORMS

Most issues of The Physiologist routinely carry one copy of the current application form (following). This form will serve for all categories of membership. Any member desiring to sponsor more than one applicant may use a Xerox copy of this form. Any application submitted on an out-dated form will be redone on the acceptable form.

One application form serves all membership categories. There are, however, specific sets of instructions for each category. Therefore it is essential that sponsors and applicants carefully attend to those instructions specific to their desired category.

GENERAL INSTRUCTIONS

FOR ALL CATEGORIES:

Use only the current application form. Check the box indicating the category of membership for which you are applying. Use the SPECIAL INSTRUCTIONS for that category when filling out the form. Type the Application. Fill out all applicable spaces. Only completed applications will be reviewed.

Alien Residents. Canadian residents should furnish a copy of "Landed Immigrant Status" form. Mexican residents should furnish a copy of their form FM-2.

The Bibliography must be submitted in the form found in the Society's journals. An example of the correct form is:

JONES, A.B., and C.D. Smith. Effect of organic ions on the neuromuscular junction in the frog. Am. J. Physiol. 220:110-115, 1974.

DO NOT INCLUDE A CURRICULUM VITAE

Send no reprints.

Deadline Dates: Completed applications received between February 1 and June 1 are considered for nomination by the Council at the Fall Meeting. Applications received between June 1 and February 1 are considered for nomination by the Council at the Spring Meeting. Applications are not complete until all materials, including sponsor's letters, are received.

QUALIFICATIONS (Except Students):

The Membership Advisory Committee uses the following 5 categories in evaluating an application:

1. Educational History. Academic degree and postdoctoral training are evaluated and assessed with regard to how closely the applicant's training has been tied to physiology.
2. Occupational History. Particular emphasis is given to those applicants who have a full time position in a department of physiology, or are responsible for physiology in another department. Relatively high ratings are given to people with positions in clinical departments and to people functioning as independent investigators in commercial or government laboratories.
3. Contributions to the Physiological Literature. This category is of major importance. The applicant's bibliography is evaluated on the basis of publications in major, refereed journals which are concerned with problems judged to be primarily physiological in nature. Emphasis is given to papers published as the result of independent research. Special note is taken of publications on which the applicant is sole author or first author.
4. Interest in and Commitment to Teaching Physiology. This evaluation is based on: (1) the fraction of the applicant's time devoted to teaching, (2) publications related to activities as a teacher including production of educational materials, and (3) special awards or other recognition the applicant has received for outstanding teaching effectiveness.
5. Special Considerations. This category permits the Membership Advisory Committee to acknowledge unique accomplishments of an applicant. These might be excellence in a specific area, or unusual contributions to Physiology resulting from talents, interest or a background substantially different from the average.

SPONSORS:

Primary responsibility for membership rests with the two sponsors who must be regular members of the Society. Sponsors should discuss the appropriateness of the selected category of membership in this Society with prospective applicants.

Each sponsor should write an independent confidential letter about the candidate using the five categories listed above to evaluate the candidate. Furnish an original and 7 copies to the Membership Secretary.

CHECK LIST:

1. Original copy of application signed by both sponsors.
2. Application on a current form, including the bibliography (1 original and 7 copies).
3. Mail the original, which has been signed by the two sponsors, plus 7 copies to:

Membership Secretary
American Physiological Society
9650 Rockville Pike
Bethesda, Maryland 20814

SPECIAL INFORMATION AND INSTRUCTIONS

FOR REGULAR MEMBERSHIP

Bylaws of the Society:

Article III, Section 2 - Regular Members. Any person who had conducted and published meritorious original research in physiology, who is presently engaged in physiological work, and who is a resident of North America shall be eligible for proposal for regular membership in the Society.

Duties and Privileges:

1. Hold Elective Office.
2. Vote at Society Meetings.
3. Serve on Committees, Boards and task forces.
4. Serve on Federation Boards and Committees.
5. Sponsor New Members.
6. Orally present or co-author a contributed paper and sponsor a non-member authored paper at the Fall scientific meeting.
7. Orally present or co-author one contributed scientific paper at the annual Federation meeting or sponsor one paper.
8. Receive The Physiologist.
9. Receive Federation Proceedings, Public Affairs Newsletters and annual Membership Directory.
10. Subscribe to handbooks and periodicals published by the Society at membership rates.
11. Register to attend scientific meetings of the Federation and the APS Fall meeting at membership rates.
12. Participate in FASEB Member's Life Insurance Program, Disability Program and in Hospital Protection Plan. (For Residents of the United States, its territories or possessions).
13. Eligible to receive the Daggs Award.
14. Eligible to be selected as Bowditch Lecturer (members under 40 years of age).

FOR CORRESPONDING MEMBERSHIP

Bylaws of the Society:

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R-5/81

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DO NOT INCLUDE A CURRICULUM VITAE

Cardiovascular Deconditioning of Space Flight

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Among the unresolved biomedical problems of manned space flight is the incomplete understanding of the associated cardiovascular "deconditioning." This phenomenon, which results from exposure to the weightlessness of orbital flight, manifests itself most remarkably upon return of space flyers to Earth. It results in a syndrome of cardiovascular instability featuring orthostatic intolerance when the subject assumes the upright posture. Principal manifestations are tachycardia, labile blood pressure, hypotension, narrowed pulse pressure, presyncope or frank syncope, impaired locomotion, and reduced exercise capacity (41).

Crew safety and effectiveness in future space missions require more precise data on the nature and mechanisms of the cardiovascular responses to space flight and effective means of preventing or controlling the adverse effects. At the request of the National Aeronautics and Space Administration (NASA), the Life Sciences Research Office (LSRO) of the Federation of American Societies for Experimental Biology (FASEB) conducted a study of cardiovascular deconditioning and prepared a scientific report[1] (30) including an assessment of available data, identification of unresolved questions, and a listing of suggestions for future research consideration. The study was done with the assistance of an ad hoc group of expert investigators.[2]

The purpose of this paper is to present a synopsis of the LSRO report (30) to acquaint potentially interested scientists with the problem of cardiovascular deconditioning associated with manned space flight and to generate research proposals[3] aimed at resolving critical questions.

Cardiovascular Responses to Space Flight[4]

Upon entering the weightless state of orbital flight, astronauts experience a headward shift of blood and tissue fluids, vascular congestion of the head and neck, and a reduction in total blood volume. There are also changes in certain regulatory mechanisms that, on Earth in the customary 1-G environment, maintain cardiovascular regulatory stability (46). The fluid shift may amount to as much as 2 liters, the major portion of which expands the pulmonary vessels and heart chambers. Astronauts have experienced a sensation of fullness in the head, stuffy noses, nasal voices, and slender legs (24, 25, 34). Soviet scientists have reported a sustained increase in jugular vein pressure and a reduction in venous pressure in the legs during space flight (14, 15). In the 185-day Salyut-6-Soyuz mission, mean volume of the lower extremities of the two crew members was reduced approximately 10%.

In the deconditioned state, mean resting inflight values of heart rate and of the arterial systolic and pulse pressures tend to be greater while mean arterial and diastolic pressures tend to be less than the preflight values (41). It is postulated, but not documented in flight, that the large, headward shift of blood volume rapidly induces a diuresis in response to the associated increase in right atrial pressure. In turn, this leads to a reduction in plasma volume, which is reflected by postflight orthostatic intolerance and impaired exercise capacity (7). A negative fluid balance, including a reduction in plasma volume, may also result from decreased fluid intake during the initial hours or days of a space mission. The inflight changes have been described as adaptive to the null gravity. Such changes have not impaired crew efficiency or well-being during flight, and they have stabilized after 4 to 6 weeks in orbit (12). With few exceptions, electrocardiographic changes observed during space flight have been uncommon (12, 15, 41, 43), and were judged to be within normal physiologic limits (12).

Yegerov (47) reported the following responses to lower body negative pressure (LBNP) in cosmonauts during long-term missions: heart rate, peripheral vascular resistance, and the arterial pulse wave velocity increased while stroke volume and cardiac output fell. The increase in calf volume induced by LBNP during flight was greater than the analogous response to simulated weightlessness on Earth. Echocardiographic measurements of cosmonauts after long space missions showed a mean 25% decrease (range: 9-42%) in left ventricular volume and suggested a loss in ventricular mass (42); however, there is no firm evidence of an actual loss of cardiac muscle mass.

[1] Copies of the report, entitled "Research Opportunities in Cardiovascular Deconditioning" are available from the National Technical Information Service, U.S. Department of Commerce, P.O. Box 1553, Springfield, Virginia 22161.

[2] Participants were: M.L. Levy, M.D., Chief of Investigative Medicine, Mt. Sinai Medical Center, Cleveland; J.H. Mitchell, M.D., Professor of Medicine and Physiology, University of Texas Southwestern Medical School, Dallas; J.R. Neely, Ph.D., Professor of Physiology, Hershey Medical Center, Hershey, PA.; C.F. Rothe, Ph.D., Professor of Physiology and Medical Biophysics, Indiana University School of Medicine, Indianapolis; K. Sagawa, Ph.D., Professor of Biomedical Engineering, Johns Hopkins University School of Medicine, Baltimore; E.H. Wood, M.D., Ph.D., Professor of Physiology and Medicine, Mayo Foundation and Graduate School of Medicine, Rochester, MN.

[3] The NASA Biomedical Research Program is conducted intramurally by the NASA Research Centers and by means of extramural grants and contracts. Qualified scientists interested in learning more about the program and in submitting research proposals should write to Manager, Biomedical Research Program/EBT-3, Life Sciences Division, NASA Headquarters, Washington, D.C. 20546.

[4] In this paper, only a small part of the literature on cardiovascular deconditioning is cited. Additional information is available in other reports, compendia, reviews, and thematic publications (1-5, 7-10, 14-19, 21, 23, 25, 26, 31, 35, 37-41, 6545, 46).

The experiences of the United States and the Soviet Union have demonstrated man's adaptability to the space environment for periods of 6 months without serious untoward biologic effects during flight (44). However, after all manned flights, including those that lasted only a few hours, some degree of orthostatic intolerance has occurred. The time required for postflight readaptation to Earth conditions has ranged from as little as 2 days to, in some cases, 4 weeks or longer. Human experience in space has been too limited in number and duration of flights to determine whether cardiovascular deconditioning is fully reversible or if it is a potential limiting factor in the length of manned space missions.

Typical cardiovascular responses to space flight were those of the nine astronauts in Skylab missions 2, 3, and 4 (durations of flights were 28, 59, and 84 days respectively), shown in Table 1.

Simulated Weightlessness

The cardiovascular effects of bed rest and other ground-based methods of simulating weightlessness are similar to those outlined above for actual zero-G, including instability of cardiovascular regulation and loss of orthostatic tolerance. Despite universal acknowledgement that the ground-based models cannot be equated physically to the zero-G environment, they do approximate certain features of weightlessness and do permit controlled biomedical studies and tests of possible countermeasures (36, 41).

Blomqvist and Stone (7) note that the hydrostatic conditions that prevail in man in the upright position on Earth change markedly when subjects are exposed to experimental bed rest, to head-out immersion in water, or to actual weightlessness. The redistribution of intravascular and interstitial fluid from the lower to the upper half of the body is the main, acute, hemodynamic effect. The mechanisms for adaptation to the relocated fluids and altered intravascular pressures associated with bed rest, immersion, or zero-G are thought to be basically similar. Hypovolemia, reduced stroke volume and cardiac output, orthostatic intolerance, and decreased exercise capacity are the common results of exposure to real and simulated weightlessness (7).

Table 1
Summary of Cardiovascular Changes During Skylab Missions*

Cardiovascular deconditioning was observed during flight; changes appeared to be adaptive in nature and tended to stabilize after 4 to 6 weeks.
Cardiovascular changes did not impair crew health or ability to function effectively in weightless flight.
Inflight lower body negative pressure tests provided a fairly reliable predictive index of postflight cardiovascular status.
Inflight cardiac electrical activity, as measured by vectorcardiogram, was not significantly altered and remained within physiological limits.
Decreased cardiac output noted in crewmen postflight; thought to be related to reduced blood volume.
Single episode of significant cardiac arrhythmia noted in one Skylab 2 crewman during exercise early in mission.
No significant decrement in work capacity or physiologic responses to exercise during flight.
All crewmen exhibited decrease in work capacity and altered physiological responses to exercise after flight, including a decrease in maximal oxygen uptake.
Skylab 3 and 4 crews returned to preflight cardiovascular status by the fourth or fifth day and the Skylab 2 crew recovered on the 21st day postflight. Increased exercise by Skylab 3 and 4 crewmen during flight thought to be a factor in improved recovery rate.

*Modified from Ref. 12.

However, some significant differences between the effects of actual and simulated weightlessness have been observed or postulated, such as the volume response of the lower extremities during LBNP. The extraordinary inflight pooling of blood in the legs induced by LBNP was documented in the Skylab missions (22), but not in most bed rest studies in which changes in leg volume during LBNP were observed. A dramatic reduction in lower limb girth develops during space flight, but is less marked in bed rest studies. On the other hand, in normal human subjects during the first 24 hours of bed rest, at a 5°head-down tilt, a mean total reduction of 0.9 liters in the combined volume of both legs was observed. According to the authors, these volume changes closely matched the initial, rapid changes found during the Skylab studies (36). Thus, head-down tilt may simulate the agravic qualities of weightlessness more closely than the supine position (27, 36).

Subjects experience suppression of vasopressin release and a marked natriuresis and water diuresis during the initial hours of water immersion to the neck and during the first day or two of bed rest (13). In addition, a kaliuresis of shorter duration than the natriuresis occurs in water immersion. Whether these changes occur during the initial 24 to 48 hours of weightlessness is not known, but they have been postulated (4).

While certain evidence suggests that central venous pressure (CVP) in human subjects remains elevated throughout long space missions (47), results of bed rest studies suggest either that CVP does not change or that it increases transiently. After initiation of 5° head-down tilt, CVP in human subjects increased within 30 minutes to peak values and returned to near control values within 90 minutes (36). However, in studies of human volunteers with indwelling venous catheters, there was no increase in CVP during 7 days of 5° head-down tilt (28).

Mechanisms of Cardiovascular Deconditioning

Tables 2 and 3 list (a) examples of phenomena observed during and after exposure to actual and simulated weightlessness; (b) known or postulated mechanisms; and, (c) some of the related, unanswered questions. These topics are treated in more detail in the LSRO report (30).

The basic cause of the cardiovascular deconditioning response is generally agreed to be weightlessness, which results in disappearance of the customary, gravity-induced, hydrostatic pressure gradients throughout the body. In zero-G, a shift in regional blood volumes occurs towards the most compliant segments of the circulation, i.e., the lungs, heart, and the systemic veins, which are only partially filled when at 1-G. This regional volume change is presumably followed by a change in total blood volume, which is caused by transcapillary fluid movements consequent to the elimination of gravitationally induced intravascular and tissue pressure gradients. In a gravitational-force environment such as that on planet Earth, such gradients are present in all body positions and are proportional to the differences in vertical height of the various capillary beds in the systemic and pulmonary circulations associated with any particular body position.

Table 2
Examples of Cardiovascular Responses and Mechanisms During Actual or Simulated Weightlessness

Observed Responses	Known or Postulated Mechanisms	Essential Missing Information
Rapid shift of intravascular and interstitial fluid to upper half of body	Absence of all hydrostatic pressure gradients; altered vascular compliance and/or capacity; altered cardiac output and blood flow; hormonal and renal changes in chronic adaptation	Acute and chronic effects on: right and left atrial pressures; pulmonary gas and blood volumes and flows; shapes and dynamics of cardiac chambers; shape and position of diaphragm; splanchnic and cerebral hemodynamics; pressure and volume receptor function
Diuresis and natriuresis during initial 24-48 h	Suppression of ADH release via stimulation of atrial pressure receptors (immersion, bed rest); Gauer-Henry reflex in zero-G? Changes in neurohumoral content of cerebrospinal fluid (CSF)?	Whether diuresis and natriuresis occur in first 24-48 h of zero-G; whether changes in CSF pressure and neurohumoral content occur; effects on ADH and aldosterone secretion
Hypovolemia of 300-500 ml develops within 24-48 h	Diuresis and increased transcapillary fluid shifts from lower body tissue spaces; headward fluid shift activates volume or low-pressure receptors; imbalance of fluid intake and output	Whether hypovolemia occurs independently of volume or low-pressure receptor function; influence of mental stress on fluid shift and diuresis; right and left atrial pressures; pulmonary hemodynamics; position, shape, pressure-volume dynamics of cardiac chambers; cardiac output and sympathetic activity; systemic vascular resistance
Relative to inflight resting values, inflight LBNP tests showed *increases* in: heart rate; peripheral resistance, mean arterial pressure, diastolic pressure, pulse wave propagation, blood pooling in legs; and *decreases* in: systolic and pulse pressures, stroke volume, and cardiac output	Reflex C-V responses to reduced blood volume; interstitial fluid in legs decreased; lower vascular tone; impaired venous return and muscle pumping; reduced arterial mechanoreceptor activity; increased vasomotor center activity; decreased response of vascular muscle to adrenergic neural activity; altered venous capacitance and/or capacity; decreased skeletal muscle tone; inflight LBNP causes large shift of blood to lower half of body; increased distensibility of lower limb veins	More accurate and complete data are needed on: confirmation of inflight vs. preflight LBNP data; sympathetic activity; systemic vascular capacity; magnitude of fluid volume shifted to lower body during LBNP; status of high- and low-pressure C-V reflex systems; explanation for decreased peripheral vascular receptor activity in presence of increased arterial blood pressure
Echocardiographic evidence of a mean 25% decrease in left ventricular volume after long missions	Hypovolemia; reduced peripheral resistance, diastolic and arterial blood pressures, net decrease in cardiac workload	Whether any *loss* of *myocardial mass* occurs

While the exact biologic mechanisms of the cardiovascular deconditioning response have not been established, several hypotheses are either under investigation or included in future research plans. These suggest: (1) a decrease in overall blood volume subsequent to the presumed increase in central venous pressure, which is thought to occur concomitantly with the onset of the zero-G environment; (2) changes in shape and position of the diaphragm and associated changes in lung volume; (3) altered cardiac output and redistribution of systemic and pulmonary blood flow and ventilation; (4) changes in venous compliance and/or capacity; (5) possible changes in reflex control of cardiovascular function; (6) changes in the densities and sensitivities of cardiovascular volume, pressure, and neurohumoral receptors; (7) altered peripheral sympathetic function and decreased adrenergic responsiveness of vascular smooth muscle; (8) impaired release or uptake of norepinephrine; (9) relative disuse of the lower extremities with loss of muscle pumping; and, (10) increased intracranial pressure leading to changes in control and production of central nervous system regulatory hormones. In addition, possible interactive effects on the cardiovascular system of abnormal environmental responses of other organ systems and regulatory functions may be significant.

The decreased inflight peripheral vascular resistance and arterial blood pressures reported by Soviet scientists (14, 15) were ascribed to augmented activity of low-pressure mechanoreceptors and greater discharge of the high-pressure receptors resulting from increased pulse pressures. The associated, sustained elevation of jugular venous pressure was considered to be a response to the hemodynamic effect of the cephalad shift of blood and tissue fluids. Skylab inflight measurements showed increased or normal levels of plasma cortisol as well as angiotensin I and a trend toward increased plasma potassium. Plasma ACTH, insulin, aldosterone, and sodium were decreased. Urinary cortisol, aldosterone, total 17-ketosteriods, sodium, and potassium increased, and there was a trend toward decreased urinary ADH, epinephrine, and norepinephrine.

Numerous investigations have suggested that the mechanisms of the cardiovascular response to weightlessness are multiple and not necessarily restricted to the attendant major fluid shift from the lower to the upper half of the body. In addition to weightlessness, other characteristics of space flight should probably be taken into account, such as the behavioral and physiologic effects of confinement, isolation, apprehension, monotony, and reduction in social contacts (29).

Exposure to weightlessness influences fluid and electrolyte balance, metabolism of minerals and other nutrients, and certain endocrine functions. Thus, many

variables are involved in assessing cardiovascular changes during complex interactions among the diverse organ systems and functions of the weightless body (38). Consequently, it would be appropriate to conduct further studies of the sequence and interdependence of changes in cardiovascular, renal, endocrine, and sensory functions associated with weightlessness or its ground-based analogues (6, 46).

Countermeasures

Attempts to prevent or control cardiovascular deconditioning have involved inflight, reentry, and postflight measures as well as experimental interventions during or after bed rest and other ground-based analogues of weightlessness. These measures have included certain drugs and hormones, inflight exercises and lower body negative pressure (LBNP), venous occlusion, fluid and electrolyte replacement before reentry, use of anti-G suits during and following reentry, and postflight supportive measures.

Expert opinion is divided about the extent of protection offered by such measures as vigorous, regularly scheduled exercise, repeated LBNP, and pre-reentry fluid and electrolyte replacement. Some investigators regard such countermeasures as marginally effective or noneffective in preventing the cardiovascular deconditioning, particularly the orthostatic intolerance, associated with weightlessness or its ground-based models. However, postflight recovery time (4-5 days) of the crews of Skylab missions 3 and 4 was significantly less than that of Skylab 2 (21 days). The use of vigorous exercise by the crews of Skylab 3 and 4 may have accounted for the difference (12). From experience with long-term manned flights, Soviet investigators are sufficiently convinced of the efficacy of such measures that they consider their inclusion during long-term missions as mandatory.

Unresolved Questions

Tables 2 and 3 list some of the issues that the LSRO ad hoc Working Group (30) considered essential to resolve. The hemodynamic significance of the absence of gravity-induced pressure gradients in the thorax is not well defined. A 15- to 20-cm vertical pressure gradient in the thorax is normally present at 1-G regardless of body position. The thoracic blood volume considerably exceeds that in the legs. Thus the absence of the pressure gradient in the zero-G environment must have significant effects on the spatial distribution of pulmonary blood and gas volumes and flows in the very compliant

Table 3
Mechanisms of Postflight and Post-Simulation Orthostatic Intolerance

	Observed Responses*	Known Mechanisms	Postulated Mechanisms	Essential Missing Information
1.	Tachycardia with body upright or with head-up passive tilt; postural hypotension, sometimes with presyncope or syncope: LBNP tolerance reduced postflight and after simulation	Hypovolemia; decreased stroke volume	Loss of vascular and muscular tone, especially lower extremities; abnormal reflex cardiovascular regulation; increased distensibility of leg veins; decreased tissue pressure in lower extremities; reduced baroreceptor sensitivity; increased vagal discharge plus existing sympathetic response to upright tilt or standing; decreased cardiac work capacity; impaired release of endogenous norepinephrine	Nature and extent of deterioration of reflex mechanisms responsible for cardiovascular function; why is degree of C-V dysfunction greater than expected from amount of hypovolemia? Effect of zero-G on (1) sensitivity, numbers, distribution of C-V mechanoreceptors; (2) thermoregulation; (3) right atrial pressure; (4) pulmonary blood and gas pressures and flows; (5) left atrial pressure; (6) functional dynamics of cardiac chambers
2.	Marked reduction in maximal and submaximal work capacity, upright and supine	Decreased stroke volume	Decreased oxygen uptake, ventilatory volume, maximal heart rate, LVED volume, and cardiac filling pressures and output; physical inactivity; reduced muscle strength, tone, blood pumping action; decreased heart size and cardiac work capacity	Nature and extent of effects on reflex mechanisms that control cardiopulmonary function; effects on C-V mechanoreceptors; functional dynamics of cardiac chambers; effect of exercise inflight and during simulation
3.	No increase in pooling of blood in legs of most bed-rested subjects during LBNP tests; marked increase inflight		Difference in responses suggests a factor in ground-based models that sustains vascular and skeletal muscle "tone"; most likely the hydrostatic pressure gradients of gravity. Periodic turning of subjects from prone to supine also probably affects results	Same as in #1 above
4.	Tolerance for acceleration of $+2.5G_z$ (eyeballs down) declined in 20% of centrifuge-experienced subjects after 24 h bed rest; tolerance less for inexperienced subjects		Hypovolemia and decreased interstitial pressure in lower extremities	Same as in #2 above

* The most frequently reported responses; however, some results are inconsistent with the responses listed above.

pulmonary vasculature. Consequently, it would have substantial effects on right and, particularly, left atrial filling pressures in the agravic environment.

A fundamental question is whether the atrial and ventricular receptors exert regulatory control of the heart and vessels and of the release of vasopressin and aldosterone during zero-G. An important associated problem is whether weightlessness induces changes in the number and sensitivity of the autonomic receptors of the cardiovascular system, including α- and ß-adrenergic receptors and the muscarinic receptors. Further, if exposure to weightlessness results in impairment of circulatory reflex control, is the defect that is responsible for postflight cardiovascular instability localized in the baroreceptors, the brainstem, the afferent or efferent limb of the reflex arc, or in the effector cells themselves?

Increased cardiac filling pressure stimulates sensory receptors in the atria and ventricles, the former eliciting an increase, and the latter a decrease in heart rate. Does cardiac filling pressure increase under zero-G conditions and, if so, which of the foregoing effects prevails?

It is essential to determine whether actual losses of myocardial tissue result from exposure to zero-G. Similarly, the nature and extent of degenerative changes in the hearts of immobilized animals and the causal mechanisms of such changes must be identified. Is there a threshold level of whole or partial body hypokinesia for induction of cardiac pathology? Finally, the operating point of the heart on the Frank- Starling curve during various phases of space flight is not well defined.

Another question to be resolved is the practical significance of the documented changes in levels of circulating and excreted hormones on cardiovascular function during and after weightlessness. Are the humoral changes triggered by fluid shifts? Does gravity exert a direct effect on biochemical processes? The two- to four-fold increase of insulin levels in human subjects during bed rest studies raises the questions of whether this occurs in weightlessness and its practical meaning. Does the simulated zero-G result in the release of an insulin-blocking agent? What is the influence of an apparent increase in insulin resistance on the metabolism of the heart and blood vessels?

A task in the NASA Biomedical Research Program on cardiovascular deconditioning involves investigation of the effects of sustained cephalad fluid shifts on the pressure and composition of the cerebrospinal fluid. An associated question concerns possible functional changes in the pituitary portal system as a result of enduring increases in jugular vein pressure during weightlessness.

There is insufficient knowledge to determine whether periodic exposures to LBNP would be an effective means of prophylaxis against certain components of cardiovascular deconditioning. If future experience favors this approach, what are the most practical means and schedule for LBNP?

The effectiveness of muscular exercise as a countermeasure is a major research issue. Questions of the types, patterns, and schedules of exercise for enhancing homeostasis of the cardiovascular, musculoskeletal, and other organ systems and functions require further investigation. For instance, inflight muscular exercise should help to maintain Earth-equivalent cardiovascular function if it is extensive enough to match the workload that prevails at 1-G. Estimates of the magnitude of the reduced workload that results from weightlessness are needed.

Some data show that, in bed-rested subjects, the anti-G suit protects against orthostatic intolerance (32, 33) and preserves $+G_Z$ (positive, headward direction) acceleration tolerance (11, 20). However, evidence that anti-G suits provide significant antiorthostatic protection at positive accelerations of <2 G_Z requires additional support, and the question persists whether an operational need exists for anti-G suits during reentry of the Shuttle Orbiter.

With regard to methodology, the validity of bed rest, water immersion, and other ground-based methods of simulating weightlessness needs resolution. A majority of the LSRO ad hoc Working Group participants (30) regard the use of ground-based models and a search for ways to improve them as essential for progress in elaborating basic mechanisms. Such models may also be useful for testing methods and devices for counteracting the adverse effects of cardiovascular deconditioning. A minority view on the subject of ground-based methodology is also a part of the LSRO report (30). It suggests that, before any substantial ground-based studies of cardiovascular deconditioning are undertaken in the future, the ground-based models of weightlessness should be validated inflight.

Questions deserving high priority concern are: (1) whether degenerative changes occur in the cardiovascular system during medium- and long-term missions, in particular, a possible loss of myocardial tissue; (2) the nature and temporal development of changes in cardiovascular regulatory control mechanisms; (3) possible changes in the density and sensitivity of the pressure, volume, and neurohumoral receptors in the cardiovascular system; (4) alterations in vascular compliance and capacity; (5) associated changes in hemodynamics; and, (6) the nature of the redistributed blood flows.

Suggestions for Future Research

The main objective of the NASA Ground-based research and analysis program in cardiovascular deconditioning is the acquisition of scientific data that will lead to practical methods of prevention or control of the syndrome. The current lack of adequate data indicates clearly the continuing need for investigations focusing on the biological mechanisms involved and improvement of technics, methods, equipment, and facilities.

Examples of the research and analysis suggestions of the LSRO ad hoc Working Group on Cardiovascular Deconditioning are listed in Table 4. In order to facilitate the investigations, the state-of-the-art in methodology and instrumentation needs substantial improvement. For instance, improved means are needed for measuring noninvasively, in living subjects, such characteristics as cardiopulmonary dimensions, heart chamber volumes, and myocardial mass. Current methods for in vivo functional assessment of cardiovascular mechanoreceptors must be improved as should methods for measuring absolute changes in venous volume. Greater attention should be given to the selection of the most suitable animal models. Animal experiments should be designed in such a way as to

Table 4. Suggestions for Ground-Based Research in Cardiovascular Deconditioning

A. Hemodynamics

Assess cardiovascular function, using multiple end points, at selected stages of simulated space missions, including the first 24 hours

Determine whether cardiac filling pressure increases or decreases in simulated weightlessness and characterize its time course

Characterize changes induced by simulated weightlessness on cardiopulmonary blood pressure relationships and their influence on cardiovascular deconditioning

Measure changes in total vascular capacitance in human and animal models of cardiovascular deconditioning

Determine changes in regional systemic and pulmonary blood volumes and blood flows and their effects on cardiovascular functional capacity in a model of deconditioning

B. Endocrine and Neurohumoral Aspects

Formulate experiments to detect the effect on cardiovascular system function associated with changes in levels of circulating and excreted hormones that have been observed in real and simulated weightlessness

Perform detailed, serial analyses of temporal changes in serum hormone levels in bed-rested subjects during simulated space missions. Candidate substances should include insulin, glucagon, catecholamines, T_3, T_4, renin, aldosterone, vasopressin, myocardial CPK isoenzymes, fatty acids, cholesterol, and high- and low-density lipoproteins

Study the influence of atrial and ventricular sensory receptors on regulation of cardiovascular function and on release of vasopressin and aldosterone in simulated weightlessness

Further define and quantify insulin resistance associated with simulated weightlessness

Measure changes in intracranial vascular and cerebrospinal fluid (CSF) pressures associated with zero-G. Identify possible related alterations in CSF composition, pituitary portal system function, and regulation of the cardiovascular system

C. Myocardial Changes

Characterize the myocardial changes that have been reported in chronically immobilized animals. Identify temporal aspects and specific etiologic factors

In studying the effects of simulated weightlessness on the heart, consider measuring changes in: (a) ionized calcium fluxes across the myocardial cell membrane, (b) circulating levels of CPK myocardial isoenzymes, and (c) myocardial hydroxyproline content

Differentiate between the myocardial and hemodynamic effects of immobilization versus postural, immersion, or other methods of simulating zero-G in animal models of cardiovascular deconditioning

D. Related Factors

Locate the sites of possible defects in reflex control of the circulation that contribute to cardiovascular deconditioning

Assess the relative importance of high- and low-pressure baroreceptors in the reflex control of the circulation during and after weightlessness

Determine in an animal model of cardiovascular deconditioning whether changes occur in the density and sensitivity of the cardiovascular adrenergic receptors in response to simulated weightlessness

Conduct studies of human subjects during bed rest in order to investigate the functional changes in baroreceptors

E. Methods, Equipment, and Facilities

Improve the methods of measuring in living subjects such characteristics as cardiopulmonary dimensions, heart chamber volumes, myocardial mass, plasma volumes, erythrocyte mass, and interstitial and total body water

Design experiments with LBNP coupled with measurement of atrial and ventricular pressures in order to study the role of associated mechanoreceptors in cardiovascular function. LBNP activates low-pressure receptors and neck suction activates the high-pressure receptors

Refine the methods of measuring baroreceptor function, per se, in conscious subjects

Conduct further validation studies of head-down tilt bed rest as a method of simulating weightlessness

Encourage investigators to use models of the cardiovascular system when they design experiments on cardiovascular deconditioning, even though available knowledge of the mechanisms involved is incomplete

F. Countermeasures

Expand the test and development of extant types of putative countermeasures to confirm their possible efficacy and to refine their patterns and means of use. Examples of putative measures are muscular exercise, LBNP, fluid and salt repletion, and combinations of these

Develop alternate means for exercising the vascular system of the lower extremities during weightlessness

Perform tests with deconditioned subjects to determine whether the anti-G suit is a practical countermeasure to decelerative stress during Shuttle Orbiter reentry

Formulate experiments to test the utility of drugs and hormones as prophylactic or therapeutic countermeasures to the orthostatic intolerance of cardiovascular deconditioning

Design a study of astronauts to (1) identify those who demonstrate relative resistance to cardiovascular deconditioning as may be estimated from inflight and postflight physiologic responses, and (2) to define physiologic and/or behavioral correlates of such resistance

eliminate spurious influences that may result from equipment and methodology employed. Computer and other models of the cardiovascular system offer possible improvements in experimental design despite the lack of complete, explicit data on the basic mechanisms of cardiovascular deconditioning. Finally, the need for unequivocal confirmation of the methodologic suitability of the currently-used or alternate ground-based models of the space flight environment, particularly with respect to weightlessness, should be clearly recognized.

Conclusions

The cumulative experience from manned space flight suggests that the effects on the cardiovascular system are tolerable and reversible, and do not interfere with inflight crew effectiveness during missions lasting up to 6 months. Postflight orthostatic intolerance has occurred after all manned flights to date, requiring supportive care to prevent possible injuries and to aid in the process of readapting to Earth gravity. Whether space missions of greater duration than heretofore will cause more profound changes in the integrity of the cardiovascular system is unknown. However, in view of the future likelihood of longer manned missions, and until such time as a reliable understanding of the basic mechanisms of cardiovascular deconditioning is acquired, and effective, practical countermeasures have been developed and proved, it is suggested that the NASA ground-based research and analysis program in cardiovascular deconditioning merits a high priority. Determining the basic mechanisms of the cardiovascular responses to space flight offers an intellectual challenge worthy of the best scientific minds in a broader segment of the biomedical research community than has heretofore been involved.

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Graphic Representation of CO_2 Equilibria in Biological Systems

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As biology advances and multicomponent systems with wide pH, P_{CO_2}, and temperature changes are encountered, it is necessary to extend the rather limited acid-base formulations of medicine and yet somehow retain comprehensibility. For example, in Rahn and Reeves' analysis (12) of water-ion (OH^-/H^+) ratios in the animal kingdom and in its clinical applications (16), one must keep track of a bewildering array of reactants, products, and ionization constants, each varying differently with temperature. Even everyday cardiorespiratory problems arising from the difference between systems open and closed to CO_2 (4,10,11) need clarification.

We present the log C-pH diagram (1-3,9,14) as extended to open and closed biological systems (6) and derive a new water-ion balance method for determining equilibrium pH. The water-ion formulation allows hydroxyl ion and proton-transfer reactions to be treated with equal emphasis. The diagram makes immediately obvious which products of OH^- transfer and H^+ transfer reactions are the "controlling products" in the sense that they determine pH. This approach may serve as an introduction to acid-base states in hypothermia and in organ systems in which the OH^-/H^+ ratio is considered to be important (12).

Water-Ion Balance Equation

Water, by itself, dissociates into equal numbers of protons and hydroxyl ions. When other species are added, the number of protons H^+_W and of hydroxyl ions OH^-_W produced by such direct water dissociation is still equal, regardless of the equilibrium pH. This is the principle of water-ion balance.

An imbalance between total $[H^+]$ and $[OH^-]$ in an aqueous solution generally occurs when molecules other than water produce, directly or indirectly, water ions in excess of H^+_W and OH^-_W. Species like NaOH and H_2SO_4 "donate" water ions directly. Species such as sodium acetate (NaAc) and CO_2 "free" OH^- and H^+ by abstracting, respectively, protons and hydroxyls from water. Before dealing with CO_2 systems we will derive the water-ion balance equation using familiar nonvolatile species as examples.

Water ions in excess of H^+_W and OH^-_W are measured by their product equivalents. For example, adding NaOH to water produces one Na^+ for each OH^- so that at equilibrium

$$[OH^-] = [OH^-_W] + [Na^+]$$

where $[Na^+]$ is the concentration of the product equivalent of the excess OH^- contributed by NaOH.

When H_2SO_4 is added to water, the equilibrium hydrogen ion concentration $[H^+]$ is

$$[H^+] = [H^+_W] + 2[SO_4^{2-}]$$

since two excess protons are donated per sulfate ion.

The acetate ion adds hydroxyl indirectly by abstracting a proton when NaAc is added to water. Thus, for a solution of sodium acetate

$$[OH^-] = [OH^-_W] + [HAc]$$

If all three species are added to water, water ions and their equivalents are produced in the following reactions

$$\begin{aligned} NaOH &\rightarrow & OH^- &+ Na^+ \\ H_2SO_4 &\rightarrow 2H^+ & &+ SO_4^{2-} \\ Ac^- + H_2O &\rightarrow & OH^- &+ HAc \\ H_2O &\rightarrow H^+_W & + OH^-_W & \end{aligned}$$

The total water-ion concentrations are obtained by simply adding to $[H^+_W]$ and $[OH^-_W]$ the concentrations of the product equivalents of the excess water ions

$$[H^+] = [H^+_W] + 2[SO_4^{2-}]$$
$$[OH^-] = [OH^-_W] + [Na^+] + [HAc]$$

The principle of water-ion balance requires

$$[H^+_W] = [OH^-_W]$$

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Combining these three equations yields the water-ion balance equation

$$[H^+] + [Na^+] + [HAc] = [OH^-] + 2[SO_4^{2-}]$$

Written generally, the equation is

$$[H^+] + [OH^- \text{ equivalent(s)}] = [OH^-] + [H^+ \text{ equivalent(s)}] \quad (1)$$

This equation determines the equilibrium pH expressed for simplicity in this paper as $-\log [H^+]$. We will show how the log C-pH diagram is used to solve the equation.

Log C-pH Diagram

The diagram consists of dissociation curves, each representing the concentration of a reactant or product vs. pH. Their shapes are fixed by each chemical system. These shapes are not changed when other chemical reactants are added. The controlling products of reactions that involve water-ion exchange are established by inspection of the dissociation curves. The equilibrium pH is found at the intersection of the two controlling product curves.

The diagram can also be used to illustrate charge neutrality (6), proton balance (7), and classical analytical approaches (13), but these will not be considered in this paper.

To find an equilibrium pH, three steps are followed on the diagram. *1*) Dissociation curves are derived from the equilibrium and mass balance equations for each open- or closed-system reactant and product. *2*) The reaction expressions are used to identify the products resulting from water-ion exchange. *3*) The water-ion balance equation is solved for the pH at the intersection of two curves established by substitution of the product equivalents in each side of the equation. The solutions can be achieved graphically by simple inspection of the diagram.

In explaining how these steps are carried out, each will be described separately in examples of biological interest, although in the actual use of the diagram, finding the equilibrium pH becomes (with practice) a single rapid visual process. The first example is the dissociation of pure water at 25 and 37°C.

Water

Dissociation Curves

The equilibrium equation is $[H^+]\,[OH^-] = K_W$. By definition $\log K_W = -pK_W$. The dissociation equations, the first from the definition of pH, are

$$\log[H^+] = -pH$$

and

$$\log[OH^-] = pH - pK_W$$

Since both $\log[H^+]$ and $\log[OH^-]$ have the form log C, these equations are represented graphically as the two bold dissociation curves (here straight lines) in Figure 1. The line for $\log[H^+]$ vs. pH has a slope of -1, and the pH $= 0$ when $[H^+] = 1$ M. The line for $\log[OH^-]$ vs. pH has a slope of $+1$, and pH $= pK_W$ when $[OH^-] = 1$ M.

Reactants and Products

The reactant on the left and the products on the right of the reaction expression are written as

$$H_2O \rightarrow H^+_W + OH^-_W$$

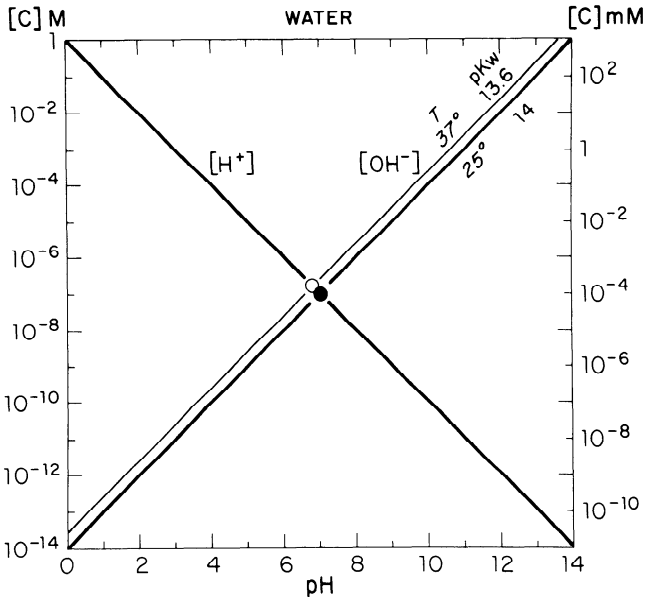

Figure 1

Log-concentration vs. pH diagram for water. Concentrations per liter of solution are shown logarithmically in moles per liter (M, *left*) or in millimoles per liter (mM, *right*). *Bold lines*, slopes of ± 1 represent concentrations $[H^+]_W$, $[OH^-]_W$ vs. pH at 25°C. Their intersection (*solid circle*) represents equilibrium pH $= pK_W/2 = 7$ and concentrations $[H^+] = [OH^-] = 10^{-7}$ M. That pH is half of pK_W is clear from symmetry of the figure. As temperature rises to 37°C, $[H^+]$ line defining pH remains fixed. $[OH^-]$ line (*thin*) and the intersection (*open circle*) shift leftward as pK_W falls to 13.6 and pH to 6.8. $[H^+] = [OH^-]$ rise to 1.58×10^{-7} M. Thus "biological neutrality" at 37°C occurs at pH $= 6.8$, and pH $= 7$ represents alkaline conditions ($[OH^-] > [H^+]$, $[OH^-]/[H^+] > 1$).

Equilibrium pH

The solution of the water-ion balance equation, obtained by substituting the products of water-ion transfer, and noting that there are no ions donated or freed by added species, is

$$[H^+] = [OH^-] \quad (1a)$$

which establishes the equilibrium pH. At 25°C, where $pK_W = 14$, the bold dissociation curves intersect at the point (solid circle) where pH $= 7$ as indicated on the abscissa and where proton and hydroxyl concentrations both have the value C $= 10^{-7}$ M as indicated on the ordinate.

At 37°C, where $pK_W = 13.6$, the thin $[OH^-]$ dissociation curve intersects with the bold $[H^+]$ curve, which cannot move because it defines pH, at the open circle where pH $= 6.8$ and where $[H^+]$ and $[OH^-]$ have both increased to C $= 1.58 \times 10^{-7}$. The pH at the neutral point has fallen to 6.8, reflecting the increased dissociation of water at the higher temperature.

The diagram lets the observer "see" quite precisely how much rising temperature raises $[H^+]$ and $[OH^-]$ by increasing water dissociation (changing position but not the shape of the dissociation curves) and by how much equilibrium pH falls (the horizontal distance that the open circle has moved to the left). The diagram continually reminds one of the definition of pH.

Open Unbuffered CO_2 System

The three steps needed to solve for equilibrium pH are now described for an open CO_2 system in which P_{CO_2} can be regulated by gas exchange.

Dissociation Curves

The system is described by the Henderson-Hasselbalch equations from which the dissociation equations are

$$\log[HCO_3^-] = \quad pH - pK_1' + \log[CO_2]$$

$$\log[CO_3^{2-}] = 2pH - pK_1' - pK_2' + \log[CO_2]$$

The first is the logarithmic form of *Eq. 5* below. The second results from combining the first with the logarithmic form of *Eq. 6*, $\log[CO_3^{2-}] = pH - pK_2' + \log[HCO_3^-]$.

As with the water-ion dissociation equations, the terms on the left have the form log C. If $[CO_2]$ is held constant by gas exchange, as indicated by the horizontal line labeled $[CO_2]$, the equations are represented by the straight lines labeled $[HCO_3^-]$ and $[CO_3^{2-}]$ in Figure 2. The $[HCO_3^-]$ line has a slope of +1 and intersects the $[CO_2]$ line at $pH = pK_1'$. The $[CO_3^{2-}]$ line has a slope of + 2 and intersects the $[HCO_3^-]$ line at $pH = pK_2'$ (see 3rd equation above). Carbonic acid concentration $[H_2CO_3]$ is a constant fraction ($^1/_{400}$) of $[CO_2]$ as shown by the lower horizontal line located 2.6 scale divisions below the $[CO_2]$ line ($\log {}^1/_{400} = -2.6$).

If P_{CO_2} and hence $[CO_2]$ are raised at constant temperature, the entire system of four lines simply shifts upward, maintaining a fixed shape. (All crossings of carbonate lines with each other occur at the previous pH values; all crossings of carbonate lines with water-ion lines move to the left).

If temperature changes, different pK_1', pK_2', and CO_2 solubility establish different crossings and a different P_{CO_2}.

Reactants and Products

When CO_2 and water react, the products appear on the right in the net reaction expressions as follows

$$CO_2 + H_2O \rightarrow H^+ + HCO_3^-$$

$$CO_2 + H_2O \rightarrow 2H^+ + CO_3^{2-}$$

$$H_2O \rightarrow H_W^+ + OH_W^-$$

The product equivalent of H^+ in the first reaction is $[HCO_3^-]$, since one proton is freed per HCO_3^- product. But two protons are freed per CO_3^{2-}, so the equivalent product of $2H^+$ is $2[CO_3^{2-}]$. Substituting the equivalents in *Eq. 1* yields

$$[H^+] = [HCO_3^-] + 2[CO_3^{2-}] + [OH^-] \qquad (1b)$$

Equation 1b applies to either an open or a closed system.

Equilibrium pH

The open-system dissociation curves are used to find the equilibrium pH. The three terms on the right of *Eq. 1b* are expressed in each pH range of Figure 2 by *the highest line representing a product of water-ion transfer.* (The CO_2 and H_2CO_3 lines can be ignored as determinants of pH because they are not reaction products.) In this case the highest such line, up to pH = 10.3, is the $[HCO_3^-]$ line. Thus *Eq. 1b* is, in practical form

$$[H^+] = [HCO_3^-] + \ldots$$

which establishes equilibrium pH. The $[HCO_3^-]$ lines intersects the $[H^+]$ line at pH = 4.51 (solid circle), thus controlling equilibrium. Inspection of the diagram makes immediately obvious that $[HCO_3^-]$ is the "controlling product." That the other products of water-ion transfer are negligible can be seen from their millimolar concentrations read from the diagram where their dissociation curves intersect the vertical dotted line at pH = 4.51

$[H^+] = [HCO_3^-]$	$= 0.03$	mM
$[OH^-]$	~ 0.000001	mM
$[CO_3^{2-}]$	< 0.0000001	mM

It can also be seen from the fact that their dissociation curves are more than two scale divisions below ($^1/_{100}$ of) the controlling product curves.

The equilibrium pH can, of course, be found by solving simultaneously for six unknowns in *Eq. 1b* and the following five

$$[CO_2] = S \cdot P_{CO_2} \qquad (2)$$

where $[CO_2] = [H_2CO_3] + [CO_2]_{diss}$ (since carbonic acid and dissolved CO_2 are indistinguishable in the sum) and S is the apparent solubility coefficient

$$T_{CO_2} = [CO_2] + [HCO_3^-] + [CO_3^{2-}] \qquad (3)$$

$$K_W = [H^+]\,[OH^-] \qquad (4)$$

$$K_1' = [H^+]\,[HCO_3^-]/[CO_2] \qquad (5)$$

$$K_2' = [H^+]\,[CO_3^{2-}]/[HCO_3^-] \qquad (6)$$

where the activity coefficients are incorporated in the apparent equilibrium constants K_1' and K_2'. The unknowns are $[CO_2]$, T_{CO_2}, $[HCO_3^-]$, $[H^+]$, and $[OH^-]$. Standard texts show how to decide which of these six unknowns can be approximated in solving for pH, but the graphic method makes these approximations obvious.

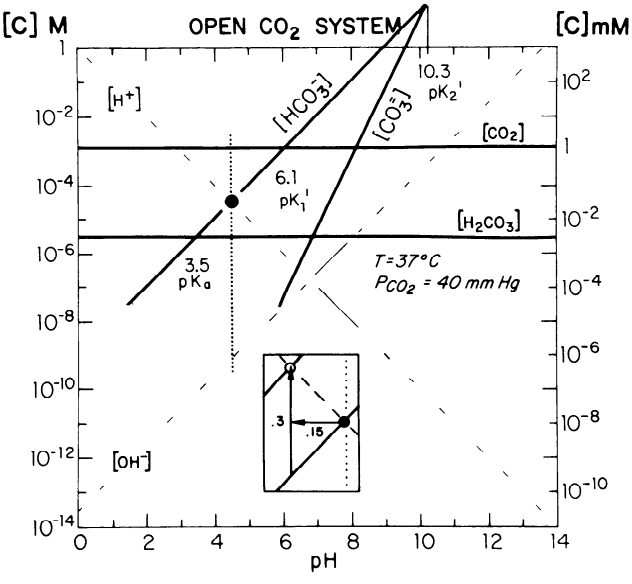

Figure 2

Log-concentrations vs. pH diagram for open CO_2 system. Coordinates are the same as in Figure 1. The following variables are plotted vs. pH at P_{CO_2} = 40 mmHg: $[CO_2] \sim [CO_2]_{diss}$, $[H_2CO_3]$ (horizontal), $[HCO_3^-]$ (slope = 1), and $[CO_3^{2-}]$ (slope = 2). $2[CO_3^{2-}]$ line that represents $2H^+$ equivalents would be 0.3 decade above $[CO_3^{2-}]$ line. T_{CO_2} curve would follow $[CO_2]$ at low pH, $[HCO_3^-]$ at intermediate pH, and $[CO_3^{2-}]$ at high pH: T_{CO_2} curve near asymptotic transitions would have the same shape as a dissociation curve in the closed system (see Figure 3). *Dashed diagonal lines* represent $[H^+]$ and $[OH^-]$. Practical water-ion balance equation $[H^+] = [HCO_3^-]$ for CO_2 in this system is used to find equilibrium pH = 4.51 indicated by *large dot* where $[HCO_3^-] = 3.1 \times 10^{-5}$ M. pK_1' is appropriate for ionic strength of biological fluids. All other concentrations can be evaluated along *vertical dotted line* at equilibrium pH (e.g., $[OH^-] = 8 \times 10^{-10}$M; at 37 °C $pK_W = -\log_{10} 2.5 \times 10^{-14} = 13.6$). When P_{CO_2} changes, all CO_2 system curves shift vertically by equal amounts, but $[CO_2]$-$[HCO_3^-]$ crossover remains at $pH = pK_1'$. Doubling P_{CO_2} raises $[HCO_3^-]$ line by 0.3 decade. Its intersection with $[H^+]$ line moves up 0.15 and to the left 0.15 decade. New pH will be 4.51—0.15 = 4.36 (*open circle* in *insert*).

Once the pH is known for one equilibrium, an acid-base disturbance can often be quantitatively illustrated on the diagram. In this aqueous system, doubling P_{CO_2} at the same temperature, and therefore at the same CO_2 solubility, raises all carbonate curves 0.3 unit in Figure 2 ($\log 2 = 0.3$). The pH falls 0.15 unit as can be seen from the leftward shift of the $[H^+]$-$[HCO_3^-]$ intersection (insert in Figure 2). Similarly if a temperature fall should double the CO_2 solibility, S, at constant P_{CO_2}, $[CO_2]$ again doubles because of *Eq. 2*. Thus the same leftward shift of the intersection is induced by cooling, if the slight temperature dependence of pK's is neglected (intersection at open circle).

Closed Unbuffered CO_2 System

The three steps needed to solve for equilibrium pH are now described for a closed CO_2 system in which T_{CO_2} remains constant because gas exchange is prevented or because, as in many living systems, CO_2 production equals CO_2 elimination.

Dissociation Curves

For low pH, combining the mass balance *Eq. 3*

$$T_{CO_2} = [CO_2] + [HCO_3^-] + \ldots \qquad (pH < 8.2)$$

with the equilibrium *Eq. 5* the dissociation equations are (1,2,9,14)

$$[CO_2] = \frac{T_{CO_2}[H^+]}{[H^+] + K_1'}$$

$$[HCO_3^-] = \frac{T_{CO_2} K_1'}{[H^+] + K_1'}$$

Straight-line approximations to the logarithmic form of these equations are shown in the graph of Figure 3:

when $[H^+] >> K_1'$ ($pH << pK_1'$)

$$\log[CO_2] = \log T_{CO_2}$$
$$\log[HCO_3^-] = pH - pK_1' + \log T_{CO_2}$$

when $[H^+] << K_1'$ ($pH >> pK_1'$)

$$\log[CO_2] = -pH + pK_1' + \log T_{CO_2}$$
$$\log[HCO_3^-] = \log T_{CO_2}$$

For $pH << pK_1'$, $[CO_2] = T_{CO_2}$ and $\log[HCO_3^-]$ vs. pH has a slope of +1. At $pH = pK_1'$, $[HCO_3^-] = [CO_2] = \frac{1}{2} T_{CO_2}$. For $pH >> pK_1'$, $\log[CO_2]$ vs. pH has a slope of −1 and $[HCO_3^-] = T_{CO_2}$. The straight-line approximations around pK_2' are similarly derived from $T_{CO_2} = \ldots + [HCO_3^-] + [CO_3^{2-}]$ and *Eq. 6*.

In the vicinity of the pK's, the graphs curve. Each curve has the same shape or its mirror image about pK. $[H_2CO_3]$ is 2.6 orders of magnitude below $[CO_2]$ as was true in the open system. If T_{CO_2} rises, all four curves shift upward but maintain the same shapes and relative position. If temperature changes, the pK's change as do the relative positions of the curves, but T_{CO_2} does not.

Reactants and Products

When $NaHCO_3$ is added to water, the following reactions lead to the products on the right

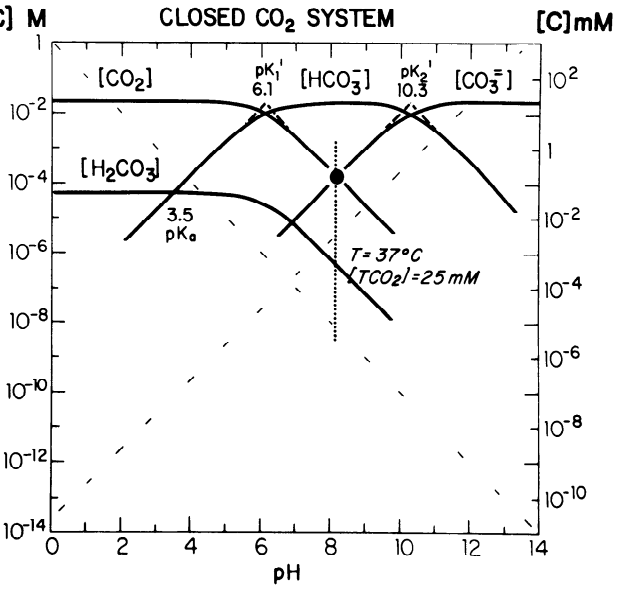

Figure 3

Log-concentration vs. pH diagram for closed CO_2 system water-ion balance. Coordinates and variables are the same as in Figure 1 except that now T_{CO_2} is held constant at 25 mM. Mass balance and chemical equilibrium constraints determine shape of dissociation curves as for weak acids or salts of weak acids (2). Practical water-ion balance equation $[CO_2] = [CO_3^{2-}]$ for $NaHCO_3$ in water of biological system ionic strength is used to find equilibrium pH = 8.2 indicated by *large dot* where $[CO_2] = 0.2$ mM. Other concentrations at this equilibrium pH can be read from graph along *vertical dotted line* as $[HCO_3^-] = 25$ mM, $[OH^-] = 3.2 \times 10^{-3}$ mM, $[H_2CO_3] = 5 \times 10^{-4}$ mM, $[H^+] = 7.9 \times 10^{-6}$ mM. As with the open system, these curves may be used as overlays when CO_2 content or pK's change. Shape of curves is independent of pK and CO_2 content.

$$NaHCO_3 \rightarrow H^+ + CO_3^{2-} + Na^+$$
$$NaHCO_3 \rightarrow OH^- + CO_2 + Na^+$$
$$H_2O \rightarrow H_W^+ + OH_W^-$$

The equivalent of H^+ is $[CO_3^{2-}]$. The equivalent of OH^- is $[CO_2]$. The Na^+ is not a product of water-ion transfer, simply appearing by direct dissociation of the reactant. *Equation 1* then becomes

$$[H^+] + [CO_2] = [CO_3^{2-}] + [OH^-] \qquad (1c)$$

This equation applies in either an open or closed system.

Equilibrium pH

When $NaHCO_3$ is added to water to form a 25 mM solution, and CO_2 exchange is prevented, the log C-pH diagram (Figure 3) immediately establishes equilibrium pH = 8.20 at the intersection of the dissociation curves of the controlling products $[CO_2]$ and $[CO_3^{2-}]$ (solid circle). The millimolar concentrations depicted in Figure 3 at this equilibrium pH are

$$[HCO_3] = 24.8$$
$$[CO_2] = [CO_3^{2-}] = 0.2$$
$$[H_2CO_3] = 0.0005$$
$$[OH^-] = 0.004$$
$$[H^+] = 0.0000063$$

The diagram shows that at pH 8.2 the $[OH^-]$ line is about 0.2×10^{-1} units below the solid circle and represents a concentration $1/50$ that of the controlling products. It is therefore not completely negligible in *Eq. 1c*. Including $[OH^-]$ yields pH = 8.19.

The equilibrium pH could again be found by solving six equations (*1c* and *2–6*) replacing P_{CO_2} by T_{CO_2} as an unknown. The algebraic solution is

$$[H^+]^2 = K_1' K_2' + \ldots \text{ or } pH = 1/2(pK_1' + pK_2') + \ldots$$

The diagram clearly demonstrates the last expression by the fact that the symmetrical $[CO_2]$ and $[CO_3^{2-}]$ curves intersect at the equilibrium pH halfway between pK_1' and pK_2'.

If more $NaHCO_3$ were added to this system, all carbonate curves would simply move upward but the equilibrium intersection would not move significantly to the right. This is a diagrammatic way of showing that sodium bicarbonate is not an alkalinizing agent when injected into a closed system, a chemical fact clinically emphasized by Odell and co-workers (10,11).

Closed Buffered System, Temperature Effects

The graphical concepts of this paper are next applied to the studies of Rahn and Reeves (12), who hypothesize that vertebrate blood acid-base systems regulate to maintain a state of constant protein ionization as the temperature varies. Blood is modeled as an aqueous solution of 130 mM imidazole (Im) in a closed CO_2 system with a 25 mM total CO_2 content.

Dissociation Curves

The CO_2 dissociation curves in this system (Figure 4) are the same as in Figure 3. The equilibrium and mass balance equations for Im are $K_{Im} = [H^+]\,[Im]/[HIm^+]$ and $T_{Im} = [HIm^+] + [Im]$. The $[HIm^+]$ dissociation curve looks like a $[CO_2]$ dissociation curve with T_{CO_2} replaced by T_{Im} and K_1' by K_{Im}. Only the dissociation curves of the controlling variables are shown in Figure 4 as bold lines at 37°C.

Reactants and Products of the Reaction

The reactions are

$$CO_2 + H_2O \rightarrow H^+ + HCO_3^-$$
$$CO_2 + H_2O \rightarrow 2H^+ + CO_3^{2-}$$
$$Im + H_2O \rightarrow OH^- + HIm^+$$
$$H_2O \rightarrow H_W^+ + OH_W^-$$

The equivalents of H^+, $2H^+$, and OH^- are the products $[HCO_3^-]$, $2[CO_3^{2-}]$, and $[HIm^+]$, respectively. *Equation 1* then becomes

$$[H^+] + [HIm^+] = [HCO_3^-] + 2[CO_3^{2-}] + [OH^-] \quad (1d)$$

At 37°C the equilibrium pH is 7.4.

Equilibrium pH from Water-Ion Balance

The equilibrium pH is found at the intersection of the curves that represent each side of *Eq. 1d*. Practically, *Eq. 1d* is determined by the "controlling products"

$$\ldots + [HIm^+] = [HCO_3^-] + \ldots$$

The same water-ion balance equation applies when the temperature decreases. The imidazole dissociation curves shift to the right by 0.017 pH unit/degree because the pK_{Im} increases. But the state of ionization of the HCO_3^- and of the imidazole protein hardly changes simply because of the low pK_1' of the CO_2 system (6.1). (The HCO_3^- line is almost horizontal and $[HIm^+]$ hardly increases at all with cooling.) This is true regardless of the nearly identical temperature tracking of the pK_{Im} and $pK_W/2$ as considered in the α-stat hypothesis (12). The pH increases very nearly in proportion to the pK_{Im} because nearly all of the total CO_2 content (T_{CO_2}) exists in the form of $[HCO_3^-]$. What is not apparent on the figure is that the solubility S of CO_2 increases significantly with decreasing temperature; thus, at low temperatures a much lower P_{CO_2} can sustain a constant T_{CO_2}.

Open Buffered System, Temperature Effects

Consider the same aqueous solution of imidazole in a system open to the exchange of CO_2, so that P_{CO_2} = 40 mmHg. The $[HIm^+]$ dissociation curves are the same as in the previous section. The $[HCO_3^-]$ dissociation curves are like those of Figure 2 for the open system. The reactants and products of the reaction are the same as in the previous section, and hence the water-ion balance equation is the same, as is its practical form. Equilibrium pH occurs at the intersection of the $[HIm^+]$ with the $[HCO_3^-]$ dissociation curves. The $[HCO_3^-]$ dissociation curve shifts upward with decreasing temperature because the in-

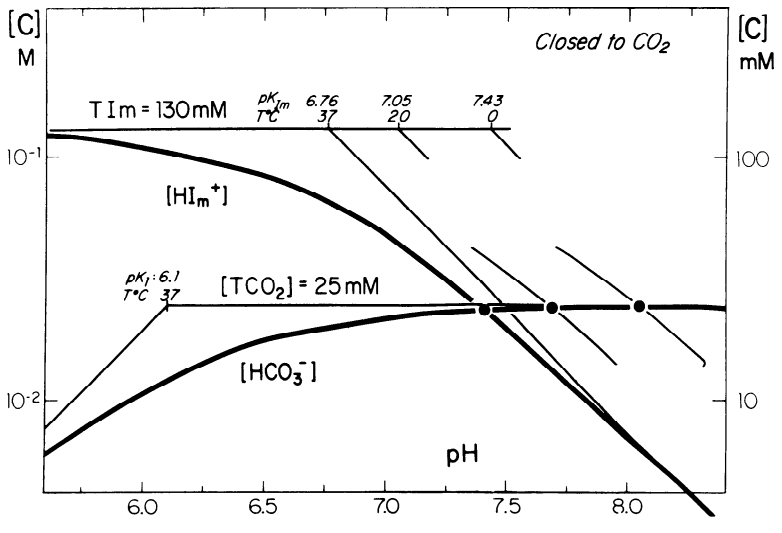

Figure 4

Graphical anaylsis of temperature dependence of equilibrium pH and ionization state of imidazole (Im) protein and bicarbonate in a closed CO_2 system. Coordinates are the same as in Figure 1. *Upper curves* represent $[HIm^+]$ for T_{Im} = 130 mM at 37, 20, and 0°C. *Lower curve* represents closed system $[HCO_3^-]$ at 37°C. Curves for 20 and 0°C are not shown because they are indistinguishable from 37°C curve in the vicinity of equilibrium. Practical water-ion balance is $[HIm^+] = [HCO_3^-]$. *Solid circles* at intersections represent temperature-dependent equilibria. pH changes nearly in proportion to pK_{Im} because nearly all of CO_2 content is in bicarbonate form at all temperatures. Im ionization fraction stays nearly constant for the same reason. Between 37 and 20°C, $\Delta pK_{Im}/\Delta T$ averages 0.017/°C. Closer examination reveals that $\Delta pH/\Delta T$ becomes progressively somewhat smaller than 0.017 as pH decreases because $[HIm^+]$-$[HCO_3^-]$ intersection moves farther below and to the right of $[HIm^+]$-T_{CO_2} intersection. This is the primary cause of decrease in Rosenthal factor below pH = 7.4

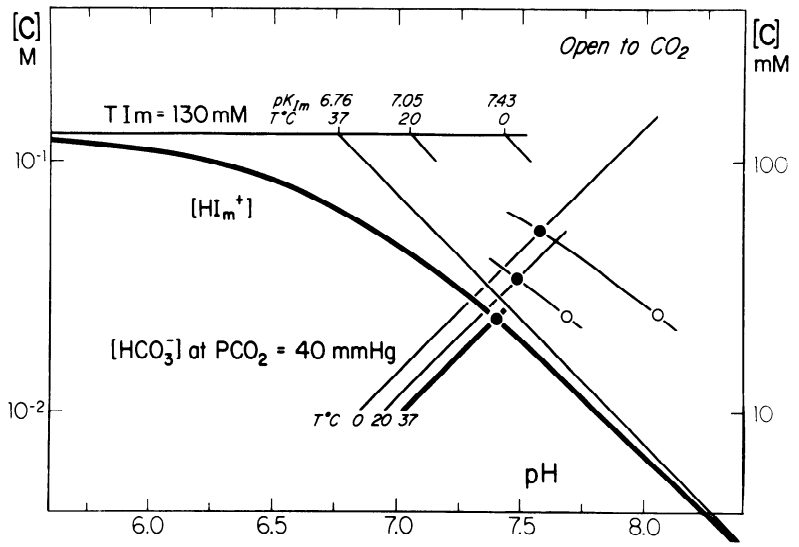

Figure 5

Graphical analysis of temperature dependence of equilibrium pH and ionization state of imidazole (Im) protein and bicarbonate in an open CO_2 system. Coordinates are the same as in Figure 1. *Upper curves* represent [HIm⁺] as in Figure 3. *Lower curves* represent open system $[HCO_3^-]$ at 37, 20, and 0°C. These lines shift to the right because of increased pK_1' and upward because of increased CO_2 solubility, the latter dominating. Hence at constant P_{CO_2} = 40, pH tends to increase only slightly and T_{CO_2} increases dramatically at *closed circle* equilibrium points. If living organism balances ventilation and metabolism to maintain constant T_{CO_2}, then ventilation must reduce P_{CO_2} to 18 mmHg at 20°C or 6.5 mmHg at 0°C to achieve equilibrium at *open circle* equilibrium point (same equilibria as in Figure 4).

creased solubility of CO_2 more than offsets the increase in pK_1. Thus at constant P_{CO_2}, the pH rises slightly while $[HCO_3^-]$ and T_{CO_2} rise significantly.

Keeping in vivo P_{CO_2} constant, a common strategy used during cardiopulmonary bypass, can be achieved by adding CO_2 to the respiratory gas mixture (8). Recent work suggests (12,16) that closely matching CO_2 elimination to CO_2 production to keep T_{CO_2} constant is physiologically advantageous. To achieve this strategy requires a level of ventilation sufficient to lower P_{CO_2} to 18 mmHg (20°C) or 6.5 mmHg (0°C) as shown by the open circles in Figure 5. This requires approximately constant or slightly reduced ventilation because metabolic CO_2 production falls with falling temperatures.

Summary

Most of the acid-base concepts we have considered were appreciated in the laboratory years ago. For example, Stadie et al. (15) anticipated many of Reeves and Rahn's equations. In 1908 Henderson (5) showed that the ability to keep P_{CO_2} constant in an open system greatly increases the buffering capacity of the body. But such biochemical truths often fail to be appreciated when expressed in the forbidding language of mathematics and are rediscovered years later at the bedside or in the operating room (4,10,11,16).

The log C-pH diagram is a means of displaying quantitatively the many variables, including temperature, that determine acid-base equilibria in biological systems. The relative importance of each species is indicated by the vertical separation of their dissociation curves at each pH. Negligible concentrations can be recognized by inspection. Concentration differences and ratios like $[OH^-]/[H^+]$, on the other hand, are often not negligible, and the diagram shows how these can be important. The inconstancy of the Rosenthal factor is explained at low pH by the small difference between T_{CO_2} and $[HCO_3^-]$. The fact that this difference is even smaller in the higher pH range of hypothermia clarifies the α-stat hypothesis. Both problems are illustrated by the relations between a straight line and a curve.

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Control of Vertebrate Respiration and Locomotion: A Brief Account

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In all skills and abilities there is timing.
M. Musashi, "Go Rin No Sho" (1645)

Man can modulate respiratory airflow at a high rate and with considerable precision to express meaningful sequences of sounds and can produce the most astounding precision work with his hands. Such complex volitional motor acts are still beyond reach for an understanding of the underlying neuronal mechanisms. A major stumbling block in unraveling such acts is that they need to be studied in humans or trained awake primates. The situation is different with (rhythmic) movement synergies such as respiration, locomotion, mastication, and the scratch reflex (e.g., 5, 9, 15, 17, 23, 24, 37, 46, 48). First, the underlying neuronal circuitry of such movements is innate; it is essential that newborn mammals breathe and suck and, in many cases, locomote. Second, they can be readily elicited under conditions favorable for application of all relevant neurobiological techniques. For example, locomotion can be elicited in the decerebrate or spinal cat and respiration continues in the decerebrate or anesthetized mammal. Moreover, the efferent motor patterns can be elicited after paralysis in reduced preparations. Third, their repetitive nature facilitates analysis. The development of such preparations in, for instance, the cat, turtle (48a), tadpole (41a), and fish (26, 49) has led to a rapid expansion of our understanding of how the central nervous system controls these types of movements. Analyses of simpler networks in invertebrates have given important insights into neural mechanisms that might apply in the more complex vertebrate nervous system (e.g., 4a, 30a, 34d, 37).

The neural substrate generating rhythmic motor patterns may be divided into four interacting components (Figure 1): *1*) a higher level responsible for the initiation and maintenance of the appropriate pattern of activity and for predictive adjustments based on environmental cues; *2*) an output stage, the motoneurons, which control muscle contraction; *3*) a brain stem or spinal network of neurons, often referred to as the central pattern generator (CPG), which when activated will produce a coordinated rhythmic pattern of input to different groups of motoneurons; and *4*) receptors activated during movement, which provide feedback necessary to adapt and adjust the ongoing movements.

Based on a tutorial lecture given at the 1982 APS Fall Meeting, San Diego.

Higher Level Control—Activation and Modulation of Movement

Any vertebrate can start or stop locomoting, change direction, or modify its gait in accordance with the environmental demands or as it so pleases. It is obvious that the nervous system has the capability to start and stop movements at appropriate times as well as modify them to environmental or internal cues. Supraspinal structures are important in this regard.

A cat decorticated at birth can still move around in an apparently normal way with well-adapted movements; it will carry out basic activities, such as seek and chew food and survive, at least in a (now) friendly environment (4, 24, 46, 48). The situation is quite different when the larger part of the diencephalon is removed as well. Although the animal can still initiate well-coordinated movements, they are very mechanical. The adaptability of the movements is lost, and the cat will no longer avoid objects and once contacting them will often try to walk through them. Breathing is relatively unaffected in these preparations.

Specific sites in the nervous system are concerned with command functions. In a variety of vertebrates, even in decerebrate animals, the central pattern generators for locomotion can be activated by stimulation in specific brain stem regions such as the subthalamic nuclei, nucleus cuneiforme in mesencephalon, pons, and the pyramids (45, 46). With weak stimulation, a slow walk may result; as the stimulation strength is increased the animal will walk faster and then switch to a trot and then even to a gallop. Thus the entire movement synergy can be controlled by a graded signal that activates descending pathways which control the general level of activity in the central pattern generators. Specific regions of the cortex, cerebellum, and brain stem will act to correct and adapt the movement to optimize the performance (see section on Role of Cerebellum).

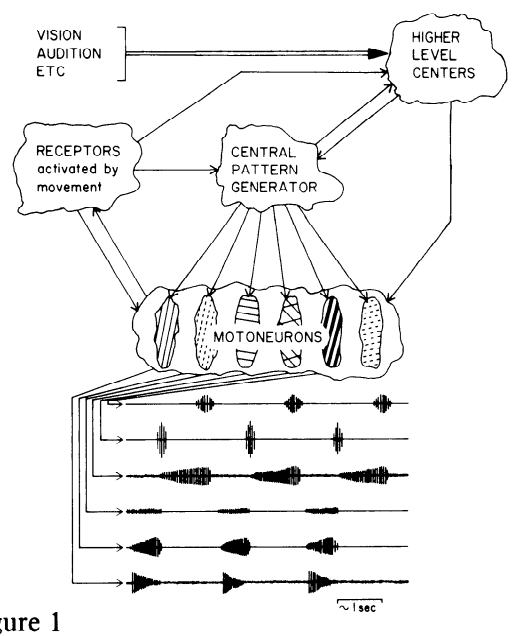

Figure 1
Generation of rhythmic movements can be considered to result from interaction among 4 components. Many different rhythmic patterns of motoneuronal activity, as indicated as neurograms at bottom, underlie resulting coordinated movement. See text for details.

Control of Motoneuronal Discharge by Excitation and Inhibition

In each movement cycle, be it a breath or a step, it is critical that the appropriate spatiotemporal pattern of motoneuronal activity be generated (Figure 1, bottom). Thus both the overall timing and absolute, as well as relative, amplitude of motoneuronal activity need to be accurately controlled; otherwise, the wrong movement will result. An increase in overall system performance, e.g., increased ventilation and faster pace, is usually produced by an increase of burst amplitude and frequency resulting from the recruitment and frequency modulation of both fast and slow motor units.

Motoneurons receive phasic excitatory and inhibitory synaptic drive from interneurons of the central pattern generator (Figure 2). The combination of rhythmic (and tonic) central pattern generator input, other input, due in part to local interactions and the biophysical, synaptic and morphological properties of the motoneurons determine the duration and frequency of the resulting spike train producing muscle contraction.

Motoneurons producing respiration are actively inhibited by interneurons during their normally silent periods (Figure 2, right), as initially demonstrated by Sears (44, see also 3). Similar patterns of inhibition are seen in motoneurons producing locomotion as well as mastication or the scratch reflex (5, 12, 30, 43, 48b). This inhibition, on top of concurrent removal of excitatory drive from the central pattern generator, prevents spurious activation that could result from receptors (or inputs of central origin) active during this part of the cycle. For the coordination of movement, the silent intervals are as important as the active periods. A noteworthy exception to this rule are jaw opener motoneurons, which lack phasic inhibition during jaw closure (5). This may be due to the need for a quick jaw opening if the teeth encounter an unexpected (hard) object during jaw closure; otherwise, serious tooth damage might result.

The viscoelastic properties of the muscle fibers activated by motoneurons together with the biomechanical system with its lever arms and mass is a major determinant of the movement trajectories that result from a given pattern of motoneuronal activity. Obviously, movement control cannot be understood without considering the apparatus at the disposal of the central nervous system (CNS), but that is not our concern in this article (see 22).

Neural Generation of Movement Synergies

Interaction of Central and Peripheral Elements (Figure 3)

The capacity for rhythmic motor output remains after manipulations that eliminate movement-related afferent feedback, such as neuromuscular paralysis or transection of afferent fibers. The motor activity in the absence of such feedback resembles the complex pattern of the intact state; it does not revert to a simple synchronized alternating rhythm (5, 9–11, 15, 17–19, 24, 27, 39, 48a, 50). Motoneurons do not play any direct role in generating their rhythmic inputs. The central networks that produce such patterns, which are located in the brain stem and/or spinal cord, are usually referred to as central pattern generators (Figure 1).

Even though a complex motor output may be produced by the central pattern generator in isolation, the full behavior requires intact afferents, which can modify the degree and duration of activity of individual muscles and the overall muscular coordination (Figure 3). In respiration, for instance, pulmonary stretch receptors activated during inspiration by lung inflation will shorten the phrenic nerve burst duration without necessarily altering the augmenting burst envelope (Figure 4). On the other hand, as elegantly shown by Cohen (8), inspiratory and expiratory recurrent laryngeal nerve activity is both shortened and reduced in magnitude, going from a plateau-like discharge in the absence of lung inflation to a gradually decreasing discharge with lung inflation (Figure 4) (see also 19). These changes are of importance in coordinating upper airway resistance, controlled in part by recurrent laryngeal nerve activity, with tidal volume during inspiration, controlled in large part by phrenic nerve activity. In other motor acts, no such precise change of the burst shape has been defined, although such effects most likely exist.

Afferent input plays a major role in control of the overall timing and pattern of activity. In respiration, von Euler and colleagues (6, 15) showed that increased chemoreceptor activity produced by increases in inspired P_{CO_2} in a vagotomized (this abolishes pulmonary stretch receptor feedback) cat will cause an increased inspiratory burst amplitude, a shortening of expiratory duration, but little or no change in inspiratory duration. With pulmonary stretch receptor feedback present (vagus intact), inspiratory burst duration will also

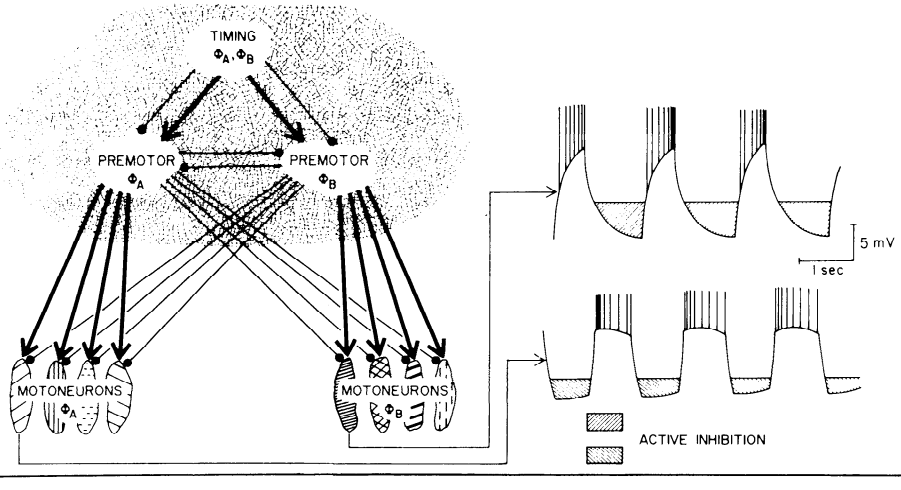

Figure 2
Active inhibition of motoneurons (and often premotor neurons) during their normally silent phase is important in coordinating rhythmic movements. *Left:* schematic of pathways responsible for this inhibition. *Arrows* represent excitation; *closed circles* represent inhibition. *Right:* examples of membrane potential shifts in 2 antiphasic motoneurons.

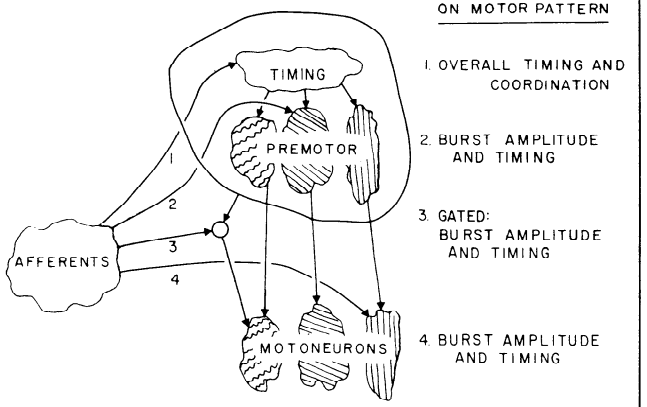

Figure 3

Afferents can alter rhythmic movements in a variety of ways as listed at *right*. Numbers correspond to pathways labeled at *left*. Possible pathways for these effects are indicted in schematic (*left*). Interneuronal gating could also be due to afferent modulation of interneuronal activity. See text for details.

shorten. Thus pulmonary stretch receptor afferents have a major effect on overall timing and selective effects on burst amplitude (Figure 4), and CO_2-sensitive chemoreceptor afferents will directly modify burst amplitude and timing.

In locomotion, feedback from the moving limb can control the duration of the support phase (Figure 3) in such a way that if the movement proceeds slower than expected, due to an unanticipated change in terrain, for example, the support phase will be prolonged, so that the step is not terminated prematurely. Conversely, if the step proceeds faster than planned the limb will go into flexion earlier. The feedback serves to adapt the limb to the various conditions it will meet in a demanding environment. It forms an integral part of the control system under all conditions but is of particular importance when the demands are high, such as when an animal rapidly accelerates to top speed or chooses to stop, turn, and so forth (2, 24, 38).

Phasic Gating of Reflex Effects

When a cat walks and a small twig touches the dorsum of the foot as the limb is moved forward during the swing phase, an elegant further elevation of the foot will be elicited, lifting the foot over the twig. A short-latency reflex path involving a few segmental interneurons is responsible (Figure 3). An identical light stimulus applied during the support phase of the step will not cause a flexion but may instead excite extensors. This is a very meaningful change in response pattern inasmuch as extension during the support phase will increase stability, whereas a reflex flexion would make the animal fall over. In each case, the ongoing phase of locomotion is enhanced, though by different alterations in motor output (20, 21). Similar phase-dependent responses occur, for example, during chewing (33) and fish swimming (49).

These phase-dependent changes in reflex response are seen with identical, except for timing, peripheral afferent stimulation. What are the mechanisms of this reflex gating? One is due to central pattern generator-induced oscillations in membrane potential of motoneurons and/or premotor neurons (Figure 5). An excitatory synaptic potential occurring during the depolarized phase may activate a number of motoneurons to fire, whereas the same synaptic potential occurring during the hyperpolarized phase may not be sufficient to elicit any action potential from any motoneuron. In addition there is a phasic gating of neurons in the reflex pathways to the motoneurons (1, 31). This gating arises from the central pattern generator (Figure 5), and it can depress the amplitude of the synaptic potentials in that phase when reflex effects would appear to be undesirable.

Since the degree of depolarization-hyperpolarization can vary significantly within a given phase and in different types of neurons, afferent effects would be expected to vary within a given phase, as well as between two different phases. An example of gating within one phase is seen with carotid sinus nerve stimulation, which has little effect on inspiratory motor pattern when delivered early in inspiration but has a marked effect that augments in strength during the second half of inspiration (13). It has been hypothesized that oscillations in carotid sinus nerve activity due to the changes in blood gases with the respiratory cycle are an important component of the information present in the signal. If so, the within phase changes in response to this activity would act as a sensitive detector of phase information in the oscillation.

Neuronal Organization of Central Pattern Generators

We have limited knowledge about how the nervous system generates the different motor acts. The last level of interneurons, often called premotor neurons, which

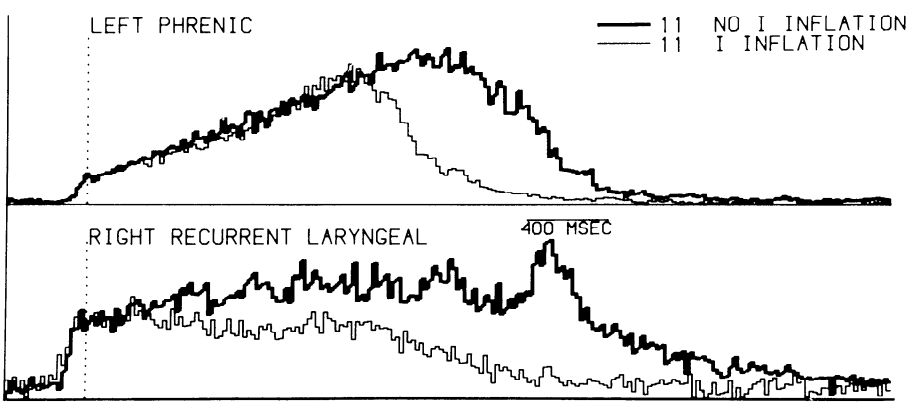

Figure 4

Changes induced in phrenic and recurrent laryngeal nerve activities by altering pulmonary stretch receptor afferent activity during inspiration (I). Traces are histograms of whole nerve activity during 11 cycles with/without (*thin/thick line*) inspiratory (I) coincident lung inflation in a paralyzed anesthetized cat. Note decrease in duration of activity with lung inflation and that recurrent laryngeal nerve activity is selectively depressed. (Redrawn from Figure 2 in Ref. 19).

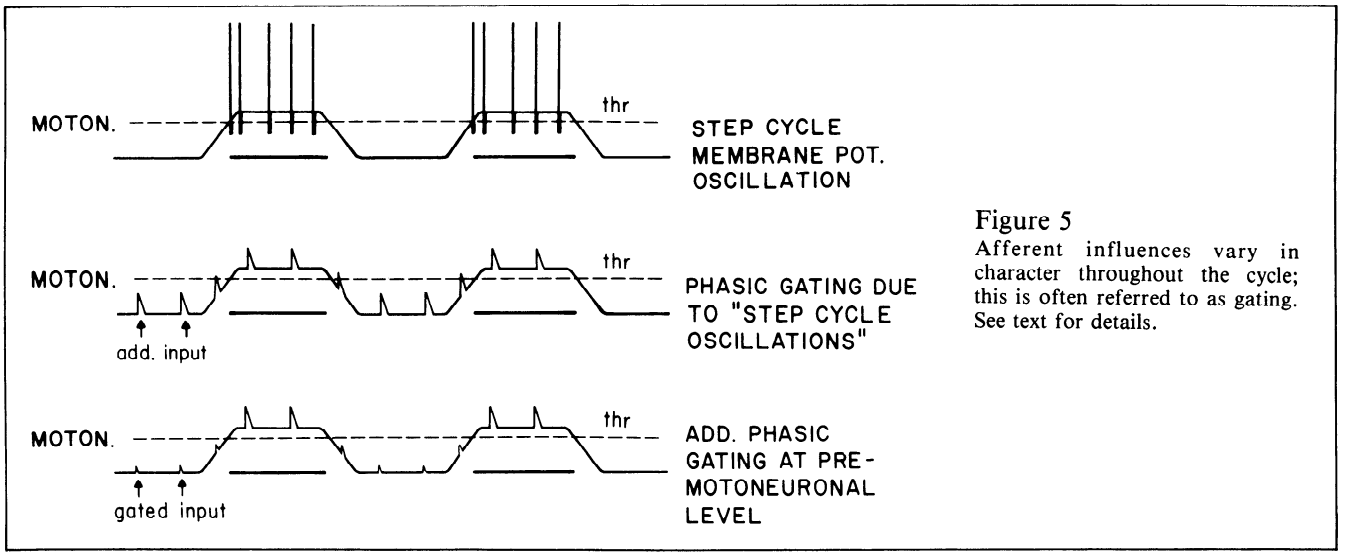

Figure 5
Afferent influences vary in character throughout the cycle; this is often referred to as gating. See text for details.

directly excite or inhibit motoneurons, is the best known (Figure 2). In mammalian respiration, descending neurons from the brain stem (nuclei tractus solitarius and retroambigualis) are excitatory premotor interneurons and neurons near the retrofacial nucleus are inhibitory premotor neurons (9, 15, 17, 34b). These premotor neurons directly effect respiratory-related motoneuronal activity. The subgroups of inspiratory and expiratory premotor neurons are themselves subject to reciprocal inhibition (41), presumbly to ensure an alternating pattern of activity (Figure 2). For some time it was thought that these premotor neurons were an essential part of the machinery that generates the overall cycle timing, but recent experiments suggest that this is not likely (17, 34a, 47a).

In locomotion, the essential features of the movement synergy can be produced by spinal animals. One type of segmental premotor neurons, called Ia inhibitory neurons, are utilized by the central pattern generator to inhibit motoneurons during their normally quiescent period (12, 16, 34). Subgroups of these interneurons project to antagonistic motor nuclei and are themselves subject to reciprocal inhibitory interactions (28) similar to the organization of respiratory premotor neurons. Another type of interneuron, the Renshaw cell, is also rhythmically active (34). Renshaw and Ia interneurons do not have any (major) role in rhythm production, but they do contribute to shaping the motor output. Although spinal interneurons that are likely to take part in rhythm generation have been found (12, 29), their precise role has yet to be determined.

Although some knowledge of the organization of premotor neurons has been gained, we do not yet understand how central pattern generators operate. Rhythmic activity could be generated by a variety of circuits ranging from single pacemaker neurons to complex networks of nerve cells. The final output pattern depends on the interactions of all neurons in the network.

If any light is to be shed on how the CNS uses its nerve cells to generate or modify a movement synergy, we need to know the functional role of the individual elements. Ultimately, this cannot be done unless measurements are made during the actual production of motor patterns. The fact that the networks for respiration, locomotion, mastication, and the scratch reflex can be studied in operation in paralyzed reduced preparations (decerebrate, spinal, or anesthetized) is of critical importance in this regard, as all relevant experimental tools can then be utilized, particularly those that allow analysis of the data in the context of the behavior. During the last few years an explosion of facts concerning the projections, transmitters, and synaptic properties of individual nerve cells and systems has taken place. As yet most of these findings have not been firmly tied to function in behavioral contexts.

The conditions now appear favorable for discovering the secrets of how the vertebrate central nervous system controls movements of intermediate complexity, such as repiration and locomotion. A lot of hard and challenging work lies ahead. The scope of this challenge is suggested by the factors that will decide the output and the operation of a neuronal network, which include *1*) the connections between all nerve cells in the network; *2*) the properties of individual synapses, including transmitters, location, the time course and amplitude of postsynaptic potentials, fatigability, and type(s) of ionic channels; and *3*) the membrane properties of the individual cells, including the role of the different ionic channels, the specific membrane resistance, and the cell morphology, particularly the relation of the dendritic tree to the spike initiating zone. Of special importance are the factors that will decide the firing properties of the cells (e.g., afterhyperpolarization), whether a cell responds with long-lasting potentials or even has an inherent tendency to oscillate as a pacemaker neuron.

At present, it is technically impossible to obtain information about each and every component of the pattern generator mechanisms; it is not certain that a complete description is necessary. Measurements of representative parts of the system should provide an adequate sample for synthesis of **testable** models. As yet, a statistical mechanics of the nervous system that would permit deductions based on readily measurable elemental properties has not been developed. Moreover, although we set as our goal the understanding of these movement synergies in man, the complexity of the mammalian nervous system might obscure the basic organizational principles. These limitations suggest the prudence of pursuing studies on lower vertebrates in parallel with studies of higher vertebrates, since the former have fewer neurons; this permits a more detailed and complete analysis (e.g., 41a, 48b). As an example of the former, the neuronal correlate of swimming can be

elicited in the lamprey, even under in vitro conditions (9, 26, 42). The role of individual neurons may start to be unraveled in such preparations.

Protean Nature of Central Pattern Generators

What changes in central organization are responsible when locomotion goes from walk to trot to gallop or when respiration is altered with sleep-wake state (17, 24, 40)? Although it is possible that separate central pattern generators produce related, but perhaps somewhat different movements, parsimony would argue for some degree of overlap. There are at least two nonexclusive possibilities.

1) The basic components producing the pattern are similar in different states, but the relative contribution of each element and/or the characteristics of their interactions (e.g., strength, sign) change.

Consider, for example, changes in locomotor pattern in quadrupeds. A separate spinal cord central pattern generator controls each limb during locomotion. The coordination of the individual central pattern generators is via interneurons, refered to as coordinating neurons (cf. 24, 28). A cat can coordinate its legs in a variety of ways in locomotion. In walking and trotting, the hindlimbs alterate, but in galloping and, in particular, in bounding they act in approximate synchrony. A simple control strategy can produce this striking change in coordination (Figure 6, left). Suppose that the two hindlimb central pattern generators are connected by two separate sets of coordinating fibers, the first producing mutual excitation leading to approximate synchrony (e.g., gallop, bound) and the second producing reciprocal inhibition leading to alternation (e.g., walk, trot). The switch from one type of pattern to another could be accomplished simply by enabling one set of coordinating fibers and disabling the other. The connection between hind- and forelimbs would be controlled in a similar manner to switch, for instance, from trotting to pacing, as a horse readily does. The same reasoning has been applied to suggest how the CNS can generate forward and backward locomotor synergy in a single limb, which requires a phase shift of 180° between hip and knee movements (12, 24, 25); in this case a parcelation of the limb locomotor pattern generator would be required.

2) Different elements are involved in the generation of pattern in different states, with the possibility of considerable overlap. Thus whole populations of cells that might be quiescent in one state could underlie the production of pattern in another state.

In respiration, there is evidence that there are different elements involved in the generation of inspiratory pattern that depend on the relative state of activity of pulmonary stretch receptors and neurons in the dorsolateral rostral pons, referred to as the pontine respiratory group (17, 18).

The abrupt termination of phrenic activity in cat (see Figure 3) is fundamentally altered when small lesions are placed in the pontine respiratory group and there is no phasic pulmonary stretch receptor activity (9, 15, 17). This suggests that these two systems contribute to the production of inspiratory termination. When one compares the activity of pontine respiratory group neurons with and without phasic stretch receptor activity produced by lung inflation, a striking difference is observed (18). When the lungs are not inflated in a paralyzed cat, pontine respiratory group neurons show a marked inspiratory modulation. However, inspiratory coincident inflation of the lungs abolishes this respiratory modulated discharge, although tonic activity persists.

This observation suggests a state-dependent change in the part of the central pattern generator producing inspiratory pattern (Figure 6, right). In each state (lung inflation, no lung inflation), either pulmonary stretch receptors or pontine respiratory group neurons provide phasic contributions to the production of inspiratory

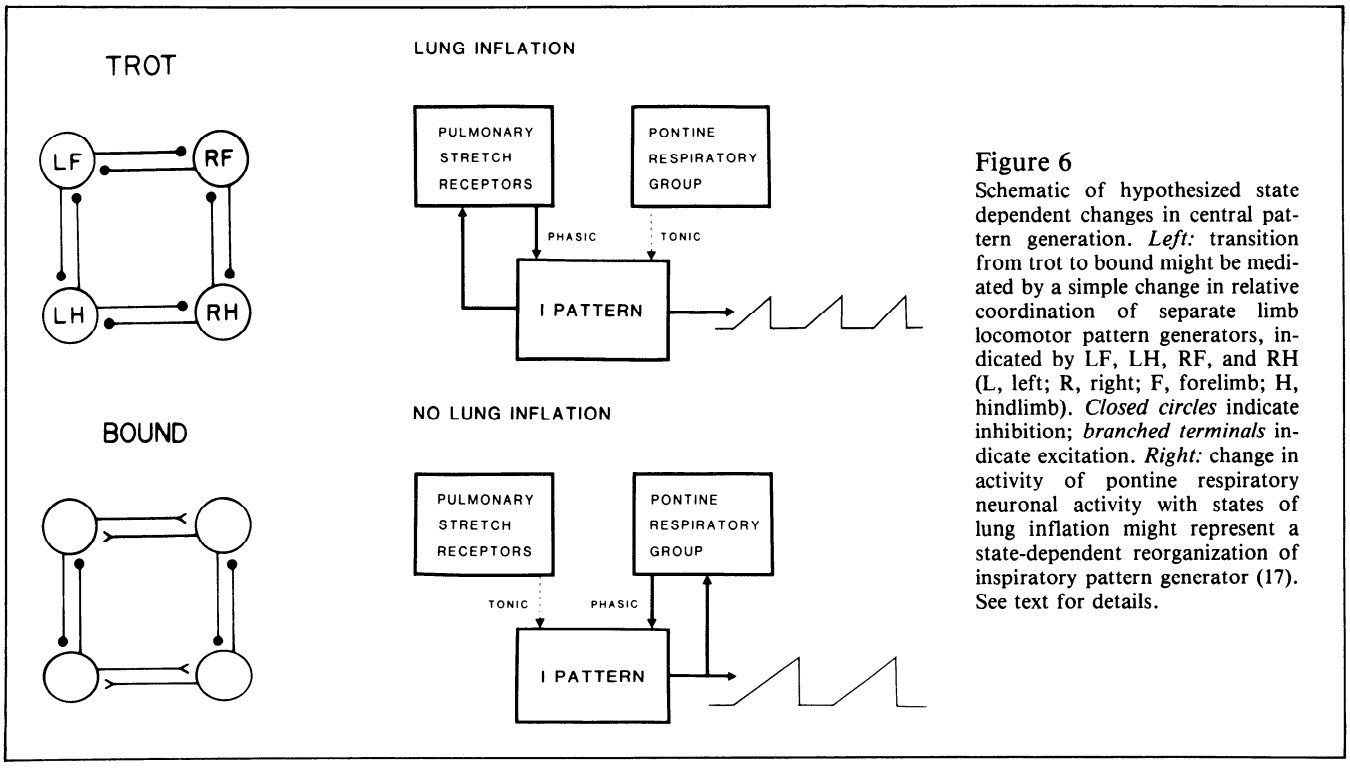

Figure 6
Schematic of hypothesized state dependent changes in central pattern generation. *Left:* transition from trot to bound might be mediated by a simple change in relative coordination of separate limb locomotor pattern generators, indicated by LF, LH, RF, and RH (L, left; R, right; F, forelimb; H, hindlimb). *Closed circles* indicate inhibition; *branched terminals* indicate excitation. *Right:* change in activity of pontine respiratory neuronal activity with states of lung inflation might represent a state-dependent reorganization of inspiratory pattern generator (17). See text for details.

phase transition with the other group providing only a tonic input. Thus the hypothesis is that there is a flip-flop in the source of phasic and tonic inputs to the respiratory pattern generator during certain state transitions.

Of course, these different experimental states do not exist in intact preparations. However, there is strong evidence that the degree of respiratory modulated pontine respiratory group neuronal activity varies with the sleep-wake state (32, 47), suggesting the possibility that a state-dependent reorganization of the respiratory pattern generator contributes to the marked changes in breathing with the sleep-wake cycle.

Role of Cerebellum

Decerebellate animals can walk and breathe, and it is therefore apparent that the cerebellum is not necessary for the generation of the basic movement synergies. On the other hand, the overall coordination in locomotion is degraded, as the movements are clumsy, with foot placement less precise and the interlimb coordination less exact. Orlovsky and colleagues (35, 36, 46) in Moscow have shown that the cerebellum receives two types of information concerning locomotor events in each step cycle: *1*) detailed information about the actual movements the limbs are making is transmitted via the dorsal spinocerebellar tract; and *2*) information about the output signals is transmitted to the motoneurons from the central pattern generator (efference copy). The ventral spinocerebellar tract informs about flexor commands and the spinoreticulocerebellar tract about extensor commands. This information is processed in the cerebellum and results in phasic activity in the main output pathways from the cerebellum to the spinal cord, leading to phasic modulation of vestibulospinal, rubrospinal, and reticulospinal neurons. These signals contribute to the perfection of the movement in each step cycle.

Integration of Rhythmic Movements

Although the rhythmic behaviors we have discussed can be elicited in relative isolation from other behaviors, particularly in reduced preparations, they are usually integrated with each other. Thus we can walk, breathe, and chew gum at the same time (although it has been suggested that this integration is adversely affected by playing too much football without a helmet).

The coordination of respiration with locomotion may be considered in two contexts: *1*) Locomotion uses energy, which increases O_2 consumption and CO_2 production. The resulting increase in ventilation is usually well matched with metabolic requirements. Both neural and humoral mechanisms contribute to this tight coupling (11a). An interesting observation was made by Eldridge et al. (14), who showed that electrical stimulation of the cat hypothalamus will both increase ventilation and induce locomotor activity. This suggests that higher levels can increase respiratory output in proportion to the locomotor drive, i.e., in anticipation of need. *2*) Locomotor and breathing patterns that have minimal energy costs are favored (27a, 34c). Although ventilation must increase during locomotion, the breathing pattern will depend on the pattern of locomotion and will certainly be different from that seen at equivalent ventilations in a stationary animal. It is commonly observed that the frequency of breathing is coupled to the rhythm of locomotion in intact animals (4). In spinalized paralyzed rabbits, synchronization of locomotor and respiratory motor nerve activity is observed (51). Since there is no evidence for a spinal respiratory pattern generator (see 9, 17), this suggests that the respiratory motoneurons in this case are activated by locomotor pattern generators.

It should also be kept in mind that rhythmic movement synergies are basic components of many of even the most refined behaviors. Respiratory control of airflow is basic to phonation and locomotion is the basis of prey catching as well as play.

Conclusion

Rhythmic motor acts are innate and among the most basic of neural outputs. They represent perhaps the most complex form of vertebrate behavior that can be studied in both intact and reduced vertebrate preparations. In the broadest sense, we have a conceptual grasp of the underlying neural organization. Research is progressing rapidly within this framework.

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Hormonal Control of Fetal Growth

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The contribution of hormones to the growth of juvenile and older animals is well documented, with growth hormone (GH) and thyroid hormones (TH) being the major growth-promoting factors (11, 50). Insulin has an essential permissive function, the sex steroids play a minor role in growth, and the adrenal steroids are contributory (11). In recent years a convincing body of evidence has accumulated to indicate that somatomedins (SM) also play an important role in mammalian growth (11). Some studies indicate that neonatal and infant mammals may be less dependent on pituitary or thyroid hormones for growth than are older animals (20, 37). In addition, striking differences in the hormonal requirements for skeletal growth occur between infancy and adulthood in the rat. The young animals are relatively more responsive to TH and less responsive to GH than are older rats (20). These differences between infant and juvenile rats suggest that the dependence on TH and GH for growth may change with development in mammals. Thus mammalian embryos or fetuses may be even less dependent on these and other hormones than are neonates or infants, or they may be dependent on different growth-promoting hormones.

Despite numerous studies, the role of hormones in the regulation of fetal growth remains obscure because several obstacles have precluded definitive analysis of endocrine involvement in this process. The hormonal environment during pregnancy is complex and difficult to control experimentally, because maternal, fetal, and placental hormones are all potential modulators of fetal growth. In addition, the procedures used to study this process all have shortcomings. Thus it has been difficult to obtain definitive data on some questions, and there are unsettling differences in apparent hormonal dependence among species. In this review we shall summarize the pertinent research with special emphasis being given to recent developments, and we shall also present some of our own data that were obtained using a new method for studying this question.

Studies on the endocrine regulation of fetal growth have involved six major approaches: endocrine ablations; examination of infants with congenital endocrine deficiencies; treatment of mothers, fetuses, or neonates with drugs, hormones, or antiserum to hormones; measurement of hormone concentrations and receptor levels during normal and abnormal development; and in vitro studies. We shall consider only some of these methods in this review.

Tutorial lecture given at the 1982 APS Fall Meeting, San Diego.

Effects of Endocrine Ablations and Congenital Deficiencies

Jost (37) was one of the first investigators to use endocrine ablation to study possible hormone involvement in fetal growth. He deprived rabbit fetuses of their pituitary glands by decapitation and found that growth of the remaining body was not affected by the lack of the fetal pituitary. The effects of fetal hypophysectomy (HX) were subsequently tested in other species. These data, combined with observations on human infants born with pituitary aplasia or congenital GH deficiency, are presented in Table 1. The fetal pituitary is not a major contributor to fetal growth in five species but appears to have a significant effect in monkeys (56) and sheep (45). Although several studies indicate that the pituitary is not a major contributor to fetal rat growth (37), Heggestad and Wells (29) claimed that a significant growth decrease occurred after decapitation and this effect could be reversed by GH replacement.

Although there is one claim that newborn humans with GH deficiency are smaller than normal (43), most other reports on human neonates with congenital GH deficiency state that they are normal or near normal in size (46, 63). Furthermore, SM levels in anencephalics are near normal, and there is no correlation between serum GH and SM levels in umbilical cord blood (21). Thus it appears that fetal GH is unessential for normal fetal growth in most mammalian species.

The effects of fetal hypothyroidism, caused either by surgical or chemical thyroidectomy (TX), or by a congenital lack of the thyroid gland, on growth of fetuses has been studied in a number of species (Table 2). Although TX of sheep and monkey fetuses causes a significant inhibition of their growth, rabbit and human fetuses appear to be relatively independent of their own TH for growth. Again, there is conflicting evidence regarding the effects of lack of TH in the rat. In one report, administration of a goitrogen to pregnant mothers decreased pup weight (15), whereas other studies involving TX of fetal rats reported no growth decrease (16). The importance of TH for growth of fetal monkeys is clearly indicated by a study in which the fetuses were encephalectomized, but their pituitaries were left in situ. Although their serum GH was reduced, their thyroid function was normal, and the fetuses showed no decrease in growth (40). These results suggest that growth decreases that accompany fetal pituitary removal may not be due to lack of GH per se but instead may result from the attendant hypothyroidism, as suggested by Gluckman et al. (23), who point out that the species which show growth decreases following HX also show decreased growth following TX.

Studies of Hormone and Receptor Levels

Measurements of hormone levels have been made in the fetuses of humans, sheep, and a variety of laboratory animals throughout gestation. Information on the ontogeny and level of hormones in fetuses permits inferences to be made about which hormones may be important for fetal growth and when these hormones may become a significant factor. For example, GH and SM in serum rise during the third trimester in sheep fetuses (5), suggesting that these hormones may become important for fetal growth near term (see below).

Table 1
Effects of Fetal Pituitary Hormone Deficiency on Fetal Growth in Different Species

Species	Cause of Hormone Deficiency	Duration of Pregnancy	Period of Observation	Growth Change	Ref.
Human	Congenital pituitary hypoplasia, congenital GH deficiency	9 mo		None	46, 63
Pig	Decapitation	113 days	Day 42 to term	None	9
Monkey	Hypophysectomy	157 days	Days 74–85 to 147	−40%	56
	Hypophysectomy		Days 114–117 to term	None*	25
Rabbit	Decapitation	29 days	Day 24 to term	None	37
Mouse	Decapitation	19 days	Day 16 to term	None	17
Rat	Decapitation	22 days	Days 13–19 to day 21	−20%†	29
			Days 16–20 to term	None	37
Sheep	Electrocoagulation of pituitary	147 days	Days 95–124 to term	−21%	45

*Although growth of the HX fetuses in this study was reduced by approximately 20%, gestation length was somewhat shortened in the HX animals and, due to the relatively small number of experimental animals, the weight decrease seen in the HX fetuses was not statistically significant.

†Although slight decreases in growth of rat fetuses following HX are commonly observed, Jost (37) states that any surgical intervention into the uterus will result in decreased fetal size, and that this, and not the lack of pituitary hormones, is the cause of the smaller size seen in HX fetuses. In support of this view, a report that normal sized HX fetuses are sometimes found in HX litters has appeared (3).

Table 2
Effects of Thyroid Hormone Deficiency on Fetal Growth in Different Species

Species	Cause of TH Deficiency	Duration of Pregnancy	Period of Observation	Growth Change	Ref.
Human	Congenital hypothyroidism, anencephaly, congenital pituitary aplasia, RTX	9 mo		None	33
Rabbit	STX	29 days	22 or 23 to 25, 28 or 29 days	None	37
Rat	Goitrogen treatment of mother	22 days	Days 15–22	−6%	27
	STX		Days 19–21	None*	35
Sheep	STX	147 days	Days 81–96 to term	−33%	33
Monkey	RTX	168 days	Days 71–88 to 150	−13%	38

STX and RTX, surgical thyroidectomy and radiothyroidectomy, respectively.

*Although the body weight of TX fetuses was 9% less than that of controls, this difference was not significant.

Likewise, the late appearance and low levels of GH in the rat fetus suggest that it is not substantially involved in the prenatal growth of that species (65).

In recent years, better systems for studying hormone levels in vivo have been developed for sheep and monkeys (8, 51). These methods have allowed continuous sampling of fetal blood through gestation with a minimum of trauma to the fetus, and the times of appearance and the levels of various hormones in the ovine fetus have been well documented (51). Furthermore, these systems permit analysis of the development of the control mechanisms for hormone secretion. For example, in the chronically catheterized sheep fetus at 90 days of age, somatostatin results in a significant decrease in circulating GH, indicating that the somatotropes are responsive to this hypothalamic hormone at that stage of gestation (23).

Studies on hormone receptor levels in tissues provide important correlative data to measurements of fetal hormone levels; they indicate when tissues may become capable of binding and responding to various hormones and have been useful in making inferences about the possible involvement of SM, insulin, epidermal growth factor, and GH as fetal growth promoters (16, 22, 72).

In Vitro Techniques

These procedures are useful for studying the ability of isolated fetal cells and tissues to respond to hormones (2). The important advantage of in vitro studies is that they permit fetal tissue to be examined under highly controlled conditions. In addition, isolated fetal cells such as chondrocytes and fibroblasts can be studied in pure preparations, eliminating the complications that normally arise in examining hormone responsiveness of a heterogenous tissue. For example, ovine placental lactogen (oPL) stimulates SM-A production in isolated fetal rat fibroblasts in vitro, indicating that oPL may be an important factor in controlling antenatal SM-A production (1). Other studies have shown that fetal tissue can respond to SM, TH, and insulin in vitro, which suggests that these hormones may have a role in fetal growth (30, 50).

Hormones Implicated in Promoting Fetal Growth

In addition to GH and TH, the involvement of several other hormones in fetal growth has been investigated. Evidence that insulin is important for fetal growth has come from a variety of sources. The offspring of diabetic mothers are larger than normal (30) because the hyperglycemia in the mothers exposes their fetuses to unusually high levels of glucose, which increase fetal insulin secretion (58). The increased insulin stimulates fetal weight gain, due predominately to increased fat deposition, but skeletal growth is increased slightly (57). Other evidence suggesting that insulin has a role in fetal growth comes from the observations that human newborns with pancreatic agenesis have decreased birth weight and length and are markedly deficient in fat and muscle development (37) and that injection or chronic infusion of insulin into rat or monkey fetuses, respectively, results in increased fetal weight (61, 70). Attempts to use experimental animals as models for the diabetic mothers have yielded inconsistent results. A recent report indicates that inducing diabetes in pregnant rats results in neonates that are larger than normal in weight (39), but other investigators found no increase in the weight of the offspring (see 39).

Placental lactogen (PL) is secreted by the fetal portion of the placenta and has been repeatedly proposed as a possible fetal growth promoter. Although the amino acid sequence of human (h) PL is very similar to that of hGH (52), the biological activities of the former are more like that of a prolactin (24). However, ovine (o) PL is more GH-like in its biological properties than is hPL. Ovine PL increases serum SM levels in HX rats and ornithine decarboxylase activity in the brain and

liver of neonatal rats (6, 34), and it partially restored growth of HX infant rats (Glasscock and Nicoll, unpublished observations). In addition, in fetal rats oPL stimulated amino acid uptake by the diaphragm in vitro (19). Neither ovine nor rat GH was effective in these tests in the fetuses. Furthermore, it has been suggested that PL maintains the relatively normal levels of SM in the HX pregnant rat (12, 14). However, some evidence raises questions about the role of PL in fetal growth. hPL has little or no growth-promoting activity in various growth tests in animals (24), and two reports have appeared of human neonates of normal size at birth whose mothers had undetectable immunoreactive hPL during pregnancy (4, 55). One of these children was examined at 4 yr, 7 mo of age, and it was found that he continued to grow normally in the infant and early childhood period. Analysis of the genomic DNA of this individual revealed that he had a gene deletion for hPL, yet his normalcy suggests that hPL may be unnecessary for fetal growth in particular and for human reproduction in general (73). However, it would be of interest to know whether these mothers compensated for the lack of hPL by secreting increased amounts of GH, and/or prolactin (PRL).

In humans and monkeys, the secretion of PL is almost unidirectional, with fetal serum levels being only a fraction of those measured in the mother (24, 56). Hence the primary functions of the hormone in these animals are apparently in the mother. Accordingly, the prevailing view on the function of hPL during pregnancy, expounded by Grumbach et al. (24), is that it acts to alter maternal metabolism to insure that the fetus will receive ample nutrition. On the other hand, in sheep and cows the PL is secreted preferentially into the fetus (48, 66). Hence, the hormone may be of more significance for growth of fetal ungulates than for growth of fetal primates. However, although oPL does have GH-like effects in rats, it has not been shown to have such effects in sheep. Thus it has not been demonstrated that any placental factors (including PL) have growth-promoting effects in homologous fetuses. The effects of oPL in rats (6, 19, 34) could simply reflect heterologous hormone effects (see 53, 54).

Prolactin has also been suggested as a possible fetal growth promoter, mainly due to its growth-promoting actions in nonmammalian species, and to some data which suggest that it may be involved in neonatal growth (54, 68). It is well established that PRL functions as a growth hormone in larval amphibians (53). Furthermore, injections of an antiserum to mouse PRL into neonatal mice (68) or administration of bromocriptine (CB-154; a drug that inhibits PRL secretion) into neonatal rats (54) resulted in decreased growth. However, in studies on infant rats, which show a 40-50% decrease in growth following HX, Glasscock and Nicoll (20) found that PRL injections had no restorative effect.

A rapidly growing body of evidence links SM to fetal growth. There is a positive correlation between SM levels and birth size of human infants, and low SM levels have been reported in infants with intrauterine growth retardation (18). Laron's dwarfs, who have low SM despite high GH levels, show a reduction in birth weight (42). Receptors for SM have been detected in a variety of fetal tissues, and the levels of these receptors sometimes exceeded those of maternal tissue (16). In addition, fetal human chondrocytes are responsive to SM (16).

The findings by Daughaday et al. (13) and Moses et al. (49) that SM-A and multiplication-stimulating activity (MSA), a form of SM found in the rat, are high in fetal and neonatal rats have been interpreted as evidence that a special form of SM could be important in fetal growth. In addition, fetal rat liver can secrete bioactive SM in vitro (62), and D'Ercole et al. (15) have postulated that SM may function as an autocrine or paracrine regulator of fetal growth, based on their findings that several fetal mouse tissues can secrete SM in vitro.

Epidermal growth factor, which has attracted much attention in recent years because of its actions on a wide range of cells in vitro, has also been suggested as being involved in some aspects of fetal growth (72).

Problems with Existing Methodologies

Although the experimental approaches described above have provided useful information, none of these procedures is totally satisfactory. Surgical approaches for determining fetal hormone dependence and/or responsiveness, such as fetal HX or TX, are technically difficult due to the relative inaccessibility and small size of the fetuses of most laboratory species. Furthermore, Jost (37) has shown that any type of surgical invasion of the uterus results in substantial growth inhibition of rat fetuses. Thus interpretation of results obtained from procedures such as fetal hypophysectomy by decapitation is confounded by the severe trauma to the fetus. Other factors complicate the interpretation of experiments that involve manipulations or treatments of either the mother or the fetus. Various abnormal conditions can alter placental growth and/or function, which in turn can affect fetal growth. Anencephaly of human fetuses reduces the size of the placenta (32), and HX of pregnant rats reduces the size of their placentas (41). Furthermore, cigarette smoking by pregnant women reduces fetal size by diminishing placental blood flow (26).

Although maternal growth-promoting hormones do not normally cross the placenta in appreciable quantities (50), placental passage of such hormones may change in abnormal endocrine states in the mother or the fetus. For example, fetuses that are HX or TX may not be completely deficient in TH because adequate quantities of these hormones may be transferred from the mother when the fetus is TH deficient. Such "compensatory placental transfer" may account for the presence of TH even in athyroid human fetuses (50).

The placenta of some mammalian species produces pituitary-like hormones, and some of these may have growth-promoting actions (e.g., sheep PL) (71). The chorionic gonadotropin produced by human placentas is gonadotropic and thyrotropic, and the placenta also produces a separate material with thyroid-stimulating hormone (TSH) activity (28). Thus HX of the fetus may not create any functional hormonal deficiency if these placental factors are secreted into the conceptus in significant quantities.

Studies on fetal hormone levels are inconclusive because the presence of even high levels of a hormone which is growth promoting postnatally does not necessarily mean that the hormone is growth promoting prenatally. Receptor studies also must be interpreted carefully; in the fetal sheep liver, GH receptors are pres-

ent, but binding of GH to these fetal receptors has no demonstrable effect (22). Furthermore, injection into a fetus of a hormone which does promote fetal growth might not result in a demonstrable growth increase if the fetus already had adequate levels of that hormone and was growing maximally (69).

In vitro techniques have been of limited value in studying the development of whole fetuses or portions of fetuses. It is impossible to sustain whole fetuses to advanced stages of development due to problems of gas exchange and nutrition for the rapidly growing tissue, and culture systems for structures such as limb buds have been plagued by limited growth and the inability to obtain normal histological differentiation (44). However, a recent report on successful in vitro culture of mouse embryos to an advanced stage of development (7) suggests that useful information may be obtained with this method in the future.

Growth of Transplanted Fetal Tissues

Our investigations into hormonal control of fetal growth have involved the development and application of a new transplant system that has allowed us to examine growth of fetal rat tissue in a variety of controlled endocrine environments (10). In our system, the forepaws of 15-day fetuses are removed and transplanted bilaterally under the kidney capsule of syngeneic 80- to 100-g female hosts. The transplants are incubated for periods up to 11 days and are then removed and various indices of growth such as wet weight, defatted dry weight, and protein and DNA content are determined. Wet weight has proven to be as reliable an indicator of growth as the other indices, and transplants are usually compared on that basis (10). At the time of transplantation various endocrine manipulations such as TX, HX, or the induction of diabetes can be performed on the host animals to assess the possible involvement of different hormones on the growth of fetal tissues.

Our initial investigations sought to determine whether the transplanted fetal tissue was a good model for in situ paw growth and development. The growth of the transplanted fetal paws was found to be similar to that of in situ paws. After an initial lag during the first 2 days following implantation, the transplants grew at a rate equivalent to that of in situ paws and they showed normal differentiation of skeletal muscle, cartilage, connective tissue, and bone (10). Accordingly, the transplanted paw growing under the kidney capsule of a juvenile host is an excellent model system for in situ development. In addition, the paw is a heterogenous tissue which should be similar to the body as a whole in its response to growth-promoting agents.

Our first experiment to test the effect of altered endocrine environments on transplant growth involved incubation of fetal paws in HX hosts. The hosts were hypophysectomized at the time of implantation, and some of them were also given injections of GH, PRL, or thyroxine over the course of the experiment. The implants were incubated for 11 days in the HX animals, and their growth was compared with that of paws that had been incubated in intact hosts for the same period of time (Fig. 1). The transplants in the HX hosts showed only 36% as much growth as those in intact hosts and only 30% of that achieved by in situ paws. The HX host rats showed no growth during this period. Thus, although the transplants are dependent on the presence of pituitary hormones for normal growth, their continued growth in the HX hosts indicates that they are partially independent of these hormones.

Neither thyroxine nor PRL was effective in restoring transplant growth in the HX hosts, but GH, at doses of 1 and 5 $\mu g \cdot g$ body $wt^{-1} \cdot day^{-1}$, restored growth to 88 and 96%, respectively, of that seen in intact hosts. Likewise, neither PRL nor TH increased host growth, whereas GH did cause partial restoration of growth. Thyroxine also did not increase the growth-promoting effect of GH on the transplants (Fig. 1). These results indicate that growth of the fetal transplants is dependent on GH in the internal milieu of the host animal. This finding would appear to be inconsistent with the in vivo studies which found that HX rat fetuses grow at a normal rate (37). The observations that immunoreactive GH appears late in gestation in the rat and is present in low quantities until after birth (65) are also compatible with the view that GH is not essential for normal fetal rat growth. The reason for the difference between our findings with fetal paw transplants and the studies involving HX of fetuses may involve SM. HX of fetal rabbits does not reduce their serum SM (31), but this operation reduces the SM-C levels of juvenile rats to nearly zero (67). Hence our transplants in HX hosts are presumably growing in an environment of marked SM deficiency, whereas the HX fetuses in utero may experience no such deficit. The growth-promoting effect of the GH injections is presumably mediated by restoring serum SM levels to normal, but a direct effect of the GH on the fetal tissue may also be involved (see 36). GH-induced metabolic effects and improved intestinal absorption in the hosts may also promote growth of the fetal transplants (47).

The role of insulin in fetal growth was examined by transplanting paws into hosts that were made diabetic by injections of streptozotocin (64). Transplant growth in these rats was 37% less than that observed in normal hosts, and insulin replacement (4.0 U/day) given to diabetic hosts restored transplant growth to normal (Fig. 2). These results indicate that insulin is necessary for normal growth of the fetal tissues. However, transplants continued to grow in the absence of insulin,

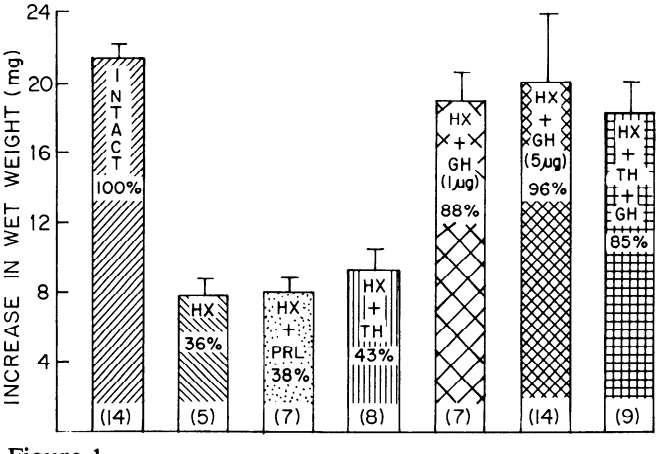

Figure 1

Growth of fetal rat paw transplants under kidney capsule of 1-mo-old syngeneic female hosts. Incubation period was 11 days, and hosts were intact, hypophysectomized (HX), or HX and treated with prolactin (PRL), thyroxine (TH), or growth hormone (GH). Number of paws in each group is given at bottom of each column. These results were published previously (10).

even though the diabetic host rats failed to grow. Thus the fetal tissue is less dependent on this hormone than is juvenile (host) tissue. Transplant growth in animals that were HX and made diabetic prior to implantation was essentially equal to that observed in transplants in HX animals (data not shown). Thus the growth decrements that accompany host HX and diabetes are not additive. Even in an endocrine environment devoid of insulin and pituitary hormones, the transplants continue to grow, increasing approximately 300% over the 11-day incubation period. Hence the fetal tissue is capable of significant growth in environments that do not support growth of the host tissue, further indicating its (only) partial independence of hormones for growth.

Insulin deficiency caused a reduction in growth of the fetal paws to about half of that observed after GH deprivation. Thus the growth of the fetal tissue appears to be relatively more dependent on GH than on insulin. The inhibitory effects of insulin deficiency and the differential effects of diabetes mellitus and HX may also be related to SM levels because insulin deficiency and HX lower SM levels in rats (60). However, diabetes, HX, and starvation cause the appearance of a SM inhibitor in rat serum (59). This inhibitor clearly complicates interpretations based on changes in SM levels per se.

Despite the fact that normal growth of the fetal paw transplants did require GH and insulin, (and presumably SM), the fetal tissue is clearly less dependent on these factors for growth than are the hosts tissues. Although GH and/or insulin deficiency reduced growth of the fetal paws, they still continued to grow to a significant degree while the hosts showed complete cessation of growth. Thus, the tissues of the rat appear to become progressively more dependent on GH, insulin and/or SM with development.

Our results also indicate that the fetal tissues can grow and differentiate normally in an environment with low MSA levels. It has been proposed that MSA mediates fetal growth and SM-C promotes growth postnatally (11, 49), and in the rat, MSA levels are highest 5 days after birth and they decline to low levels by 25 days post partum. Thus, our hosts would presumably have low MSA levels in their blood.

Conclusions

Comparative studies on the hormonal requirements for fetal growth indicate that considerable diversity exists among mammalian species. This diversity may be due in part to the fact that the fetuses of various species have different developmental histories and that they are frequently studied in stages which are not strictly comparable. For example, neonatal rodents, which are altricial, are similar in development to late gestation fetuses of precocial species such as the sheep or guinea pig. Thus the acquisition of hormone dependence or responsiveness that may occur during the third trimester of the sheep may not be acquired by a rat until sometime after birth. For example, if we assume that TH are not necessary for growth in early fetal stages but that dependence on these hormones increases with development, then species that are altricial may not show significant TH dependence until some time postnatally. In contrast, fetuses that reach relatively advanced stages of development in utero may acquire a significant degree of TH dependence before birth.

Although the available evidence does not allow any meaningful generalizations to be made about which hormones are needed for normal growth of mammalian species, it is clear that several endocrine factors are probably of importance in this regard. The role of SMs as fetal growth promoters is becoming apparent. These factors may prove to be the most important and widespread regulators of fetal growth among mammalian species. These insulin-like growth factors may be produced by many or all of the tissues of the conceptus starting early in gestation, and they may function in an autocrine or paracrine manner (15). The other hormones which affect fetal growth may modulate the production of the SM. Later in development the ability of tissues to produce SM autonomously apparently diminishes, and the participation of GH, TH, and insulin may then become obligatory for the production of adequate levels of SM. These other hormones apparently promote growth in other ways and thus act synergistically with the SM.

The new procedure of fetal paw transplantation that we have developed will allow meaningful answers to be obtained on some unresolved questions about hormonal requirements for the growth of fetal tissues. This procedure allows us to determine which hormones are needed in the internal milieu of the host to support normal growth of the fetal tissues. This technique could profitably be applied to other species in which syngeneic animals are available or could be used to study fetal tissue development from a variety of species in a host such as the nude mouse, which would alleviate histocompatability problems.

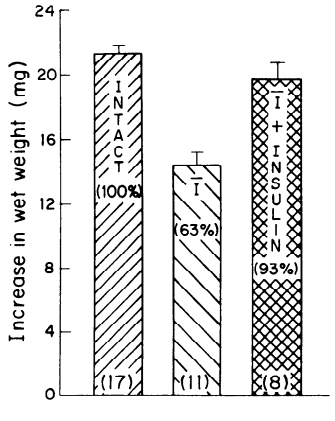

Figure 2
As in Fig. 1 but in hosts that were intact, diabetic (Ī), or Ī and given insulin replacement therapy at a dose of 4.0 U/day.

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Computers in Physiology Teaching: How Can APS Help?

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Last Fall three members of the American Physiological Society (Harold Modell, Joel Michael, and Stephen Tzankoff) independently suggested to the Society's Education Committee that interest in using computer-based education (CBE) materials in physiology teaching was growing but that some centralized source of information and assistance about this technique would do much to further the development of this area. All three commentators proposed that APS would be the most appropriate group to organize such an effort.

The Education Committee quickly decided that the time was indeed ripe for considering such a proposal, and Perry Hogan, James Randall, and I volunteered to pursue this idea. Our efforts yielded two concrete results: *1*) a survey of current efforts in this field and *2*) a Workshop held at the 67th Annual FASEB Meeting in April 1983. This paper presents a summary of the responses to the survey and an overview of the discussion that occurred at the Workshop.

The Survey and Its Results

A brief survey was written soliciting information about who is using CBE materials in physiology and how they are using them. We also solicited opinions about what steps are needed to facilitate the development of this area. The survey was sent to all chairmen of physiology departments and to others known to be active in some way in this area. Over 300 surveys were sent out and 117 replies were received. The results illuminate the current status of this field and raise important questions about what role(s) APS ought to consider playing.

The first surprise, to me at least, lay in the fact that 32 of our respondents were located at junior colleges, colleges, or small ("non-research") universities; almost all of these individuals were solely involved with undergraduate teaching. For those of us working at medical/graduate institutions (83 respondents) this level of activity at undergraduate schools represents a generally untapped resource to which more of us ought to have access.

Seventy-five percent of the respondents were currently using computers in teaching physiology. Of the 31 nonusers only 2 indicated that they had no interest in becoming involved.

The most popular use for computers was in running simulations of physiological systems. This was also the application that most people wanted to use in the future. The next most popular use was in the lecture hall, where the computer is used to generate "demonstrations" or sophisticated audiovisual graphics. Data processing in student "wet labs" and presentation of "lessons" were about equally popular. Computer applications in testing and evaluation were the least common, although many people are doing this, and many are interested in this application for the future.

Most CBE activity is carried out on "personal computers" (microcomputers), with 68% of the respondents using such machines for all or part of their teaching effort. Twenty-six percent use their institution's central mainframe machine, 22% use a minicomputer, and a handful of people are using the PLATO system.

And of the people using microcomputers, 91% indicated that they were using an Apple. (Whether this situation will continue in the future will be hotly debated until the future is here!)

Three-quarters of current CBE users are writing at least some of their own programs, most using BASIC (73 respondents) or FORTRAN (23). PASCAL seems to be increasingly popular, although the absolute number of users is still small.

Nonusers agreed that access to existing CBE materials would be a significant aid in getting them started in the field. It was also felt that "ideas" about software (languages, authoring systems, graphics packages) and its use in writing teaching programs was important, as were ideas about how to use computers most effectively in education. A number of respondents indicated that what they really needed was more money, hardware, or at least more time!

In response to the question about the role that APS should play the two most frequent replies were *1*) evaluation of existing programs and *2*) centralized distribution of programs to interested potential users.

The Workshop

If nothing else, the results of the survey suggested that we could expect a heterogeneous audience at the Workshop, with an appreciable number of individuals being relatively unfamiliar with computer-based education. It was therefore decided to preface the planned group discussion with three brief presentations in which some of the issues in the field would be outlined.

Harold Modell (Virginia Mason Research Center, Seattle) began by discussing the steps to be taken when one enters the world of CBE. The first step is to answer a number of education-related questions in order to establish guidelines for the design of the teaching aid. While this process applies to all teaching aids, it is especially important in CBE. Once the computer program is written (with inputs and outputs defined), it is less flexible, less easily changed, than other types of teaching aids.

The first question to ask is, "What is the goal of the exercise?" Although this question may seem obvious, it is important to realize that, with CBE materials, the same program skeleton may be used with a variety of input-output schemes to accomplish vastly different goals. Having established the goals, one must next decide if the computer is really the best vehicle to use. Depending on the setting, a number of "classic" CBE applications (e.g., programmed learning) may be best presented using other media.

If the computer is the vehicle of choice, guidelines that will govern the development of the teaching aid must be established. This is done by answering a number of questions related to the goals of the exercise, the setting in which it will be used, the background of the students who will use the aid, and a variety of other factors. To illustrate this process the steps leading to one "philosophy" of CBE development (4, 6) were reviewed, and a series of "laboratory exercises" (5) arising from this philosophy were described.

The goals and guidelines of the exercise help to define what equipment is necessary and what software (e.g., language) is most appropriate for the CBE material.

Allen Rovick (Rush Medical College, Chicago) next turned to a discussion of some types of exercises that one can develop for use in a teaching situation. He began by pointing out that one must consider the role that CBE activities will play in one's course. This can range from merely supplementing the offerings of an otherwise conventional course to serving as the primary educational resource for an independent study program. The comments that followed were equally applicable to use of CBE at any point along this continuum.

There seems to be a widespread, if not deliberately arrived at, consensus that the focus of CBE in physiology should be on fostering problem-solving skills and integration of concepts rather than using the computer as a programmed textbook, rote memory device, or a provider of routine drill.

Two different kinds of exercises involving problem solving were described. **Unit lessons** deal with limited subject areas, with the student interacting with the computer in a question and answer mode. Each response by the student elicits an additional response from the computer. This feedback may simply inform the student about the correctness of his/her choice, it may reinforce correct answers with additional information or correct errors with suitable explanation, or the response may direct the student to the necessary remedial assistance if his/her performance has been unacceptable.

A computer **simulation** mimics the behavior of something and hence may be manipulated to explore the factors that generate the behavior being simulated. Simulations range in "size" from those that model a single input-output relationship (length-tension relationship of muscle; 3), to those that model a single organ system (cardiovascular system; 2, 7), to those that mimic the behavior of essentially a whole organism (1). They can be used in a laboratory-like context in which the user "does experiments" on the system. Or it can be embedded in a lesson in which the model's behavior is the subject for the dialogue between student and computer. A novel variant of this latter form was described by Dr. Rovick; HEARTSIM (7) utilizes a model of the cardiovascular system called MACMAN (2) and overlays on it a didactic component that requires the student to predict the response of the system to certain inputs. It then attempts to correct the student's errors of fact or conception through interactive dialogue.

The meeting next turned to the more specific question of some of the problems that are inhibiting more extensive development of CBE in physiology (or any of the basic medical sciences) and what role APS might play in finding solutions to these problems.

James Randall (Indiana University, Bloomington) identified a number of key problems. Hardware development has advanced much more rapidly than has educational software development. The basic reason for this shortage of software is that its development is given low priority by the persons best qualified to produce such materials. This is, in part, due to the perceived lack of rewards (particularly career advancement) accompanying such activities. Publishers have been reluctant to get involved in this area because of concerns about

the size of the market (programs are easily copied, authors and users freely exchange materials). Materials that have been produced tend to be written solely from the perspective of the author and his/her course needs, making "portability" a problem. The proliferation of hardware systems, each with significant differences (operating systems, graphics capabilities, etc.) has compounded the problem of portability. And materials that are available have generally not undergone any peer review or evaluation. Finally, there has been too little communication between authors and between authors and potential users.

At this point the meeting was opened to comments and suggestions from the floor. It was clear that these problems were not seen as being insurmountable. The sentiment of the group can be described by a series of propositions about which there seemed to be a concensus.

The problem of portability is a real one, but there are no simple, acceptable answers. Standardization of CBE materials is not likely to be possible at this point in the development of the field; hardware will continue to change over the next few years and it is not yet clear what system, or kind of system, will capture a significant share of the market. Furthermore, we do not yet know which approaches to CBE are the most effective as teaching tools.

Communication between people active in CBE, or wishing to become active, needs to be improved. APS journals may play a role here, and the programming of more CBE sessions for future APS and FASEB meetings needs to be pursued.

One particularly helpful form of communication could be provided by a central catalog of existing CBE programs, complete with enough information to enable a potential user to determine which programs might meet his/her particular needs. APS, working through the Computer Service Office of FASEB, is currently organizing such a catalog. Individuals interested in listing their programs in the catalog or those interested in accessing the catalog can contact FASEB Computer Services (see accompanying box).

However, for a variety of reasons, some legal and some technical, it does not seem feasible to involve APS or FASEB in the actual distribution of programs.

The existence of a catalog will also be an important first step toward another function that appears to be needed, the peer review of CBE materials. Whether commissioned or volunteered, reviews of programs could be carried out and the conclusions published, perhaps in *The Physiology Teacher,* much as textbooks are currently reviewed.

There is also a need for a mechanism to provide assistance to institutions seeking to begin utilizing CBE. For many people the local environment (institutional and/or geographical) cannot provide the support needed by the novice trying to get underway. APS may be able to play a role here in bringing together those seeking help with those individuals experienced in CBE who are willing to help.

Another possible vehicle for helping individuals to begin using CBE in their teaching would be a workshop on writing CBE materials that might be held at the 1984 FASEB Meeting or the 1984 APS Fall Meeting. This possibility is currently under investigation.

Perhaps the most important step that would advance the field of computer-based education would be the recognition or acknowledgement by the discipline (particularly by chairmen and deans) that the generation and publishing of "good" CBE materials is an intellectual and professional activity on a par with the generation and publishing of "good" science. It is likely that this would unleash the creative efforts of many talented people and would result in much more activity in the field.

Finally, it must be kept in mind that CBE activity is growing in **all** of the basic medical sciences and that methods and techniques developed in one discipline may have significant use in other areas. We need to encourage the widest possible participation in the development of CBE by members of other disciplines, and other Societies in FASEB, to take advantage of all available resources.

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The American Physiological Society, in collaboration with the Federation of American Societies for Experimental Biology (FASEB) Office of Computer Services, is undertaking a project to catalog computer programs used in the teaching of physiology and other basic medical sciences. Material intended for all educational levels (undergraduate, graduate, medical/dental, etc.) is of interest. Listing of programs in the catalog will not in any way limit your freedom to distribute (or not to distribute) your programs. It will only provide information about the existence of your programs to people having an interest in this information.

To list material in the catalog or receive the catalog information form contact: Manager, FASEB Computer Services, 9650 Rockville Pike, Bethesda, MD 20814 (301/530-7028).

For more information about this project contact: Dr. Joel Michael, Dept. of Physiology, Rush Medical College, Chicago, IL 60612 (312/942-6426). Rush Medical College, Chicago, IL 60612 (312/942-6426).

A Random Molecular Motion Basis for Equations of Neutral Solute and Fluid Flow

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The currently accepted equations describing neutral solute and fluid flow across a selectively permeable membrane were derived by a thermodynamic analysis (2). However, because of lack of practical understanding of these equations by many teachers, the equations have either been ignored in favor of using only the Starling equation, or they may be presented dogmatically to the student without derivation. Presentation in this way leaves the student with the choice of accepting the equations without complete understanding or rejecting them and avoiding research in the area of transcapillary fluid and solute movement.

The object of the present work is to describe fluid and solute flow across a selective membrane due to hydrostatic and osmotic forces in a more basic manner, starting with Newton's laws of motion. This simpler derivation has been useful in understanding the intuitive basis for Kedem and Katchalsky's derived thermodynamic parameters as well as the mechanisms involved. Furthermore, the results of this derivation suggest a different perspective for the relationship between the Starling equation for "fluid" flow (3) and the relation proposed by Kedem and Katchalsky for "volume" flow (2) than has generally been understood.

Theory

A Kinetic Definition of Pressure

A good place to begin this discussion is by defining pressure. The physicist's definition of pressure is the force acting on a surface per unit area of that surface. In liquid solutions, the force results from random molecular collisions with the surface. The force produced by each molecule colliding with a surface can be described by Newton's second law as

$$F = m\, \mathrm{d}Vx / \mathrm{d}t$$

where F is force, m mass, and Vx the velocity component in the direction perpendicular to the surface.

This equation shows that the force increases with the mass of the molecule and also with the rate of change of its velocity. Furthermore, the pressure of the liquid is the sum of all the forces exerted per unit area by all the individual molecules at any given time. However, the velocities of the colliding particles are not identical. Rather, there is a range of velocities which is determined by the temperature of the solution and the mass of the molecules in the solution. Under these conditions, $\mathrm{d}Vx / \mathrm{d}t$ can be expressed as an average and the above equation can be rewritten as

$$\text{pressure} = F / \mathrm{SA} = R\, m\, \dot{V}$$

where F is force, SA surface area, R rate of molecular collision per unit surface area, and $\dot{V}$ average $\mathrm{d}Vx / \mathrm{d}t$ for all collisions as determined by temperature and molecular mass.

A Simplified System for Analyzing Membrane Dynamics and the Principle of Reflection Ratio

From the above definition of pressure, the dynamics of a simplified membrane system can be analyzed. The system, illustrated in Figure 1, consists of two solutions separated by a selective membrane. The selectivity of the membrane is considered to be homogeneous. In other words, the probability of passage or reflection of each type of molecule that comes into contact with the membrane is constant regardless of the exact location of contact on the membrane. The probability of reflectance from the membrane (r) is defined for each type of molecule as a **reflection ratio,** and the probability for passage will be $1 - r$. This discussion would obviously be trivial if the reflectance properties for solvent and solute were identical; therefore, when discussed individually the subscripts s and f are added so that the solute reflection ratio is designated as r_s and solvent, r_f.

The materials in solution also have specially defined characteristics. The solution on each side of the membrane is well mixed, meaning that regional differences in concentration, temperature, density, and so forth do not occur in either of the two solutions. The solute molecular mass is designated as m_s and the solvent molecular mass, m_f.

Potential Pressures of Solvent and Solute, Respectively, and Their Relationship to Hydrostatic Pressure

The following general definitions apply to the solutions on either side of the membrane in the system illustrated in Figure 1. The pressure produced by reflection of solvent molecules from the right side of the chamber wall directly parallel to the membrane is designated Π_f. Since the solutions are well mixed and no regional differences occur, this pressure is the same as the pressure that would be produced on either side of a barrier placed anywhere in between area A on the lateral wall of the chamber and the membrane. This pressure would also be expressed on the right side of the membrane when $r_f = 1.0$ and is termed the **solvent potential pressure.** In a similar manner, the solute molecules produce a pressure on area A, which is also expressed on the membrane when $r_s = 1.0$. This is the **solute potential pressure** (Π_s). These two potential pressures can be defined in terms of the rates of molecular reflection from area A, or from the membrane when $r_s = r_f = 1.0$, as

$$\Pi_f = R_f\, m_f\, \dot{V}_f \qquad (1a)$$

and

$$\Pi_s = R_s\, m_s\, \dot{V}_s \qquad (1b)$$

The sum of these potential pressures will be the total or hydrostatic pressure of the solution, or

$$P = \Pi_f + \Pi_s \qquad (2)$$

These equations, therefore, define the relationship between hydrostatic pressure and the potential pressure of the solvent and solute components of the solution. Although potential pressures usually are not defined in this manner, this definition is consistent with elementary physics. According to this definition, therefore, potential pressures are expressed as real pressures only when the surface is completely impermeable, i.e., r_f and $r_s = 1.0$. When the surface is permeable (r_f and $r_s < 1.0$), the potential pressure will be only partially expressed as a real pressure. Since the total rate of molecular reflection of both solvent and solute from a permeable surface is by definition

$$r_f R_f + r_s R_s$$

the real pressure exerted on the membrane under this condition will be

$$r_f \Pi_f + r_s \Pi_s$$

Flow of Solvent and Solute Through the Membrane

The obvious cause of the difference between potential pressure and the observed real pressure is that some of the molecules are not reflected from the membrane, but pass on through. These molecules create a unidirectional flow through the membrane (j_f) which can be expressed as

$$j_f = (1 - r_f) R_f$$

where j is the flow in molecules per unit time per unit membrane area. Similarly for the solute molecules

$$j_s = (1 - r_s) R_s$$

The unidirectional flow can be expressed in terms of volume by multiplying the mass per molecule of the substance (m), and dividing by the density of the substance (ϱ). The result for either solvent or solute is

$$j = (1 - r) R m / \varrho$$

or

$$j = [(1 - r) m / \varrho] R$$

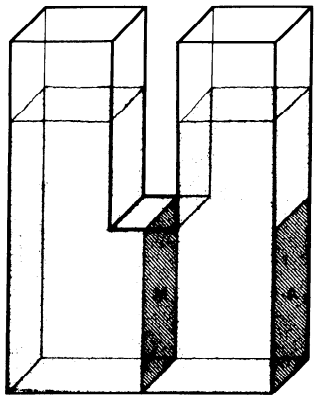

Figure 1
Idealized system for analysis of solvent and solute flows due to random molecular motion.

This relation can be expressed in terms of the potential pressure by rearranging and combining with *Eq. 1a* and *1b*. The result is

$$j = [(1 - r) m / \varrho] \Pi / m \dot{V}$$

or

$$j = [(1 - r) / \varrho \dot{V}] \Pi$$

Net Flow Across the Membrane

Each of the preceding relations can be applied to the solutions on either the right (1) or the left (2) side of the membrane in the system illustrated in Figure 1. The net flow (J) for each species of molecule across the membrane is the difference between the flow to the left and the flow to the right or

$$J = j_1 - j_2$$

which is

$$J = [(1 - r) / \varrho \dot{V}] \Pi_1 - [(1 - r) / \varrho \dot{V}] \Pi_2$$

or

$$J = [(1 - r) / \varrho \dot{V}] \Delta\Pi \qquad (3)$$

where $\Delta\Pi = \Pi_1 - \Pi_2$.

Solvent Conductance and Solute Conductance Through the Membrane

Equation 3 applied to net flow of solvent alone becomes

$$J_f = K_f \Delta\Pi_f \qquad (4)$$

where K_f is the conductance of the membrane for the solvent which is

$$K_f = (1 - r_f) / (\varrho_f \dot{V}_f) \qquad (5)$$

Similarly, for solute

$$J_s = K_s \Delta\Pi_s \qquad (6)$$

where K_s is the solute flow conductance of the membrane for the solvent and is equal to $(1 - r_s) / (\varrho_s \dot{V}_s)$.

Equation 5 can be used to interpret the meaning of K_f, which has been called the **fluid flow conductance.** The first term in this equation $(1 - r_f)$ can be interpreted as the area of the membrane occupied by pores expressed as a fraction of the total area of the membrane. This term therefore is the fractional membrane area available for diffusion of solvent molecules. The second term in this equation ($\varrho_f \dot{V}_f$) is a function of the density of the solvent and of temperature and molecular weight, which are the principal determinents of $\dot{V}_f$. We see therefore that the value of K_f depends on the membrane, the nature of the fluid, and the temperature.

Derivation of the Starling Equation

The difference in hydrostatic pressure across the membrane (from side 1 to side 2) as calculated from *Eq. 2* can be expressed as

$$\Delta P = P_1 - P_2 = \Pi_{f1} + \Pi_{f2} - \Pi_{s1} - \Pi_{s2}$$

or

$$\Delta P = \Delta\Pi_f + \Delta\Pi_s$$

where $\Delta\Pi_f = \Pi_{f1} - \Pi_{f2}$ and $\Delta\Pi_s = \Pi_{s1} - \Pi_{s2}$.

Using this relation and *Eq. 4*, J_f can be expressed as

$$J_f = K_f (\Delta P - \Delta\Pi_s)$$

This equation, when expressed in this manner, may be recognized as the Starling equation (3). The preceding paragraphs therefore provide a theoretical derivation of the Starling equation from first principles.

Derivation of Kedem and Katchalsky Equation and Concept of Reflection Coefficient

The difference between the Starling equation and the Kedem and Katchalsky equation is that the latter calculates total volume flow (J_v), which includes solute flow (J_s) in addition to the solvent flow (J_f) calculated by the Starling equation. The sum (J_v) of J_f and J_s can be found by adding *Eq. 4* and *6* to produce

$$J_v = K_f (\Delta P - \Delta \Pi_s) + K_s \Delta \Pi_s$$

This is one form of the Kedem and Katchalsky equation, but it can be further reduced to the form in which it is usually known by introduction of the concept or **reflection coefficient,** the symbol for which is σ

$$J_v = K_f (\Delta P - \sigma \Delta \Pi_s) \qquad (8)$$

where

$$\sigma = 1 - K_s / K_f \qquad (8a)$$

or

$$\sigma = 1 - [(1 - r_s)(\dot{V}_f p_f)] / [(1 - r_f)(\dot{V}_s p_s)] \qquad (8b)$$

The definition of σ, the reflection coefficient (5), is complicated. It is different from reflection ratio, a term that we have already defined. To help understand the reflection coefficient, consider the condition of equal molecular mass for solute and solvent molecules as well as equal density of the substances, whereby *Eq. 8b* becomes

$$\sigma = 1 - (1 - r_s) / (1 - r_f) \qquad (8c)$$

For a porous membrane $1 - r_s$ is the effective pore area available for penetration of a solute molecule and $1 - r_f$ is the effective pore area available for penetration of solvent molecules. The difference between effective pore area and true area is that molecules cannot pass if the center of mass of the molecule is within one molecular radius of the side of the pore. In this model σ would be equal to 1.0 minus the ratio of the effective pore area available for solute exchange to the effective pore area available for solvent exchange. To test this relationship Durbin (1) compared measured reflection coefficients with calculated coefficients based on estimations of this effective pore area ratio. The correlation was reasonably good, which lends support for this derivation.

Other support was provided by Pappenheimer (4). Although Pappenheimer did not discuss the reflection coefficient per se, he did indicate that the true osmotic pressure should be different from the van't Hoff pressure by a factor equal to $1 - D_s / D_f$, where D_s is the restricted diffusion coefficient of solute and D_f restricted diffusion coefficient of water. This factor would therefore be analagous to σ, and the above factor is essentially identical to the expression in *Eq. 8a.*

Summary

The analysis presented in this paper shows that the Starling equation and the equation derived by Kedem and Katchalsky (2) are compatable as long as distinction is made between volume flow (J_v) and solvent flux (J_f). Furthermore, simple physical bases have been provided for the Starling equation, the Kedem and Katchalsky equation, and the relation between the reflection coefficient (σ) and the restricted diffusion constants for solute and solvent as proposed by Pappenheimer (4).

The major importance of this analysis, however, is the method used for the analysis rather than the direct results. The simple methods that have been used can also be used to predict the theoretical behavior of a nonsteady-state system in which solutions are not well mixed. Also, though it has been difficult to apply standard thermodynamic relations to systems in which membrane selectivity is characterized by different-size pores, the theoretical behavior of such a system could more easily be described using the present methods. The use of rather simple equations to describe these processes is important, therefore, not only in understanding the physical processes involved but also in describing more complicated physical processes.

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Book Reviews

Basic Neurophysiology. Beverly Bishop

Garden City, NJ: Medical Examination Publishing, 1982, 602 pp., illus., index, $22.50

This is the third version of "questions in neurophysiology" composed by the author as components in a self-study system in neurophysiology. The second, published in 1973, was one-third the length of the present version. *Basic Neurophysiology* contains over 1300 questions and about 300 pages of text. In addition, at the end of each unit (chapter) there is a listing of textbooks, with chapters for reading, classical books, audiovisual materials, and films. The whole package of questions, references, films, etc. is used by the author in teaching neurophysiology to a variety of students.

Basic Neurophysiology is not a textbook. Each unit begins with a brief text to be read in preparation for the questions and the use of the other reference materials. The quality of the text portions, the extent of topic treatment and usefulness of the text in providing answers to the questions varies greatly. There are only 8 pages on membrane phenomena, 15 on spinal cord circuits of which 6 are on Renshaw inhibition, but there are 37 pages on central synapses and 23 on nerve-muscle physiology. There are no units on hearing, vision, or chemical senses, but there are 35 pages on the masticatory system. The futility in trying to use the

short texts as guides to the questions is pointed out from a random check of about 7% of the questions in each unit. Only about one-third of the answers could be found, but it was not unusual to locate answers in other units. Students are expected to consult and read the reference texts. I do not think it should be assumed that most students will have ready access to the many references or will necessarily use them in preference to study of a single comprehensive textbook.

The unevenness of presentation and coverage of text topics is not balanced by the reasonably up-to-date good sections, such as those on central synapses, development of the cerebellum, joint and muscle receptors, and anatomy of the masticatory system. Students will be puzzled by such things as giving widely different values in three different places for the number of neurons in the brain, identifying stellate, fusiform, and pyramidal tract neurons as the basic types of cortical cells, and questioning whether the substantia nigra projects to the striatum but later describing nigra-striatal dopamine fibers. Blocks of questions are organized under headings which frequently do not correspond to those in the unit's text.

Basic Neurophysiology can be used as a study aid. Students can select questions under a heading for self-examination. An index of question topics or headings would have facilitated this use. Unfortunately the textbook references for the necessary consultations are now mostly out-of-date. Several excellent comprehensive texts on the nervous system (neurophysiology, neuroscience) have appeared in the last two years. Students may be best advised to study one of them before attempting to use the appropriate questions in *Basic Neurophysiology*.

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Review of Human Physiology.
H. F. Winter and M. L. Shourd

Philadelphia, PA: Saunders, 1982, 536 pp., $16.95; Canada $22.05

This text is aimed at helping the student with self-assessment. The chapters comprise a number of cognitive objectives, each one followed by several multiple-choice questions, the answer code being given at the end of the book. The text is a companion to Guyton's *Textbook of Medical Physiology,* and the chapters correspond to those in Guyton's book. This obviously limits the use of this volume, although it could be used with other textbooks. This would present some problems, because even for Guyton's *Human Physiology and Mechanisms of Disease* only an overlapping chapter-by-chapter correlation is given and many topics are handled differently in each textbook.

The layout is helpful with a learning objective at the beginning of each section, but the multiple-choice questions that follow are not all to the same standard. As someone who has helped set up a computer bank for multiple-choice questions in physiology, I am only too aware of the problems in producing the approximately 4,800 questions given, especially when there is only a single correct response. It may have been a little too ambitious to produce quite so many questions (several per page of Guyton's text), and it may give the student a false impression of the amount of information which they should know. Multiple-choice questions largely test factual knowledge, but more effort could have been made to test understanding. The questions generally take the form of a statement with two or three words missing, and the student has to select the correct combination of missing words. If one is not used to the format, it can be a little disconcerting at first. In some questions the missing words are interdependent and some thought is required, e.g., Question 17, page 129: "The most important — (D, direct; I, indirect) effects of autonomic activity upon coronary blood flow are those which alter the activity of — (A, alpha receptors; C, cardiac cell muscles)." In other questions two separate pieces of information are required so that fact alone is tested, e.g., Question 49, page 449: "Somatomedin formed in the — (E, epiphyses of long bones; L, liver) functions as an — (A, inhibitor; M, intermediate) for the effects of somatotropin upon cartilage and bone growth." A number of questions require correct labeling of a given diagram. More questions based on illustrations or figures could have been used, especially with regard to problem solving and the interpretation of data. This is not a book for the "high flyer" but could be of value to the less imaginative student or one uncertain as to their degree of achievement. By the way, if you are still puzzling, the answers are I, C and L, M.

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Medical Physiology: Textbook Study Guide.
James L. Poland and Jerry W. Poland

Garden City, NJ: Medical Examination Publishing, 1982, 206 pp., $13.50

It surprised me to find two self-assessment books as companion to one single text. Guyton's *Textbook of Medical Physiology* is obviously widely used. It is not a recommended text in my department, but this may have something to do with the fact that 33% of our academic staff (Professors Green and Neil) have written texbooks of physiology. Such aids to study as this volume are of value in that they give the student confidence in what they know and help identify areas of weakness. This is becoming increasingly important as the staff-to-student ratio falls. The questions in this book follow what for me is a more usual format of an initial statement or stem followed by four or five options. In some instances there is one correct answer; in others one or more answers may be correct. For this second case, a key is given, e.g., "circle A if 1, 2 & 3" are correct, so that effectively the answer is a single correct response. This can be confusing as the key varies in successive sections. The same criticism applies to this volume as to the one by Winter and Shourd in that the emphasis is on factual knowledge with little attention to application or comprehension. Among the 800 questions, however, there are some problems. This volume is produced in camera-ready copy and is quite well set out. Being a small paperback it could fit into a largish pocket to allow review in spare moments.

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