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A Publication of the American Physiological Society | Volume 25, Number 6 | December, 1982

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The Physiologist (ISSN 0031-9376) is published bimonthly by the American Physiological Society, 9650 Rockville Pike, Bethesda, MD 20814. Subscriptions: Distributed with the Physiology Teacher to members as part of their membership; nonmembers and institutions, $30.00 per year in the United States; elsewhere $40.00. The American Physiological Society assumes no responsibility for the statements and opinions advanced by contributors to *The Physiologist.*

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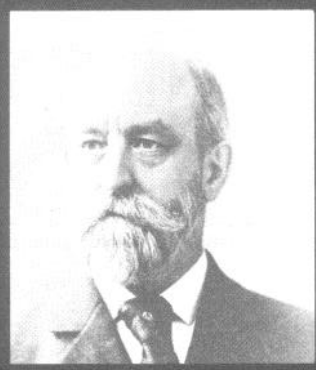

The 27th Annual BOWDITCH LECTURE

Electrogenic Ion Pumps and Other Determinants of Membrane Potential in Vascular Muscle

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Several factors determine the membrane potential (E_m) of muscle cells of blood vessels. Since contraction can be shown to be a function of E_m, it is important to consider the electrical factors that generate the E_m the elements that allow E_m, to change, and the connection between E_m and contraction in vascular muscle cells. These processes have been the focus of the research in my laboratory for the last decade, and it is the exploration of these questions which I will address.

Membrane excitability provides signals for activity in many types of nerve, muscle, and secretory cells. The importance of studying E_m in vascular muscle derives from the generalization that the cell membrane is the major determinant of intracellular Ca^{2+}, which is maintained at very low concentrations in virtually all kinds of excitable cells. In general, intracellular Ca^{2+} determines the level of tension maintained by muscle cells.

In vascular muscle, as in most excitable cells, steady-state changes in E_m principally determine cellular activity. Spiking responses, typified by propagating action potentials, are more commonly known but are found in a minority of cells, whereas graded depolarizations are found in more striated and nonstriated muscle cells (50, 51). Most arterial muscle cells operate by graded depolarizations, as illustrated in Fig. 1, without membrane spikes that would be analagous to action potentials (28). Even in the spiking type of vascular muscle (e.g., hepatic portal vein), the occurrence, duration, and frequency of spiking appears to be controlled by slowly changing steady-state E_m levels (23). Whether the excitation events are graded or all-or-none, it is ion movements that determine activity of muscle cells, and it is by glass microelectrodes filled with electrolyte solutions that the electrical consequences of ion movements are defined. Therefore, understanding membrane excitation in vascular muscle has resulted principally from intracellular recording of E_m for which very high quality glass microelectrodes must be used.

Vascular muscle excitation differs from that in cardiac muscle in two ways: 1) initiation of contraction is not associated with an action potential; and *2*) the time course of change of E_m does not form a characteristic shape. The valid measurement of E_m in vascular muscle is difficult because the widest diameter of vascular muscle cells is only 2 μm (making them the smallest of any cells in mammals) and because there is no action potential from which to judge the quality of the impalement. Exceptional vascular muscle cells show spikes, usually without propagation, and these cells are searched for in some situations, including the most difficult (single cell) experiments in order to validate the recording technique (26).

To return to the mechanism by which E_m controls tension in vascular muscle, there is a range of E_m for each type of vascular muscle over which tension changes significantly for each millivolt change in E_m. Figure 2

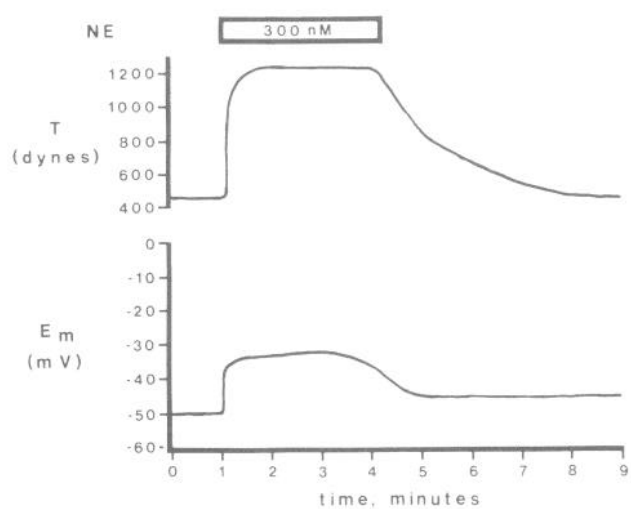
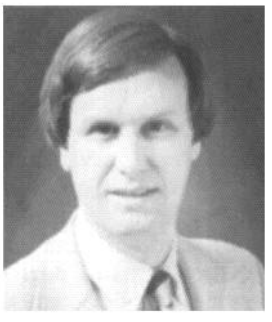


Figure 1
Graded depolarization and tension maintain a steady state during 300 nM norepinephrine (NE) stimulation in rat caudal artery. These drawings are based on original data records and emphasize the parallelism between tension and E_m which is typical of commonly studied arteries. Both E_m and tension levels remain relatively constant for up to hours during stimulation by vasoconstrictors, which can explain tone in blood vessels.

shows this relationship in the rat caudal artery and in frog skeletal muscle twitch fibers. The entire contraction range is accounted for by less than 20 mV, and in the steep part of the curve, 14 mV determine 80% of the total tension. Stated another way, a 4-mV depolarization can mean an increase of 30% of maximum tension in caudal arterial muscle. In skeletal muscle, a similar relationship exists, although fast skeletal muscle fibers normally do not maintain an E_m more positive than threshold potential for more than a few milliseconds. In Fig. 2 the authors have changed E_m in skeletal muscle by graded depolarization with increasing extracellular K^+ to generate the curve of tension as a function of voltage (35). Normal excitation in fast (twitch) skeletal muscle would involve an action potential that sweeps completely through that voltage-tension range in less than a millisecond.

In contrast, excitation of vascular muscle initiated by neuronal release of norepinephrine (NE) would cause graded depolarization at a maintained level, making the voltage-tension relationship (Fig. 2) a reflection of the physiological phenomenon (see Fig. 1). Notice the close relationship of tension and voltage in the steep part of the curve—a ΔE_m of only a few millivolts would cause a large contraction or dilation. Whereas the data shown in Fig. 2 are the results of depolarization of the vascular *muscle* with various K^+ concentrations, a similar curve is generated when NE is used as the depolarizing agent, as suggested by Fig. 1. This type of relationship has also been found to occur in several other blood vessels that have been extensively studied, e.g., rabbit main pulmonary artery, rabbit ear artery, rabbit saphenous artery, rat, guinea pig, and dog mesenteric arteries, dog carotid artery, cat, rabbit, and rat cerebral arteries, and hepatic portal vein (28). Even though there have been recent reports of contraction without depolarization in coronary arteries of the pig and guinea pig (36, 39), there are sound reasons for studying the mechanisms controlling E_m in vascular muscle, particularly those mechanisms that are important for slow changes in maintained levels of E_m.



Ralph Kent Hermsmeyer, born in Litchfield, Illinois in 1942, has been a member of the American Physiological Society since 1972. He completed his Ph.D. at the University of Illinois, Urbana in 1968, and then spent 2 years as a postdoctoral fellow in the Department of Physiology at the University of Virginia, Charlottesville. In 1970, he joined the Department of Physiology and Biophysics at the University of Nebraska School of Medicine, Omaha, as an Assistant Professor. In 1973, he moved to the Department of Pharmacology of the University of Iowa College of Medicine, Iowa City, where he is currently Professor. Dr. Hermsmeyer was honored in 1975 with the Louis N. Katz prize from the American Heart Association. He received a Research Career Development Award from the National Institutes of Health from 1975-80. In 1977-78, he was Visiting Professor of the Physiology Institute of the University of Berne, with awards from the F. Hoffman-LaRoche Research Foundation for Scientific Exchange and Biomedical Collaboration with Switzerland and the Swiss Foundation for Cardiology. He is a member of the Editorial Boards of *Blood Vessels* and *Circulation Research*. His family consists of his wife, Bobbie, and his 9-year-old daughter, Amanda.

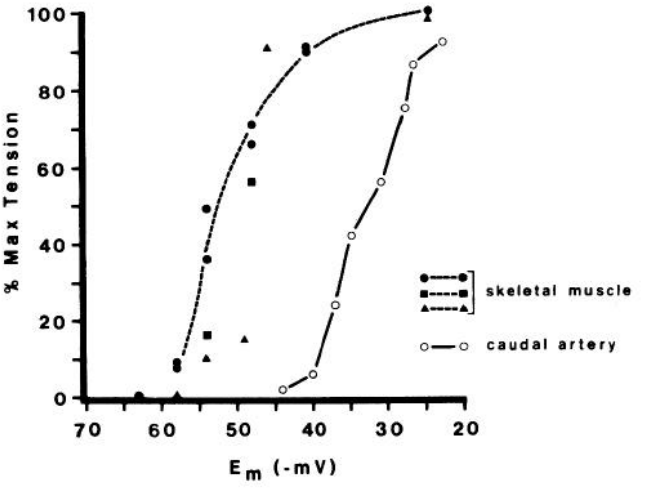


Figure 2
Voltage-tension relationship for rat caudal artery is shown on same axis as that for frog twitch skeletal muscle, where both experiments involve alteration of E_m by depolarization in solutions of various K^+ concentrations. Skeletal muscle data are taken from Ref. 35 and show that although an action potential sweeps through a much wider range, it is that E_m over a 14-mV range which accounts for most of the tension. Rat caudal artery has a very similar range of 14 mV which accounts for 80% of the total tension, even though the axis is shifted. These data suggest a steep dependence of tension on voltage in both vascular muscle and skeletal muscle. [Reprinted from Hermsmeyer et al. (33) with permission.]

The four most important influences on vascular muscle membranes are probably ion conductances, ion gradients, electrogenic ion transports, and membrane surface charge sites. It is these four influences on E_m and their combination which will be discussed.

Ion Conductance Contributions to E_m

Changes in ion conductances cause depolarization in response to NE and other vasoconstrictor drugs or cause hyperpolarization in response to vasodilator drugs. Movement of ions through membrane "channels" accounts for the major part of ion movements and must be considered as the dominant controller of E_m (29, 37).

Evidence for changes in ion conductance are based on several kinds of experimental data, none of which by itself is completely definitive. Conductance of the vascular muscle cell membrane to K^+, Na^+, Ca^{2+}, and Cl^- can be independently determined by variation of one ion at a time in the extracellular fluid, with measurements of the E_m and membrane resistance. Data from current clamp, rather than voltage clamp, experiments have provided the more reliable data for vascular muscle because of the difficulty in achieving adequate spatial homogeneity of voltage in multicellular preparations to allow proper voltage clamp analysis.

As one varies the K^+ gradient across the cell membrane, for example, the resultant change in E_m and membrane resistance can be interpreted in terms of the change in K^+ conductance. The key equation useful in such analysis is the chord conductance equation (17), which is

$$E_m = \frac{g_K}{\Sigma g} \times E_K + \frac{g_{Na}}{\Sigma g} \times E_{Na} + \frac{g_{Ca}}{\Sigma g} \times E_{Ca} + \frac{g_{Cl}}{\Sigma g} \times E_{Cl}$$

Each g term in the equation is the conductance, and the

fraction of total conductance for K^+, for example, would be $g_K/\Sigma g$. The E_K represent the K^+ equilibrium potential as defined by the Nernst equation. This relationship, which holds in the steady state, allows one to approximate how much the conductance for each of the principal ions contributes to E_m if the variation in extracellular ion concentration, and therefore the change in gradient, is for a short enough time that the intracellular ion concentration does not change. In general, if measurements can be made within a 10-min period in blood vessel segments, the movement of intracellular ions will be small enough not to seriously complicate the analysis (23, 24).

Membrane resistance (r_m) must be measured together with E_m because it is from r_m that the total conductance is calculated. In fact, Σg, the total conductance, is the inverse of cell membrane resistance, or $\Sigma g = 1/r_m$. This means that not only the E_m that results from the combination of conductance and equilibrium potentials for each of the ions but also the total resistance to ion flow through the membrane (r_m) must be measured at the same time in each experiment. The success of those measurements largely determines the validity of the data allowing analysis of ion conductances contributing to vascular muscle membrane potential. Because vascular muscle cells are so small, these r_m measurements are best made by current injection through the microelectrode which is recording E_m by the electronic configuration that allows nulling out the injected current pulse (6, 52). Although this method (single-electrode input resistance, r_{in}) has been criticized because current spread from a point source has the danger of artifacts (15), each type of cell should be considered separately. The balance of how much current must be injected by what quality electrode to change E_m enough for r_{in} measurement is favorable for use in vascular muscle cells, although strict criteria for acceptance of data must be used (24, 29). The several sources of artifact will result in rejection of a large fraction of attempted measurements, but the method can be very useful in single cells or when cells are not well coupled (24, 52). In fact, single-electrode current injection r_{in} data provide the best fit for ion flux (radioisotope) data and fit the electrophysiological generalization of specific membrane resistance ($R_m = r_{in} \times$ cell surface area) in the range of 1,000–10,000 $\Omega \cdot cm^2$ (58).

It is also important to realize the role played by the equilibrium potential for each ion in this equation. The equilibrium potential for K^+ (E_K) is the most negative (−90 mV) and provides the basis for the resting E_m and the state of relaxation in vascular muscle. Small changes in the ionic gradient would normally occur either because of changes in extracellular fluid or intracellular K^+ concentration. One example of a change found as part of a disease mechanism emphasizes the importance of measuring equilibrium potentials. That example is the lower intracellular free K^+ concentration found in arterial muscle cells of spontaneously hypertensive rats (SHR). As a result of the lower intracellular K^+ activity, and consequently less negative E_K, the caudal arterial muscle cells in SHR have a less negative E_m under the influence of depolarizing drugs like NE, with the resultant increase in the tension generated by NE (18, 24). As the K^+ currents are the most important for relaxation of the cells, the smaller K^+ gradient leads to a lesser ability of the SHR arterial muscle cells to relax, apparently contributing to the increased peripheral resistance characteristic of this genetic form of hypertension (27).

Notice that changes in any of the equilibrium potentials for ions would be important in some phase of contraction and relaxation in arterial muscle. A smaller Na^+ gradient, which is most likely to result from increased intracellular Na^+, would result in less depolarization under the influence of a drug that mainly increased Na^+ conductance. The Cl^- equilibrium potential in several types of vascular muscle is approximately −15 mV (37), which appears to correspond to the limiting value for depolarization by drugs. It is likely that the level of maximum depolarization is influenced by a Cl^- conductance, although Cl^- seems to have only undetectable effects on the resting E_m. Nevertheless, the Cl^- contribution to E_m may be rather poorly understood because there is at present no explanation of why intracellular Cl^- activity should be higher than is predicted by the resting E_m, unless there is active regulation of intracellular Cl^-. Such an active Cl^- transport could well shift the slope of depolarization curves for drugs that cause a large increase in Cl^- conductance.

Ca^{2+} provides the most extreme example of the importance of changes in ion gradients. Not only would there be depolarization of E_m with increased influx of Ca^{2+}, but increased tension is also caused by increased free intracellular Ca^{2+} concentration. It has not been possible to measure the Ca^{2+} equilibrium potential (E_{Ca}) by the use of alterations of extracellular fluid because of Ca^{2+} effects on ion conductance and because so much of the intracellular Ca^{2+} is not in the free ionic form. Besides free ionized Ca^{2+}, the myoplasm contains Ca^{2+} bound to proteins, phospate, sulfate, and other negatively charged binding sites. Ca^{2+} is localized in organelles (i.e., sarcoplasmic reticulum and mitochondria). Even any Ca^{2+}, Cl^-, Na^+, or K^+ that is not sequestered or bound would only be partially ionized in the myoplasm (or in any water solution), as is demonstrated by physical-chemical measurements of ions in solution (8).

There is an important distinction between total intracellular concentration and that which is in the free ionized state. Actually, the free ionized element, for which the term *ion activity* is appropriate, is the term correctly put into the Nernst equation. It is only the ion activity (rather than total element content) that is important for E_m. All of the other atoms that exist within the muscle cell (besides the free ionized form) are completely invisible to any measurement of E_m or resistance. Measurements made by atomic absorption spectrophotometry or by electron-probe microanalysis would give the total elemental content and not discriminate free ionized from other forms of a given atom. This means that measurements which detect K^+, Na^+, Ca^{2+}, or Cl^- activity, such as variation in E_m and r_m with changes in ion gradient or, more directly, ion activity sensed by ion-selective electrodes, are very important for understanding membrane events. On the other hand, the information from radionuclide analysis, atomic absorption, and the electron probe can be very useful because the total content of an element is defined. When this information is used together, a better understanding of operation of the muscle cell emerges. It is worthwhile noting that Ca^{2+} is a very special case because measurement of the gradient depends on determining intracellular Ca^{2+} activity. More description of the Ca^{2+} measurements follows (see below).

Contributions of Electrogenic Ion Transport to E_m

The next major determinant of E_m is ion transport across the cell membrane, which is distinct from ion conductances described above. As the previous discussion has demonstrated, ion transport would contribute to E_m indirectly by establishing the intracellular ion concentrations and, therefore, the gradients that translate into equilibrium potentials for each ion. A large change in the rate of transport of an ion across the cell membrane could then lead to a change in concentration (and gradient) that could appear as a change in E_m. The active transport of ions across cell membranes is an energy-consuming process that appears especially important in the case of Na^+ and K^+ ions (for review see Refs. 18, 20), those very ions which seem most important in determining the resting potential and contributing importantly to changes in E_m during exposure to drugs. Several other kinds of transport, presumably existing in vascular muscle, involve carrier-mediated transport that would not consume energy but would importantly influence the final ionic gradients. These carrier-mediated transports are not well understood in vascular muscle at this time and are an area of needed additional research. The important point is that several kinds of ion transport probably exist in vascular muscle, of which we are aware of only a few.

One important contributor to ion transport is the electrogenic (voltage-producing) transport of Na^+. It is the electrogenic transport of ions, mainly Na^+, that has been studied intensively in the last few years, allowing a better appreciation of its immediate role in determining E_m (29). Haddy's group (3, 12, 14) correctly pointed to the Na^+-K^+ pump as a mechanism for vasodilation, based on hemodynamic data and ion transport experiments, and in doing so called attention of many of us to the hypothesis. The suggestion has proved important, because the electrogenic Na^+ pump plays a role that is at times only slighty subservient to ion conductances in determining E_m. In vascular muscle as in several other kinds of cells, the activation of electrogenic Na^+ transport can cause a marked hyperpolarization as the positively charged Na^+ is moved out through the cell membrane with a lesser number of K^+ moved in at the same time. The ratio of ion movement in vascular muscle might well be variable, and there is evidence for a defined limiting ratio of three Na^+ moved out of the cell for each two K^+ moved in (45, 54). The result of this electrogenic pumping of Na^+ is a hyperpolarizing influence that translates into relaxation of the vascular muscle cells. Hyperpolarization by electrogenic ion transport is important not only at rest but also under the influence of vasoconstrictor drugs. The balance of ions transported to the passive ion conductances discussed above is such in vascular muscle that electrogenic ion transport contributes about 10 mV potential at rest and contributes at least 5 mV during a large contraction in response to a high NE concentration (25, 27, 29). These data suggest that electrogenic ion transport is a constant modulating influence on the degree of contraction or relaxation through shifts of E_m by a few millivolts.

In fact, the change in E_m contributed by electrogenic ion transport, although small, can cause a very significant decrease in tension produced by the vascular muscle. It might at first seem that small changes in E_m would be relatively insignificant in terms of tension. In the flat parts of the voltage-tension curve, at resting E_m and also at highly depolarized levels (more positive than −20 mV), that is true. Changes of 4 or 5 mV are found on activation of electrogenic ion pumping during depolarization by moderate or even maximal concentrations of constrictor agents (9). In the steep part of the voltage-tension curve, 5 mV of hyperpolarization are much more significant than 10 mV at resting E_m . It is the nature of the electrogenic ion transport process that the voltage change produced will be dependent on the r_m, such that as the constrictor causes increases in ion fluxes through the membrane, r_m will be decreased and the voltage generated by the electrogenic ion transport will be less because voltage = current × resistance (and current is constant). Nevertheless, the attenuated contribution of electrogenic ion transport to E_m is sufficient to cause important shifts in tension. It is logical to think of electrogenic ion transport as a constantly modulating influence that causes, in effect, movement down the voltage-tension curve as it is activated. Conversely, in the face of a given level of electrogenic ion transport, one could also see a shift upward on the voltage-tension curve if there were inactivation of electrogenic ion transport. In fact, since the depletion of energy sources might be expected in damaged or dying vascular muscle cells, a theoretical mechanism that could cause increased vasoconstrictor sensitivity of such cells (and possibly spasm) might be the reduction in the contribution of electrogenic ion transport due to the loss of adequate metabolic supply to keep the activity level constant.

The conclusion that an electrogenic ion transport system exists in vascular muscle has been based primarily on experiments designed to stimulate such an active transport process while recording the electrical and mechanical consequences of electrogenic pump stimulation (20, 27) and has not been without controversy (42, 43). The most important concepts supporting electrogenic ion transport as the explanation for additional contributions to E_m (beyond those made by ion gradients discussed above) are *1*) the transient changes in E_m on changing the key parameters that regulate active ion transport and *2*) the time course of those changes. Experimentally, demonstration that electrogenic ion transport is involved is from the return of K^+ to the extracellular fluid bathing cells that have been exposed to zero K^+, a maneuver which I will refer to as the *K^+ return experiment* (see Fig. 3).

On exposure of vascular muscle to low extracellular K^+, there is an inhibition of the active transport process regulating intracellular Na^+ and K^+ that is widely believed to be through the ouabain-sensitive Na^+-K^+-ATPase enzyme located in the cell membrane (18, 20). The ouabain-sensitive Na^+-K^+-ATPase is highly sensitive to the concentration of K^+ in the extracellular fluid, being nearly completely inhibited by reduction of K^+ to micromolar levels (18). When a strip of arterial muscle is suffused with zero K^+ solution for a period of 15 min or more, there will be a buildup of intracellular Na^+ by a few millimolar and depletion of intracellular K^+ by a few millimolar because the Na^+-K^+ pump activity is decreased. That is, intracellular K^+ 30-fold greater than that in the extracellular fluid and intracellular Na^+ 15-fold less than that in the extracellular fluid is normally maintained in vascular muscle (37). As the result of accumulation

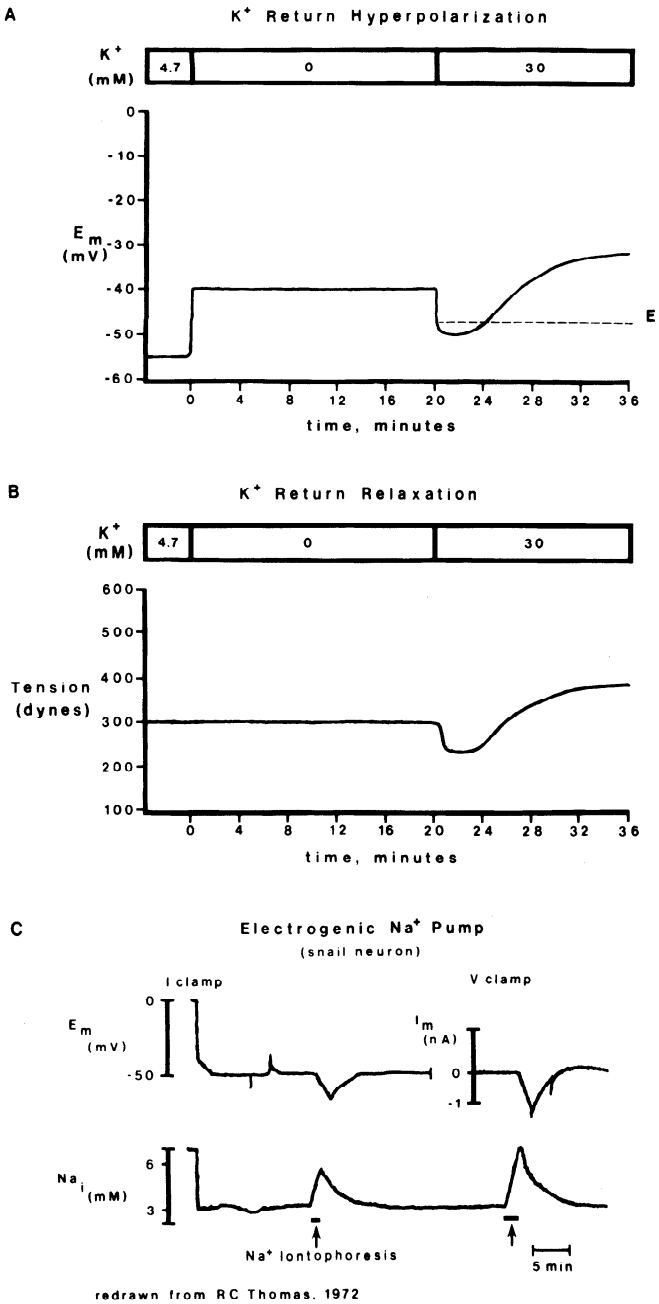


Figure 3

Evidence that electrogenic ion transport contributes to E_m and that Na^+ is the ion species likely to be involved is shown *A-C*. In *A*, transient hyperpolarization of rat caudal artery on return to K^+ is shown, where duration depends on Na^+ loading as determined by duration and magnitude of inhibition of Na^+ transport. This hyperpolarization would be blocked by low temperature, Li^+, or ouabain. The most important feature is that hyperpolarization on return to K^+ exceeds K^+ equilibrium potential, E_K (-47 mV). In *B*, transient relaxation on return to K^+ has same time course as hyperpolarization in *A*. Tension has been induced by 100 nM NE to put E_m in the range of tension in voltage-tension coupling curve. This pair of records, though recorded from 2 different strips under different conditions, suggests direct control of tension by E_m in rat caudal artery, which has previously been demonstrated (33). In *C*, direct demonstration of transient hyperpolarization of snail neurons folowing iontophoretic intracellular injection of Na^+ is given by corresponding increases in intracellular Na^+ activity, as detected with Na^+ selective microelectrodes (redrawn from Ref. 54). Notice that time course of E_m and Na^+ activity change is the same. In other experiments not shown, other ions injected into the cell failed to cause such a hyperpolarization.

of intracellular Na^+ during zero K^+, when the active transport process is allowed to resume by the return of extracellular K^+, there will be stimulation to a high level of active transport, which is electrically detectable when more Na^+ ions are moved out of than K^+ ions into the cell. As the activity level of the transport process is strongly regulated by intracellular Na^+, the K^+ return experiment provides a mechanism for instantaneous stimulation by returning extracellular K^+ after increasing intracellular Na^+ by zero K^+. On K^+ return, there is an exaggerated contribution of the transport process to E_m for 1-10 min. In fact, the transient hyperpolarization seen on K^+ return in the K^+ return experiment is strong evidence for stimulation of an electrogenic ion pump.

However, it is well to remember that there are several possible causes for hyperpolarization when one changes K^+ concentration. One such mechanism might be that the return of K^+ increases K^+ conductance (21, 23), which in itself would be a hyperpolarizating influence (see the chord conductance equation above). The best experiment to distinguish between the possibilities of stimulation of active transport and increase in K^+ conductance is the same K^+ return experiment, with the added feature that instead of returning to normal 5 mM K^+ solutions, one returns to a K^+ concentration which could only give depolarization based on the K^+ gradient-in other words, choosing a K^+ concentration that would give E_m less negative than that found during the zero K^+ solution by Nernst potential calculations. The experiment then must give either one answer or the other because there either will be hyperpolarization, which could only come from a non-K^+ gradient process, or there will be depolarization, which would indicate that changes in K^+ conductance were probably involved (24). The outcome of the experiment is that such a maneuver into high (30 mM) K^+ concentration gives an unmistakable transient hyperpolarization which indicates electrogenic ion transport (24, 27, 29) (Fig. 3). In fact, the data recorded are strong support for the hypothesis that electrogenic ion transport gives the hyperpolarization because the hyperpolarization exceeds the K^+ equilibrium potential, meaning that it could not have been generated by ion gradients alone.

The high K^+ return experiment thus stands as crucial evidence supporting the electrogenic ion transport model in vascular muscle (29). Other data to support the idea come from other known characteristics of the electrogenic ion transport system. First, the electrogenic ion transport, by being an active energy-consuming process, is highly temperature sensitive. Thus one can, instead of using zero K^+ and return to K^+, produce a steady depolarization in low temperature (e.g., at 16°C) that is very similar to that produced by zero K^+. On return to normal temperature (37°C), there is a transient hyperpolarization of a few minutes, dependent on the time of exposure to low temperature. As in the K^+ return experiment, the buildup of intracellular Na^+ (integrated over time) detemines the degree of activity on stimulation of the electrogenic ion pump (24). Another known characteristic of the active transport of Na^+ is the inability of the Li^+ ion to substitute for Na^+ in the transport process. Although inhibition of Na^+-K^+-ATPase by ouabain can also be used to block the electrogenic ion transport, the results are less satisfactory because high (>0.1 mM) ouabain concentrations are

necessary in the rat (24). Na^+ substitution experiments are a more desirable approach to detemining if the hyperpolarization on K^+ return involves Na^+. Several kinds of Na^+ substitution experiments are possible to test whether the process has the features of the electrogenic pump, with the Li^+ experiment perhaps the most definitive because the others have the disadvantages of either changing the ionic strength or causing pronounced direct effects on membrane ion conductances (e.g., choline). When the extracellular Na^+ is replaced by Li^+, the vascular muscle cells depolarize to nearly the same level as that found in zero K^+ solution or at 16°C. When the exposure to zero K^+ occurs, E_m does not change further, and on return to K^+ there is no transient hyperpolarization in Li^+. If one returns to 30 mM extracellular K^+, there is only the depolarization predicted by the E_K (31). The experiments so far described support the existence of electrogenic ion transport which contributes to E_m.

Although the concept of an electrogenic ion pump had been first postulated for nonstriated muscles (13), and later assumed to be the electrogenic transport of Na^+ (22), which is the best studied of the ion transport processes, it is only recently that the ionic species involved in vascular muscle was supported by experimental data (31). Even though the early prediction that electrogenic ion transport would be important in $E_m$was made for nonstriated muscles, the difficulty in collecting experimental data from such preparations makes the establishment of such a process in these cells very difficult. The strongest evidence for the establishment of an electrogenic Na^+ transport process comes from neurons and other large cells, which are subject to multiple electrode impalement for simultaneous recording and manipulation of intracellular contents. The stimulation of electrogenic Na^+ transport by iontophoresis of Na^+ into snail neurons through a microelectrode gave the direct demonstration of a transient voltage directly dependent on intracellular Na^+ (Fig. 3*C*). Nevertheless, it is possible to do several tests of the ionic species involved in vascular muscle, especially basing those experiments on the known characteristics of electrogenic Na^+ transport in the more thoroughly studied large neurons.

The Li^+ experiments previously mentioned are one such set of experiments designed to test whether the electrogenic ion transport was indeed Na^+ or might be for some other ion. Electron-probe experiments also help to establish electrogenic ion transport as being Na^+. With the electron probe, one measures total intracellular content of each ion. However, it is not possible to distinguish between, for example, Na^+ that is in free ionic form in the myoplasm from that which is compartmentalized or bound and thus unavailable for ionic movements. The free ionic Na^+ that is important for determining E_m can only be sensed by measurements of E_m or by Na^+-selective microelectrodes. The electron-probe microanalysis allows the determination of buildup of intracellular Na^+ during Na^+ loading in zero K^+ and depletion of Na^+ during Li^+ replacement. Electron-probe data confirm by time course, magnitude, and direction of change that the ion species involved in the extra (nongradient) component of E_m found in rat caudal artery is Na^+ (31). This does not preclude the possibility that other electrogenic ion transport systems, perhaps involving Ca^{2+}, might also be involved under different ionic environments, or as the result of drugs acting on the cell membrane (30). However, the electrogenic transport of Na^+ as a contributor to E_m does seem to be established, at least in rat caudal artery (29).

One example of the importance of the electrogenic ion transport is given by the mechansim found to explain at least a major part of the increased NE sensitivity found in peripheral arteries from sponstaneously hypertensive rats (SHR) compared with their (geneticall-y matched) Kyoto-Wistar normotensive control rats (WKY). On comparing the rat caudal artery from SHR and WKY, a difference in the return to K^+ experiment appeared that implicated electrogenic ion transport as being altered in this form of genetic hypertension. The K^+ return experiment always yielded a larger hyperpolarization and relaxation in the SHR than in WKY (24, 25, 27). Early experiments by Haddy and coworkers (19, 47, 48) suggested that altered Na^+-K^+ active transport may be part of the cause of some forms of animal hypertension. Work in this area has recently suggested a humoral inhibitor of the Na^+-K^+ pump (a heat-stable ouabain like factor) that is found in several forms of hypertension may be an important contributor to increased peripheral resistance, perhaps linking the anteroventral third ventricle to the Na^+-K^+ pump (49). Experiments by laboratories measuring only relaxation in other models of hypertension have supported this observation, suggesting a high degree of activity of electrogenic ion transport in certain animal models of hypertension (56, 57). However, rat deoxycorticosterone acetate-salt and Dahl forms of hypertension appear not to have the same type of altered E_m due to electrogenic transport as appears in SHR (31).

It might seem at first paradoxical that in the SHR, where there is greater than normal peripheral resistance, one finds increased electrogenic ion transport, which is a hyperpolarizing (and therefore relaxing) influence. However, electrogenic ion transport probably is not the primary change in the arterial muscle cells of SHR. Instead, increased electrogenic ion transport probably reflects the accumulation of intracellular Na^+ and the lower intracellular K^+ that were also found in these experiments (27, 31). In fact, under the influence of smaller K^+ and Na^+ gradients, NE would cause greater depolarization because the smaller ion gradients produce a more positive E_m. Even though the electrogenic Na^+ pump might contribute a few additional millivolts to keeping the membrane more hyperpolarized, the increased ion conductances (and therefore ion movements) during stimulation by NE overpower the hyperpolarizing influence on the electrogenic ion transport, resulting in greater depolarization by NE (i.e., the gradients predominate during NE). Thus the depolarization by NE (and the tension) is only greater at mid to higher NE concentrations (24, 27, 29). The lack of change of a threshold for NE probably represents the offsetting influences of smaller K^+ gradient and a larger electrogenic ion transport. Nevertheless, the increased depolarization and contraction at mid to higher concentrations of NE are probably what causes the increased peripheral resistance in at least the caudal artery of the SHR.

Furthermore, we have been able to use this altered basis for E_m (altered E_m electrogenesis) to determine that the altered membrane properties are not inherent in

the muscle cells but are instead a result of the trophic influence of the sympathetic nervous system, which appears to cause the smaller K^+ and Na^+ gradients and perhaps causes the compensatory increase in activity of electrogenic ion transport. These experiments were carried out by cross-innervation between the substrains using transplantation to the anterior eye chamber. We found that the membrane type (as defined by NE sensitivity and E_m at 16°C, indicating the K^+ gradient) and degree of activity of electrogenic Na^+ transport depended on the innervation to which the artery was exposed, rather than the substrain from which the artery was taken (1). These results suggested that it was a sympathetic trophic influence on the arterial muscle, not an inherent property of that muscle that was genetically coded, which led to the high degree of NE sensitivity and therefore increased peripheral vascular resistance. In this series of experiments, we sought to determine whether it was in fact the sympathetic innervation (as opposed to other influences in the host animal such as circulating compounds) that caused the crossover of membrane properties. The design was to first denervate half of the anterior eye chambers, into which the artery would be placed, by superior cervical ganglionectomy a few days before the transplantation. Without the sympathetic innervation, the caudal artery muscle did not change its type during the course of the experiment. In those animals where the innervation process was allowed to take place, we again found crossover of membrane properties (1). These data strongly suggest that a trophic influence of the sympathetic nervous system (5) is important in establishing the altered membrane gradients and electrogenic ion transport process in SHR arterial muscle compared with that of WKY. This example of a mechanism for the increased peripheral resistance shows how alteration of ion gradients and electrogenic ion transport can result in altered contractile behavior. Other examples relating trophic effects to supersensitivity involving altered electrogenic ion transport activities have recently been reviewed by Fleming (16).

Surface Charge

Surface charge sites of vascular muscle membranes have been little studied and are in need of further definition. Experiments on other kinds of cells, e.g., cardiac muscle cells, have identified that there is a layer of charge on the surface that determines the local environment of ions in the region of the cell membrane and may even supply ions moving through the membrane during activation (40, 41). There would thus be an important influence of the cell surface coat, or glycocalyx, on vascular muscle E_m and contraction. In fact, there is a substantial amount of Na^+ associated with vascular muscle cells, as identified by the electron probe, for which there seems no other explanation than some sort of binding that is not easily displaced in preparatory steps (38). Furthermore, there are data suggesting that La^{3+}, which causes a decrease in ion conductances through the membrane presumably by binding to surface charges, importantly intereferes with not only contraction but also relaxation steps (59). These experiments on surface charge are approached at present through elimination of the negative (sialic acid) sites with enzymes such as neuraminidase or phospholipases (41). Unpublished experiments from my laboratory suggest there are difficulties in using and interpreting neuraminidase on vascular muscle cells. Even brief exposure to low concentrations of neuraminidase seem to alter the ability of the cell to contract and relax.

Other ways to approach the surface charge question on vascular muscle might involve the use of physical parameters, such as pH. Of course, the sensitivity of vascular muscle to pH is well known and appreciated, but the mechanism causing those changes in contraction has not yet been thoroughly explored (53). Although the major influence might be simply the gradient of H^+ across the cell membrane and especially the change in intracellular pH, it is also possible that H^+ changes might alter the surface charge as well. To systematically establish a role for surface charge, it would be necessary to use a series of buffers to change extracellular pH, and perhaps also to control other ions in the extracellular solution. Combinations of pH and Ca^{2+} buffer experiments might be used to further identify the importance that surface charge of vascular muscle membranes might play in E_m and control of contraction.

Stochastic Elements

Even though it is likely that the mechanisms already discussed probably account for the E_m and the corresponding changes in tension in vascular muscle, there remain important features of the excitation process not yet considered that influence the state of contraction or relaxation. The time course of exposure to agents which change E_m and the "memory" effects caused by previous stimulation or relaxation of vascular muscle influence the subsequent exposure to vasoactive agents. Taking NE for example, vascular muscle constriction will be greater for most blood vessels if a given amount of NE is applied as several pulses at some optimal interval (e.g., 15 s) than it would be if the NE were continuously applied at the same concentration.

Several mechanisms are probably involved in the altered response to pulsatile vs. continuous NE. One that must be important is the desensitization phenomenon that occurs on continuous exposure to NE (2, 32). Such desensitization might be expected to reduce the maximum response by 50%. Furthermore, there are additional factors beyond desensitization that make even the simple contraction of a vascular muscle in response to NE complex to analyze. Another mechanism that is almost certainly involved is the shift in ion gradients after more than 10 min of NE stimulation. In all types of vascular muscle so far studied, there is strong evidence for an increase in permeability to Na^+, Ca^{2+}, and K^+, and there is also evidence for increased Cl^- conductance in response to NE (37, 38). Thus, within seconds, the ionic movements across the cell membrane begin to change, although not enough to alter gradients more than slightly during the first few minutes. The low intracellular Na^+ and Ca^{2+} begin to be measurably increased while the relatively high (with respect to extracellular fluid) K^+ and Cl^- tend to decrease. This effect is more important in vascular muscle than in practically any other type of muscle cell found in mammals because vascular muscle cells are among the smallest diameter cells that exist, being only 2-5 μm in diameter at their widest point, which is near the nucleus (Fig. 4) (44, 50). The cells then taper to very small diameters (about 1 μm) near their end portions, which means that the cells have an enormous surface-to-volume ratio about (about 1 $\mu m^2/\mu m^3$). The evidence from single-cell experiments is

consistent with distribution of adrenergic receptors throughout the vascular muscle cell (32), so that an increase in membrane permeability to all of these ions would occur throughout the entire surface area of the cell. Changes in intracellular ion concentrations measured by electron-probe microanalysis or by ion flux experiments in vascular muscle occur within only a few minutes after NE exposure (29, 33, 37). Thus ion redistribution in vascular muscle cells is an important phenomenon that changes the response to addition of NE, dependent on how recently and to what extent the vascular muscle has been previously depolarized (and to what extent ion gradients were changed). Of course, different vasoactive agents would be expected to differently affect ion conductances, making the situation a rather complex one.

It is likely that such a dependence of the ionic balance on previous stimulation underlies phenomena commonly recognized in tension experiments, e.g., where isolated segments of vessels need to be "primed" with several midrange doses of NE until they reach their maximum and reproducible responsiveness to NE. A simplified preparation like the rat caudal artery, in which innervation has been destroyed by 6-hydroxydopamine (4), has been refined to the state that contractions are reproducible for more than 12 h. Even with these preparations, there is an increase in responses upon stimulation during the first three or four exposures to NE, which probably reflects the l-h rest allowed after dissection and nerve ending destruction, and stretch back to in situ length, during which the cells might have reached a steady state of low intracellular Na^+ and Ca^{2+}. The priming doses of NE might supply Ca^{2+} to intracellular storage sites, which then could be released in subsequent contractions to give greater tension.

Of course, this means that in simply trying to record tension from blood vessels, whether in situ or in vitro, the act of measuring the response is in fact altering the contractile process to be studied. Therefore, a well-defined protocol for stimulation of the tissue at certain intervals (chosen to give the most reproducible and physiological steady state) needs to be worked out for each individual preparation. In fact, there are great difficulties in any laboratory switching from one preparation to another, e.g., to compare the same artery from different animals or different arteries from the same animal species. The first months of working with a new preparation, especially if it is simply used at the optimum conditions for the blood vessel most familiar in the laboratory, are likely to yield results that will later suggest the experiments were carried out under suboptimal conditions. The different optimum protocols for different arteries will lead to invalid "differences" from one preparation to the next because what is the optimum for one preparation is far down the curve for the other.

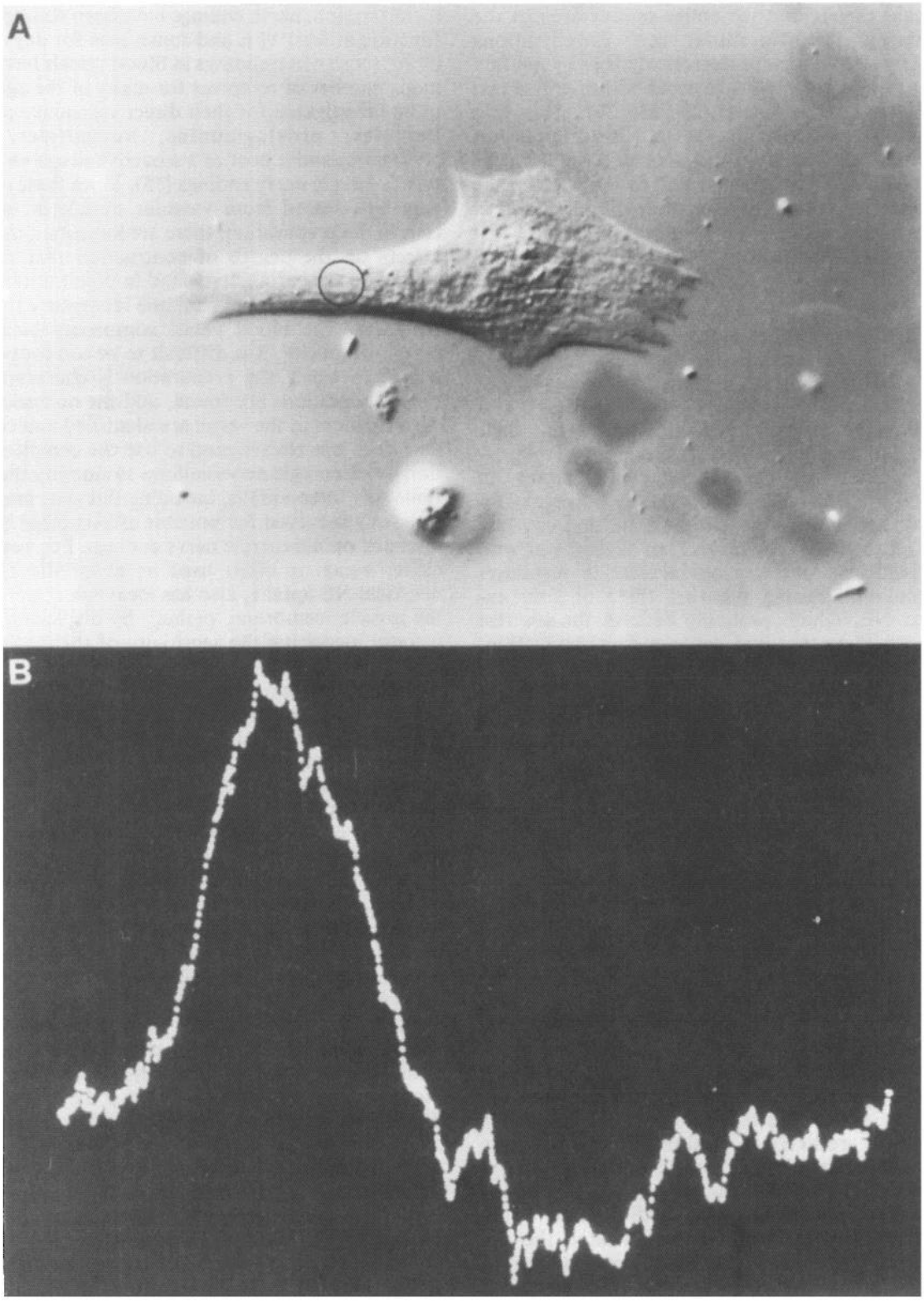
Even the problems cited above assume that the preparation has been simplified to eliminate influences of nerve endings on the process. In fact, many experiments are done with arteries merely dissected from the animal, with adrenergic nerve endings intact and capable of taking up and releasing enormous quantities of NE (10). Thus, many properties ascribed to vascular muscle cells may well originate from the adrenergic nerve endings in the preparation. For reasoning about changes in muscle cell membranes, it is important to identify and to control the neural elements in the preparation. Even though the nerve will have been cut in the dissection, nerve endings have been demonstrated to function at least 12 h and sometimes for days. Furthermore, those nerve endings in blood vessels have an enormous number of receptors for many of the agents likely to be investigated for their direct vasoactive properties. Peptides, prostaglandins, nucleotides, cardiac glycosides, and a host of vasoactive drugs have actions on adrenergic nerve endings (55). Since these substances may be released from vascular muscle or endothelial cells in the preparation, there are important modulatory effects on the degree of contraction that might also enter into the variability found in preparations from 1 h to the next, as well as from one laboratory to the next.

Because the blood vessel complexity belies its apparent simplicity, it is difficult to be too cautious in the degree to which the preparation is characterized, optimum conditions are found, and the nonvascular muscle influences in the vessel are identified and controlled. One does not always need to use the complete destruction of adrenergic nerve endings to simplify the preparation. Any intervention, including this one, must be continuously surveyed for possible effects other than those intended on adrenergic nerve endings. For example, cocaine, which is often used as a specific blocker of neuronal NE uptake, also has local anesthetic effects on the muscle membrane, perhaps by displacing Ca^{2+} and directly increasing the sensitivity of the muscle cells to NE.

Even if one can completely eliminate the neural influences on vascular muscle in an isolated preparation, the situation will still be complex because of the possibility that both α- and β-receptors, perhaps existing as their α_1, α_2, β_1, and β_2 subtypes, complicate the picture. Not only will there be different interactions and affinities, but different responses within a cell to activation of the receptor (e.g., time course differences, changes in high-energy phosphates, and protein phosphorylation) can lead to a situation difficult to interpret. In fact, the suggestion that one might not have identified all the adrenergic receptor types in vascular muscle (34) could be explained with only known receptor types when a full analysis of all muscle adrenergic receptor actions is known. Especially when one considers that there could be a change in the number of available receptors for interaction based on previous stimulation as a memory factor for the cell membrane, it would be possible to find explanations for virtually all of the data so far reported.

To deal as an experimentalist with this very complex situation, one needs to try to divide the problem into parts to make the attack on the problem manageable. The need for meticulous characterization and optimization of all factors for each blood vessel has already been alluded to, but it is important to mention here that wherever critical experiments are being conducted, a timed protocol should be followed. The long-term exposure of vascular muscle to significant stimulation, if that stimulation involves large increases in membrane ion conductances, will dull the response to be found and complicate interpretation of the data. For example, where E_m measurements are being made, it has been extremely important to expose the cells to NE, phenylephrine, serotonin, angiotensin, and other

Figure 4



Ca^{2+} transient in a single cell is shown along with an isolated single cell from which such measurements are made. *A*: photomicrograph of a single azygous vein muscle cell between spontaneous contractions, by differential interference contrast (Nomarski) at a magnification of ×900. For measurements of intracellular Ca^{2+} by the arsenazo III optical technique, area of measurement was about 3.4 μm^2, as is shown by 1.2-μm-radius circle on photomicrograph in *A*. *B*: Ca^{2+} record represents subtraction of Ca^{2+}-sensitive and Ca^{2+}-insensitive wavelengths (660–580 nm) for arsenazo III and gives time course of Ca^{2+} entry during a rapid contraction of a single azygous vein cell (sweep duration = 800 ms). These fast contractions are more easily detected than slow aortic cell contractions because of their phasic nature. Arsenazo III was introduced into the cell by incorporation into liposomes, which were taken up by the cell. Correlation between intracellular Ca^{2+} activity, as sensed by arsenazo, and cell contraction seems to be sufficient for intracellular Ca^{2+} to explain development of tension.

vasoconstrictors for a limited period of time, for which we find the best compromise is 15 min in segments of rat caudal artery. During the last third of the 15 min there may be significantly altered ion gradients, but since the distribution of ion gradients will be dependent on the single cell, and we have found substantial variability among cells in every preparation studied both by E_m and by electron-probe measurements, the variability introduced during the last 5 min is not too severe. Because of the practical problem of performing enough impalements during the time period, a 15-min data collection period is optimal, at least for caudal artery. On initial exposure of the caudal artery to these vasoconstrictors, there are approximately 3 min during which only part of the cells appear to be responding to the NE, which apparently must diffuse through layers of cells, and is either binding or being taken up into some of those cells in the process. Therefore, in caudal artery, we have found that the 10-min time window between 5 min after applying the drug (or changing ionic solution) and 15 min allows the maximum response to be found without excessive shifts in ion gradients. On return of the cells to normal solution, 90% of recovery occurs over approximately 10-12 min. All cells appear to recover by 15 min, the time when we would shift to the next concentration of vasoactive drug or combination of drugs. Even though such considerations seem methodological, they are very important to emphasize here because they involve the mechanisms of excitation-contraction coupling in vascular muscle. By recognizing that preparations will give different responses based on membrane "memory" and other stochastic considerations, we will be better able to understand and predict how to alter membrane factors in the excitation process.

The Ca^{2+} Consequence of E_m

The results of these changes in E_m are changes in tension. Although it is possible that tension changes exist which do not depend in any important way on E_m, such a mechanism in vascular muscle remains poorly defined, with most of the evidence favoring the importance of E_m except under conditions of further tension development in an already depolarized preparation (33). To understand the contraction process, a better comprehension of the relation among depolarization, Ca^{2+} release, and Ca^{2+} uptake into cell organelles is needed. The process of excitation-contraction coupling has not been defined in detail and can only be vaguely included to explain the stochastic features of vascular muscle, but it could be that this Ca^{2+} release step is the important variable.

To explain further, perhaps repeat stimulation is not only making more Ca^{2+} enter the cell to be available for release by the sarcoplasmic reticulum, but also within the cell the same amount of Ca^{2+} is redistributed to sites that more efficiently release (or less avidly take up) Ca^{2+} to explain increased responses on repeat stimulation. Such a mechanism would be analogous to the staircase phenomenon in the heart discovered by (and named after) Bowditch (11). To find out whether such a mechanism exists, it would be necessary to measure intracellular free Ca^{2+} in different regions of the cell and associated with different organelles. Contraction data alone would not be proof because of the complexity of factors discussed above that make interpretation more difficult in vascular muscle. Data from Ca^{2+} flux experiments give kinetic fractions and the total Ca^{2+} amount with which intracellular localization data must be fitted. However, no anatomical correlation of the various fractions of Ca^{2+} is possible until one uses an optical method, such as measurement with Ca^{2+} indicators. The available Ca^{2+} indicators include the bioluminescent protein, aequorin, and the two metallochromic dyes, arsenazo and antipyrallazo (7). With these substances, it is possible not only to quantitate free ionic Ca^{2+} within the cell but also to localize, within the limits of the light microscope, the area where Ca^{2+} is found.

Another promising technique for understanding the time course of Ca^{2+} release during a single contraction is provided by Ca^{2+}-selective microelectrodes, which have recently been used on the nonvascular smooth muscle preparation of isolated cells from the toad stomach (H. Yamaguchi, personal communication). These nonstriated gastric muscle cells show a time course of Ca^{2+} release consistent with a direct contractile activation by free intracellular Ca^{2+}. Experiments with aequorin have shown a close correlation between the aequorin Ca^{2+} signal and the degree of contractile activation also in mammalian (dog) gastric muscle cells (46). Recent experiments in my laboratory have provided the first arsenazo signals from isolated single vascular muscle cells, showing a rise in intracellular Ca^{2+} activity that correlates closely with the simultaneous contraction (Fig. 4). Although development of the technology for isolated single vascular muscle cells has been a many-year process and the adaptation of Ca^{2+} indicators for these isolated vascular muscle cells proceeds slowly, it now appears possible to study the effects of sequential applications of vasoactive agents and ionic alterations with simultaneous recording of E_m, intracellular Ca^{2+} activity, and contraction during direct visualization of the single cells.

Conclusions

With this survey of the excitation process in vascular muscle, it is clear that much remains to be learned. Research progress over the last several years seems to have come about through studying the unique features of vascular muscle that make it different from other muscles, rather than trying to force the characteristics of vascular muscle to fit a model generated for skeletal muscle. Indeed, the appreciation that there are different types of vascular muscle gives better accuracy about prediction of the operation of each because of the variability that exists throughout the cardiovascular system.

One very important feature of vascular muscle that has emerged is operation within the steep part of the voltage-tension curve. This means that even in the steady state the vascular muscle will be strongly influenced by small changes in E_m, such as are contributed by electrogenic ion transports. Indeed, the demonstration that there is the direct mechanical correlation of activation of the electrogenic Na^+ pump is an important clue to better understanding vasoconstriction and vasodilation. The implication is that small changes in E_m make a large difference in vascular muscle instead of just being a minor modifier, as is the case in some neurons and skeletal muscles.

An exciting new area for exploration is measurements of intracellular Ca^{2+}. Both the localization of intracellular uptake-release sites for Ca^{2+} and the determination of the time course of Ca^{2+} changes during a contraction seem feasible, as well as logical, next steps in understanding control of contraction of vascular muscle by membrane excitation.

This research was supported by National Heart, Lung, and Blood Institute Grants HL-14388 and HL-16328 and Research Career Development Award HL-00073 (to K. Hermsmeyer).

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Announcements

International Symposium on Surfactant System of the Lung

An International Symposium on the Surfactant System of the Lung will be held in Rome on 2-4 March 1983. *Topics*: Biological and Preclinical Aspects; Methodology; Clinical and Therapeutic Aspects; Surfactant in the Bronchial Tree; Mechanisms of Clearance of the Tracheobronchial Tree. *Information*: Fondazione Giovanni Lorenzini, Via Monte Napoleone, 23-20121 Milan, Italy; Phone: (02) 70.22.67 or 78.38.68; Cable; LORENZFOUND.

IUPS Satellite Symposium on The Peripheral Circulation

An IUPS Satellite Symposium of the Peripheral Circulation will be held at Newport Beach (Sydney) on 5-6 September, 1983. *Topics*: Structure-Function Relationships; Reflex-Local Control; Noninvasive Assesment; Hormonal Aspects; Microcirculation (including Vascular Smooth Muscle Control); Pharmacology of the Peripheral Circulation. Free communications are sought for the program. *Information*: Dr. Stephan N. Hunyor, Cardiovascular Unit, Royal Shore Hospital, St. Leonards, NSW 2065, Australia. Abstracts and regulations deadline: 31 January, 1983.

Past President's Address

I Think I Would Rather Watch Them Make Sausage

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There are two things I am told that no one should ever see being made if you are to appreciate the product. One is sausage; the other is legislation.

Having grown up in rural Minnesota a few miles north of the Iowa State Line, I am most familiar with the business of making sausage. Since moving to the national capital area I also have become familiar with the business of making legislation.

Offered the choice, I think I would rather watch them make sausage.

My choice is not to imply that the business of sausage making has improved all that much. In fact, the truth of the matter is that the basic recipes for making both sausage and legislation have remained unchanged for some years.

What has changed, however, is technique. The sausage makers have simplified their techniques, while the legislative system has become more complex and more cumbersome. This is due, by and large, to the growth and the development of public interest groups, a phenomenon that has impacted most significantly on both the legislative and the executive branches at all levels of government. This ever-increasing involvement in the affairs of government by public interest organizations—both the for-profit and the nonprofit groups—was actually triggered just 10 years ago by a most unlikely incident within the governmental structure itself. I am referring to the almost comic burglary of the Democratic National Committee headquarters at the Watergate complex in June 1972. But while the burglary itself is nearly forgotten, the backlash of the total Watergate episode continues to this day to have its effects at every level of the legislative process, as well as upon how affairs of state are conducted by national governmental agencies.

Since the Watergate days, citizens from all walks of life have become increasingly involved in the business of the Congress, Federal agencies, state general assemblies, and local government. The public-at-large—and I do include physiologists in this group—is no longer content to permit either appointed or elective bodies to continue to operate in a vacuum as they did at one time.

This populist involvement in the legislative process is well documented by the quantum leaps in recent years in the number of letters and telephone calls legislators receive daily; the marriages of unlikely partners to form single issue, public interest coalititions; the proliferation of political action committees which provide funds for both the incumbents and the challenging office seekers; and the development of grassroot networks by professional, educational, and scientific societies, including the American Physiological Society.

Prior to this year the Society's involvement in governmental affairs was confined primarily to monitoring and reporting those Federal activities that could affect physiologists. This was accomplished largely through the efforts of three Society committees whose members on occasion went to Capitol Hill to discuss the current issues and by the Society having designated representatives who met with the public affairs sections of other organizations, including the Federation of American Societies for Experimental Biology, the Association of American Medical Colleges, the National Society for Medical Research, and the American Institute of Biological Sciences.

The creation this year of a grassroot network and the engaging of a public affairs consultant by the Society represent a marked departure from this tradition. However, this decision by Council to move the Society's interest in public affairs closer to the mainstream of government was neither hasty nor abrupt. Actually, the decision was 20 years in the making.

The first to publicly cite the need for the Society to become more involved in the affairs of government was Horace Davenport. He said in his address as past president in 1962 that "...the purposes of the Society are public ones: to do what we can to make conditions most favorable for productive thought..." (1).

However, Dr. Davenport then backed away from this premise by adding: "...but after reflecting that most of us depend for all of our research support and a large fraction of our salaries upon the good will of the Congress I decided that the hinting of the imperfections of its altruism might be impolite. We do not exert political pressure; we are its objects" (1).

Loren Carlson was more direct about the Society's need to increase its role in governmental affairs when he said from the same past president's platform in 1969: "We can no longer live in an ivory tower and insulate ourselves from political, economic, and social pressures" (2).

And five years later Daniel Tosteson described the need he saw for the Society to become a resource of information for those who legislate and administer laws and regulations. By and large, his observations were the basis for Council's decision to increase Society activities in government affairs. Dr. Tosteson said in his past president's address in 1974:

"During the past year I have spent a lot of time in Washington. I have had occasion to become acquainted with persons working in the executive and legislative branches of the Federal Government as well as in such organizations as the Association of American Medical Colleges and the Institute of Medicine.

"I am impressed that most of the persons working in these organizations are industrious, intelligent, and dedicated, but relatively poorly informed about the nature of basic research, particularly in its relation to the accomplishment of specific goals, and about graduate and health professions education.

"Often the background of these individuals is in the law or one of the social sciences such as economics or sociology. Physiologists could contribute much to the knowledge of these individuals about the health research and education programs which they seek to

legislate and administer" (3).

Dr. Tosteson's observations – particularly the statement that physiologists can contribute to the knowledge of those who legislate and administer programs – and the increased activity of the animal welfare activists shaped Council's decision to increase Society activity in the area of governmental affairs by appointing the consultant and creating the grassroot network.

This decision does not imply that the Society has embarked upon a broad course of direct lobbying, which is prohibited in substantial amounts under the Internal Revenue Service's tax exemption for 501(c)3 organizations which are the nonprofit groups designated as scientific, educational, or charitable. However, to serve as a conduit to government for information concerning legislative and regulatory activities is a legitimate function of the Society and is a role that should involve all physiologists.

This role is not an easy challenge. The issues confronting the research community are many and diverse. Among the issues are the reduction of federal funds for research and research training after institutions have become almost wholly dependent upon these funds; setting aside of research funds for small businesses; new prohibitions for both obtaining animals and using animals in the laboratory; proposal to set aside research funds for the sole purpose of developing nonanimal models; increased restrictions relating to the standards of animal care, accreditation, inspection, and mandated involvement of community representatives in research practices requiring the use of animals; and the move toward the decentralization of government which now has made many national concerns also the same concerns of government at the state and local levels.

Because of the growing number of issues that have a direct bearing on physiology today and for the future, there is a paramount need to make our concerns known now to those who legislate and administer programs affecting all physiologists. The shift toward decentralization of both the government and the issues is one of the major reasons for establishing the grassroot network and appointing a governmental affairs consultant.

The effects of decentralization are already evident; since January we have seen more than two dozen state and local proposals introduced in governmental bodies that would restrict investigators and/or limit their use of animals.

The trend toward decentralization of government is here and will continue no matter what Federal Administration is in office in 1984. And as this trend continues, the regulations governing science and research will undoubtedly become somewhat diffused and confused. Perhaps the most significant reason for this is the increase of activity by the public interest groups, each with somewhat different perspectives, already at work in statehouses and courthouses, as well as on Capitol Hill. The public's interest in the affairs of government has now grown to a point where there is no longer any bill or regulation proposed that does not bring out from the grass roots a barrage of information and anecdotal evidence from both critics and proponents.

Therefore the Society must also fulfill the role as the clearinghouse and resource for factual information, not propaganda, concerning those activities involving physiology, not only at the national level but at the state and local levels as well. The Society would be failing its constituency if it did not assist its members within each state when they are confronted with such issues.

Because laws and regulations are considered, debated, and enacted primarily on information provided by concerned individuals and public interest groups who are being heard at all levels of government, the need for physiologists to provide factual information is acute. Our professional futures and the scientific methods that we will be permitted to use in the conduct of research will be determined, by and large, by the information from all sources, both friendly and hostile.

To meet this challenge the Society has identified one member in each state who has expressed an interest in government and who is knowledgeable about legislative activities for the purpose of monitoring and reporting on state and local issues that could either aid or adverseley affect the work of physiologists. And I stress the words "monitor and report on state and local activities," because this is not considered to be direct lobbying, per se.

This 50-member grassroot network is known officially as the Public Affairs Advisory Committee and is guided and supported in its efforts by a five-member Public Affairs Executive Committee, headed by John Shepherd, and is assisted by the governmental affairs consultant, William Samuels. Orr Reynolds also provides valuable input.

The function of the Public Affairs Advisory Committee basically is twofold. The first I have described, that is, to identify and monitor all legislation and regulation pertaining to biomedical research that is being considered or proposed by state, county, or municipal governments within the member's state and to keep the Society informed of these actions and subsequent developments.

The second function is to provide both the Society and the Congress with comments and suggestions regarding national issues. This is a vital activity because it allows the Society to speak with an unified voice in expressing the concerns of physiologist as a whole, and it also provides the members of the Congress with that important piece of information as to how a particular law will affect their constituents back home.

During the six months the Committee has been officially in existence, it has achieved a remarkable record of successes. At both the state and local levels, individual Committee members were successful in halting a variety of legislative initiatives that would have restricted researchers and their use of laboratory animals. Included in these local efforts was a bill here in California that would have prohibited all pounds in the state from releasing unclaimed animals to approved research institutions.

The situation in California, as well as similar situations in Michigan, Illinois, and Florida, involved requests for assistance from the Society's National Office staff. In the case of California, the Society coordinated its efforts with the state universities and state health associations. Much of the data and information the Society provided to the legislators in that general assembly related to the experiences of other states where similar laws have been enacted, particularly with respect to cost factors. We have been told that this information contributed significantly to the defeat of that bill.

At the national level the comments and recommendations from Committee members and their letters to Congressional committees and their own representatives were major factors in the revisions of HR 6928, more

commonly referred to as the Walgren Bill.

Staff members of several House committees, as well as the personal staffs of several of the Representatives involved with the Walgren Bill, have reported that the input from the scientific community, in general, and the physiologists, in particular, had a major bearing on some of the revisions of the bill.

One such revision involved eliminating a provision that would have given those grant proposals that made reference to the development of alternative methods a second chance for funding if the grant proposal had been approved but not funded after the initial peer review. Largely because of the letters from the Society's grassroot network and others, the Society along with three other organizations were invited by the Committee chairman to draft an amendment that would eliminate the second-chance funding and still provide encouragement for the development of alternative methods. The amendment proposed by the Society, the Association of American Medical Colleges, the National Society for Medical Research, and the National Association of State Colleges and Land Grant Universities was accepted unanimously by the committee.

Despite success in getting some of its major concerns changed in this bill, the Society still does not favor the legislation because of the costs for each institution in administering the act and in accreditation. It has been estimated that the total direct cost to institutions will be at least $1,150,000,000 (billion) over the 10-year lifespan of the bill.

Furthermore, the Society is concerned with the subjective restrictions placed on the investigators regarding their use of animals, the increased costs for the acquisition of animals and performance of research, and the requirements for accreditation that exempts only the smallest of facilities which are those most likely to have the biggest problems regarding the care and use of animals.

These and other concerns will be addressed by the Society at the Congressional hearing to be conducted by the House Subcommittee on Health and the Environment during either the lame duck session at the end of this year or at the start of the 98th Congress in January. It can be anticipated that the Senate will also conduct hearings when this bill is considered by that chamber next year.

What can be inferred from this is that there will be some kind of legislation enacted by the Congress, probably in 1983, that will regulate further the use of *all* laboratory animals in those areas involving Federal support funds for research, testing, and experimentation. Efforts by the scientific community to delay such legislation by conducting a two-year study to determine the impact of HR 6928 on research institutions was defeated in the House of Representatives in September. The defeat of this proposal followed the delivery of thousands of letters from humane organizations and animal rights groups to every member of the House just prior to the vote to consider such a study. The grassroot pressures for some kind of research animal reform legislation is now unbelievably enormous.

While the Society does not support the bill in its present form, ironically there are several humane organizations and animal welfare groups who also do not support the bill, in some cases for many of the same reasons. Perhaps Charles Dudley Warner best described this situation 100 years ago when he was associate editor of *The Hartford Courant*. He said, "Politics make strange bedfellows" (4). The only thing I could add is that I am not sure who is doing what to whom.

Up to this point I have described the background for Council's decision to have the Society serve as a major channel for providing information to government and how this newly created approach can and has performed. My parochialism on this point was by intent, but is not meant to infer that the American Physiological Society has become the focal point for all legislative issues involving research and education.

Working in concert with other national scientific and educational organizations, the Society has accepted the lead role for only those issues of particular interest to physiologists, such as the Walgren Bill, amendments to the Animal Welfare Act, and funding that would permit the continuance of the U.S. Department of Agriculture's Animal and Plant Health Inspection Service for inspection of animal facilities. (It has been proposed that this function be turned over to state agencies and humane societies.)

In the three areas I have mentioned the Society has played the lead role. Aside from the amendments to the Walgren Bill, the Society prepared and presented statements and testimony before Senate and House committees on agriculture, budget, and appropriations regarding the funding for the Agriculture Department's inspection program and coordinated efforts with House staffs on proposed amendments to the Animal Welfare Act which later were incorporated into the Walgren Bill.

The Society continues to look to the Federation of American Societies for Experimental Biology for its leadership in those areas of general interest to basic biomedical scientists and to the Association of American Medical Colleges for its leadership in the areas of concern to medical educators and investigators. Similar roles relating to other areas of research have been accepted by the National Society for Medical Research, the American Institute of Biological Sciences, the Intersociety Council for Biology and Medicine, and others.

Together we have identified the common goals in presenting to government at all levels a unified voice speaking of the concerns scientists and educators have in preparing for the 21st Century, which is closer in time to us today than is that time between today and when Dr. Davenport said from this platform 20 years ago that the Society should be heard in the halls of government.

We are an increasing number. The scientists now alive comprise 90 percent of all scientists who ever lived. What we as a community of professional scientists and educators can accomplish—or fail to accomplish—in the decade of the 1980s may very well have a telling effect for the generation of scientists and educators who follow us.

Our goal is known, and our mission has been described. And if we are to be effective, much of this effort depends upon a responsible membership. As I conclude my final Presidential act tonight I look forward not to years as an elder statesman, but rather to joining with you as a responsible and active member working to achieve the goals before us in this challenge.

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A Backward Look From Far Above Cayuga's Waters

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Prologue

Many of the basic discoveries in the biomedical sciences have been made by animal physiologists, and these discoveries have been widely used in human and animal medicine and to improve the efficiency with which animals produce food. Fifty-three percent of all food consumed in the United States is derived from livestock and poultry, and these foods have higher quality nutrients than the plants consumed by animals. Animal products supply two-thirds of the protein, one-third of the energy, one-half of the fat, four-fifths of the calcium, and two-thirds of the phosphorous in our diets (5).

Through their teaching and research, Cornell physiologists centered in the College of Veterinary Medicine, have made major contributions to these developments for a great many years. Today, physiology at Cornell, as at many of our major institutions, has become a complex, almost all-inclusive, field covering subjects ranging from molecular biology to interactions of large animals with their environments. The Department of Physiology in the College of Veterinary Medicine at Cornell played a major role in all of these developments. Thus we have focused our attention on that department and the men who developed it. Logically, the history of physiology at Cornell can be divided into three eras: an early period (extending from 1868 to 1932), the middle years (1932 - 1960), and a "modern" era (since 1960).

The Early Years (1868–1932)

At the opening of Cornell University on October 7, 1868, the only building on the site that was to be its campus was Morrill Hall. Even that building still required the emplacement of windows and doors. Nevertheless the faculty had been selected and the various departments had laid out their courses of study.

The College of Natural Science was under the guidance of Dr. Burt Green Wilder (Fig. 1), who had been appointed Dean in 1867 and remained at the university until retirement. He had a M.D. degree from Harvard Medical College and had served in the Civil War as a surgeon in the Northern Army.

At the onset, Wilder taught most of the courses, which included comparative anatomy, physiology, and zoology. The student received a broad education in the natural sciences and at the end of four years was awarded the degree of Bachelor of Science. To add to the student interest, Professor Wilder maintained a menagerie in the basement of Morrill Hall. Sometimes the interest turned to pandemonium, e.g., when the monkeys invaded the classroom during a lecture or when a bear chewed a student's arm!

When McGraw Hall was completed, the cat colony, whose tenants were used for anatomy and physiology demonstrations, was moved into the lower reaches of the new building. There were problems, and Wilder, although unorthodox in many ways, was sensitive to criticism, especially when it came to the care he gave his cats. On the door of the cattery he hung a self-composed sign (1)

Snugly housed,
Fully fed,
Happy living,
Useful dead

However, the flea problem was almost overwhelming, and the janitor who lived next door habitually wore fly paper, with the sticky side out, around his ankles.

Wilder's lectures were inspiring and his approach to the laboratory work attracted many an inquisitive student. One of these, Theobald Smith, the famous American pathologist, is said to have commented to Wilder years later, "It was a fortunate thing for us that your laboratories were so small and crowded, because all of your work was done in the presence of your pupils, and we could not very well escape the infection of your enthusiasm (6)."

Figure 1
Burt Green Wilder.

Wilder clearly demonstrated the advantages of using the *Necturus* (a salamander with permanent gills) for teaching physiology. The histological features of this animal are easily studied because of their size. For instance, the blood cells are of sufficient size to be seen with the naked eye. The frog was another animal used for laboratory demonstration. During the warm months, the supply was plentiful but in the winter months it dwindled. To ensure a steady supply of frogs and other aquatic animals, Wilder had a "frog spring" constructed along Fall Creek. This aquarium was enclosed to protect it from predators as well as the winter storms.

From the beginning, a museum of zoology and physiology was established. It consisted of a remarkably well-mounted collection in ornithology, which was carefully classified; a conchological collection from the South Atlantic and Pacific coasts; the modeles clastiques of Dr. Auzoux of Paris, illustrating comparative anatomy, physiology, and zoology; and the models and specimens collected by Professor Wilder.

Dr. Wilder gave nearly 20 years of lectures on the principles of physiology. These lectures were given three times weekly and were continued as a required course until 1896, at which time they became elective. As further inducement to the students, the President's Prize in Physiology was offered for the best notes on the lectures of Professor Wilder. A course in experimental physiology was given in 1880 and 1881 but was later abandoned for want of suitable apparatus.

Because he held a double appointment in the Colleges of Agriculture and Natural Science as Professor of Veterinary Medicine Dr. James Law was involved with the instruction of many of the same students who attended Dr. Wilder's lectures and demonstrations. Among the subjects he taught were anatomy and physiology of domestic animals. By 1872, these courses had been expanded to five hours weekly. The textbooks in veterinary physiology consisted of Colin's *Physiologie des Animaux Domestiques* and Marshall's *Outlines of Physiology*. After the wooden laboratory building was built on the present site of Goldwin Smith Hall much of Dr. Law's laboratory teaching was carried on there.

In 1873 a young man from Crumhorn Lake, New York, began his training at Cornell under Wilder. His name was Simon Henry Gage (Fig. 2), and he thought he would like to become a physician. However, within a short time he was convinced that his place was teaching and remained at Cornell throughout his career.

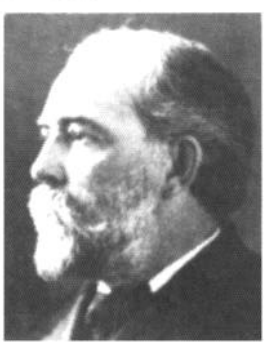

Figure 2
Simon Henry Gage.

Figure 4
Pierre Augustine Fish.

Figure 3
Wilder's brain collection.

Professor John Henry Comstock reminisced on the occasion of Gage's 65th birthday concerning the devotion of Gage to his work and to Professor Wilder.

"Dr. Wilder was collecting brains of mammals (Fig. 3) for Agassiz (this was before he began his own collection) and he became greatly excited at the possibility of securing a specimen from a camel. To him, it seemed that the obvious thing to do to was to outfit Gage with a bottle of chloroform and a dray and tell him to produce the carcass of the camel.

"He had confidence in his assistant's resourcefulness and no doubts of his success, and in this he was not disappointed.

"In spite of the fact that the beast was found not to be feral and that there was a financial claim to be satisfied, and in spite of the fact that it did not drop asleep at the first whiff of chloroform, there soon appeared on the campus a truimphant procession headed by Sincebaugh's dray upon which was the carcass of the camel and, astride it, Eugene Corson, waving his hat."

Dr. Wilder, in later years, recalled, "In the fall of 1873 a freshman, Simon H. Gage, succeeded John Henry Comstock as helper in the laboratory. His zeal and ability, his prompt mastery of microscopical methods, his patience, and especially his early manifestation of the rare and precious quality which may be designated as morphological insight, caused him to be entrusted more and more with the personal instruction of laboratory students, whose numbers and requirements were then rapidly increasing" (7). (It wasn't until 1873 that the microscope came into general use in the department. Up to that time, only one such instrument was available.)

While Gage's interest was primarily in the area of histology, embryology, and microscopy, he made many contributions to physiology. The influence of both Wilder and Law had a profound effect on him. His interest in physiology grew with the years and his training under these two men probably helped him to guide young students in the natural sciences in an era when the disciplines were not so clearly defined.

One of Gage's protégés was Pierre Augustine Fish (Fig. 4), who graduated from Cornell in 1890 with the degree of Bachelor of Science in Natural History. For a period of five years he taught physiology and neurology under Professor Gage and took graduate work which

Figure 5
Laboratory session in physiology and pharmacology, New York State Veterinary College. Dr. P. A. Fish standing at extreme left.

led to a Doctor of Science degree in 1894. His summers were spent at the Marine Biological Laboratory, Woods Holl,[1] Massachusetts, under the guidance of Professor Bumpus of Brown University.

The Bureau of Animal Industry was looking for a man to assist Dr. V. A. Moore in 1895. Gage advised Fish to take the position because the New York State Veterinary College was beginning to cast about for a faculty, and this seemed to be a good opportunity for Fish to get some training for a position in the new physiology department that was to be formed.

While working at the Bureau of Animal Industry, Fish attended night sessions at the National Veterinary College in Washington, DC, and obtained a D.V.S. degree. When the Veterinary College began its academic sessions in the fall of 1896, Dr. Fish was prepared and he received an appointment as head of the Physiology Department in the new college. His title, at that time, was Assistant Professor of Comparative Physiology, Pharmacology and Therapeutics. He continued his studies, in addition to his administrative and teaching duties, and was granted a D.V.M. degree in 1899. He thus became one of a very few men who ever obtained two academic veterinary degrees.

During the early years of the Veterinary College, the Department of Physiology provided instruction in a number of disciplines. Added to the lectures and laboratory in physiology were the lectures in pharmacology and the laboratory in pharmacy and urine analysis.

Dr. Law's annual report for the academic year 1897-98 notes that Dr. Fish found his work interfered with at first by the unfinished condition of his laboratory, but notwithstanding he conducted a most thorough and successful course of classroom and laboratory work, including special researches by individual students in digestive ferments and other normal secretions (Fig. 5).

The lectures and recitations in pharmacology and the laboratory work in pharmacy proved highly successful in an educational sense. By establishing the most intimate practical relations between pharmacology and pharmacy on the one hand and the clinical work on the other, the interest of the student in both is greatly enhanced and his progress correspondingly secured.

The course in comparative veterinary physiology was considerably extended over the year 1896-97, and Dr. Fish had established some practical laboratory work on digestion, sanguification (hemopoiesis), and secretions in the different genera of animals. This new departure proved so attractive that students and postgraduates from other parts of the University availed themselves of this new type of training. Medical students still received their instruction in physiology in the College of Arts and Sciences, and therefore the classes at the Veterinary College were primarily for veterinary students.

By 1899 the number of students attending the classes in physiology and materia medica had increased tenfold. This necessitated the appointment of an assistant and distribution of the work in materia medica and therapeutics over the three-year course in veterinary medicine. The first assistant was Edith J. Claypole, M. S.

In 1901 Carl Wallace Fisher, V.S., was made assistant in physiology and Walter Wells Hoover assistant in physiology and materia medica. Eight courses in physiology and pharmacology were given in 1902, requiring the help of five assistants of various grades. This number had been reduced to two when the academic year 1904-05 began. Both of these were veterinary graduates from the class of 1904, Howard J. Milks and Wilford B. Mack. The following year, Milks was retained as a teaching assistant in both physiology and pharmacology.

Dr. Milks' place was taken during the year 1906-07 by Dr. Frederick Henry McNair. The following year Dr. Lee Seldon Backus held the position.

During the summer of 1908, Dr. Fish attended Western Reserve, and on his return a small animal clinic was established under his direction. Previously, small animals brought to the college for treatment were divided according to their ailment between the medical and surgical clinics under the direction of Dr. Law and Dr. Williams. Space was now provided for small animals and this clinic became part of the Department of Physiology.

[1]The modern spelling is Hole.

The assistants to Dr. Fish were increased to three for the academic year 1908-09. Howard Welch, B.S., B.S.A., was appointed assistant in physiology, pharmacology, and small animal clinic. Two demonstrators were also appointed, Frank S. Wood and Frank E. McClelland. Students were assigned to the small animal clinic for six actual hours per week, thereby increasing the teaching load considerably.

The situation was remedied by the time school opened in the fall of 1909. Mr. Charles E. Hayden, A.B., was appointed assistant in physiology and in addition to these duties he undertook the course in veterinary medicine. He obtained his D.V.M. in 1914 and became the first permanent assistant to Dr. Fish.

It was in the fall of 1909 that the small animal clinic became a separate department under the direction of the newly appointed Dr. Howard J. Milks. Chauncey E. Cook was assigned to assist him. In addition to their clinical duties, these men were assigned the courses in pharmacology, pharmacy, and therapeutics.

These two developments finally focused the activities of the department primarily on physiology, the one exception being urine analysis. Under the able guidance of Dr. Hayden (Fig. 6), this subject remained in the department until a clinical pathologist was appointed in the late 1940's. Doctors Fish and Hayden were the mainstays of the department from 1910 to 1929 with the exception of 1918 and 1919, when Dr. Fish was in the military service and Dr. Hayden was acting head with H. E. Marsh as instructor. Their philosophy was clearly stated in the annual reports of those years: "It is the aim of this department to select from a wide field of important topics those which will be of greatest use to the student in comprehending the vital processes of the animal body. Without a complete understanding of the normal functions it is useless to attempt progress in the proper conception of diseased conditions."

In 1908 Dr. Fish began investigations into the digestibility of "bob-veal." It was illegal, at the time, to offer veal for sale under the age of four weeks. This restriction was enforced because of a common belief that veal of less than four weeks was harmful, although there was no scientific proof that such was the case. The evidence showed that veal under four weeks had a higher water content but was wholesome in other respects. The "bob-veal" proved palatable and nutritious to sixteen families (75 people) on whom the meat was tested. It was also found that digestion with artifical gastric juice showed no difference from market veal.

From 1920 to 1924 Professor Gage and Dr. Fish (2) carried on a joint project investigating the small particles in the blood chyle, which they first named chlyomicrons. These paricles had been seen by others, but their significance had remained unknown.

With use of the dark-field microscope and the feeding of fat labeled with a red dye, Sudan III, they were able to trace the fat particles through the various stages of absorption. Experiments were carried out in the dog, cat, sheep, cow, horse, chicken, and human. Their results were first reported at the Annual Conference for Veterinarians in January 1921. Later reports were published in the *Annual Report of the NY State Veterinary College* (3) and the *Journal of Anatomy* (4). This work still stands as a classic example of the early investigations in the field of fat absorption.

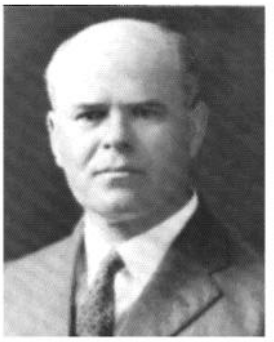

Figure 6
Charles E. Hayden.

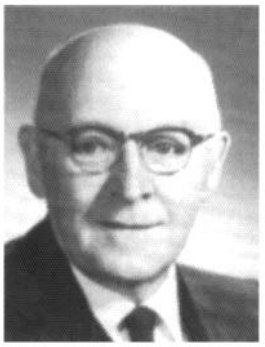

Figure 7
Henry Hugh Dukes.

With arrival of Dr. Charles E. Hayden in 1909, interest in the chemistry of blood, urine, and milk began to increase. Over the years this interest gradually increased until the department personnel spent most of their time, outside teaching commitments, studying the body fluids in health and disease. Dr. Hayden contributed much to the knowledge of blood chemistry in azoturia, milk fever, acetonemia, pullorum disease in chickens, pregnancy disease, stiff lamb disease, icterohematuria in sheep, and canine eclampsia. He also developed a field test for acetonemia in cattle and a mastitis test based on the chlorine content of milk. Normal blood chemical values in most domesticated animals came within Dr. Hayden's investigative efforts.

On two occasions, Dr. Hayden took on the administrative duties of the department. While Dr. Fish was in the military service (1919-20) Hayden served as acting head and in 1931-32, after Dr. Fish died, he again assumed that position.

The Middle Years (1932-1960)[2]

Perhaps the most significant single event for the development of the entire field of veterinary physiology was the appointment, in the summer of 1932, of H. Hugh Dukes as Professor and Head of the Veterinary Physiology Department at Cornell (Fig. 7). During the next 28 years he and his students became preeminent in the field of animal physiology and a number of related fields, especially nutrition, endocrinology, and reproductive biology. His text, *The Physiology of Domestic Animals*, first published in 1933, still represents the standard for the field. Dukes authored the book through the first seven editions (until 1955). The eighth and ninth editions were edited by Melvin J. Swenson of Iowa State University and had some 45 collaborators. The book has been translated into Spanish, Serbo-Croatian, Hindi, and Chinese and reprinted in English in the Philippines. The tenth edition is now in preparation by Dr. Swenson.

Dukes came to Cornell from Iowa State University, where he was an Assistant Professor of Veterinary Physiology for eight years and Assistant Professor of Veterinary Research (Physiology) for three years. He found the Physiology Department in a somewhat run-down condition. Research in the department at Cornell

[2]A history of the Department of Physiology, New York State College of Veterinary Medicine, Cornell University, Ithaca, *The Middle Years (1932-1960)*, by H. Hugh Dukes, is available on request from the Department.

was mainly oriented toward chemical analyses, and experimental approaches to physiology were lacking in both the teaching and research.

The Depression was in full swing, and money to institute new programs and obtain new equipment was scarce. Dukes was equal to the task. He cajoled the recently appointed Dean Hagan, who had hired him, into making a small fund available for developing an experimental physiology course. By repairing equipment on hand and making frequent trips to the local dime store and his wife's kitchen, he was able to start an experimental mammalian physiology course. Few courses have had as great an impact on the development of animal scientists. During the ensuing years, the course was taken by large numbers of veterinary and graduate students majoring in a number of closely allied fields and had strong influences not only on their technical skills but on their research philosophies in later life as well.

By 1942 Dukes had begun to develop the lecture-demonstration method of teaching physiology for which he became famous. Recognizing the need to supplement his standard lectures, he turned to the Physics Department at Cornell for help in developing the instrumentation necessary to illustrate the principles of physiology. He was eminently successful and developed the art of lecture-demonstration in physiology to a degree that has not since been equaled. In 1946 at a meeting of the American Veterinary Medical Association in Boston, he described his method of lecture-demonstration teaching to a group of physiologists and pharmacologists. So much interest was aroused that short courses on the demonstrations were organized at Cornell. These courses, given in the summers of 1948 and 1950, were popular and well attended.

Dukes' lecture-demonstrations were meticulously prepared and rarely failed. Occasionally, however, a demonstration would fail to give the expected result. These occasions usually turned out to be great treats for the students: a superb analysis of the cause of the failure usually followed, and it was on these occasions that Dukes' remarkable sense of humor was at its best.

During the years immediately following the end of World War II, a great many of the graduate and the veterinary students were returning servicemen. Of these students Dr. Dukes stated: "In all my years of teaching I never had a finer group of students to work with. Many of them had lost four years or more of educational time as a result of the war. They were generally eager learners and a pleasure to teach, even though they made the faculty work harder to meet their demands." It was during this era that a truly remarkable number of outstanding scientists and leaders in the physiological sciences were turned out at Cornell. In addition to the veterinary students, nearly 300 graduate students completed minors in physiology during Dukes' 28 years at Cornell. The number of these students who later became national and international award winners in animal science, veterinary medicine, endocrinology, nutrition, biochemistry, and reproductive biology is truly remarkable. The departmental staff also received a number of national awards during this period.

During a large part of Dukes' tenure the Department of Physiology was housed in James Law Hall. Laboratory and animal space were minimal. Animals, from frogs to a steer with a rumen fistula, were kept in a renovated boiler room in the basement. "Bill," the fistulated steer, became famous. His picture appeared in many national publications, and he was viewed by many thousands of visitors during the annual Farm and Home Weeks and on other occasions.

During the early 1950's the College of Veterinary Medicine was relocated to a peripheral area of the campus, and in 1957 the Department of Physiology moved into its new quarters and immediately expanded its operations. The Laboratory of Radiation Biology, with Dr. Cyril L. Comar as Director, became a part of the department. Dr. Wasserman and Dr. Lengemann also joined the department at this time. Several years later, physical biology was made into a separate department. A physiological chemistry group, led by Dr. Morley R. Kare (later to become Director of the Monell Chemical Senses Center at the University of Pennsylvania), was built up and began to produce significant research results. During this period (the late 1950's), the Chicago Tribune rated various aspects of America's ten finest universities; the Department of Physiology was one of ten at Cornell rated as distinguished.

A number of truly outstanding scientists and teachers were members of the faculty during this period. The department was particularly noted for its work on digestion in ruminant animals. This work was led by Dr. Robert W. Dougherty, who joined the department in 1948. Dr. Dougherty established a world-wide reputation as an authority in this field and drew students, visiting professors, and fellows from all over the world. He later became head of the Physiopathology Laboratory at the National Animal Disease Center at Ames, Iowa.

Dr. Charles E. Hayden remained active until his death in 1948. His work on metabolic disorders in animals was internationally known. Dr. Joseph A. Dye, a specialist in intermediary metabolism, joined the department in 1940 and soon became internationally recognized in the field of ruminant intermediary metabolism. Dr. Joseph Gans, the first Professor of Pharmacology in a College of Veterinary Medicine, arrived in 1957. Pharmacology has flourished at Cornell and is now a separate department.

Dr. Dukes probably will be remembered principally for his teaching and writing. Over the years, however, he, his co-workers, and graduate students did a considerable amount of research work. Following are some of the research topics undertaken during the various periods of his career: enzymic action of extracts of the duodenal gland regions of several species; studies on ruminant digestion including rumination, regurgitation, intestinal motility, cecal secretion, and absorption from the rumen; studies on the circulation of the pig; hemoglobin studies in fowl; energy metabolism of the hen; electrocardiographic studies in the horse, sheep, and dog; carbohydrate metabolism in the hen; and the effect of environmental temperature on the cardiac output of cattle.

It is not possible to document all of the graduate assistants and others who worked in the Physiology Department during these years. However, their influence has been felt in practically every Animal Physiology Department in the United States and Canada and a number of departments in Europe, Asia, and South America as well. Many of them have become department chairmen and college deans. They include, among others: Jesse Sampson (Illinois), A. Gordon

Danks (Cornell), A. C. Gonzaga (Philippines), Henry T. Batt (Guelph and Toronto), Loyal C. Payne (Kansas and Iowa States), Carolyn Sprague (Illinois), Harry G. Downie (Guelph), A. Donald Rankin (Colorado State), Orland Soave (NIH), Louis Nangeroni (Cornell and FDA), Esther McCandless (McMaster), James J. O'Toole (Iowa), Louis P. Phaneuf (St. Hyacinthe, Quebec), Joseph Tonzetich (British Columbia), William Medway (U. of Pennsylvania), Walter C. Bowie (Tuskegee), Jonathan Adler (Israel), John M. Bowen (U. of Georgia), David Glazier (Ireland), Arthur Arsonson (Minnesota and North Carolina State), Paul F. Mercer (Western Ontario), Robert Twardock (U. of Illinois), Jay R. Georgi (Cornell), Wellington Moore (USPHS), Dan N. Tapper (Cornell), A. N. Taylor (Baylor), Ayusa Pichaicharnarong (Thailand), Roberto de Souza (Belo Horizonte, Brazil), Vicente de Paulo Costa Val (Belo Horizonte), José Tabarelli Neto (São Paulo, Brazil), and N. Aspiotis (Thessaloníki, Greece).

Epilogue

Dr. Dukes' retirement in 1960 marked the end of a truly golden era of animal physiology at Cornell. In the intervening years, physiology has continued to grow, and as at other institutions its organization has become increasingly complex. In addition to the Department of Physiology in the College of Veterinary Medicine, a Section of Physiology (a part of the Division of Biological Sciences) represents physiology university-wide. Collectively, our research budgets dwarf the total budgets that existed in Dukes' time. More than 30 separate physiology courses are now taught on the campus. Like other institutions, we, too, have gone "cellular"; more than half of our research effort is at the cellular level and at least one-third of our teaching concerns cell physiology. None of these things could have occurred had not the traditions for high-quality physiology teaching and research been laid down under the leadership of Burt Green Wilder, Simon Gage, Pierre A. Fish, Charles Hayden, R. W. Dougherty, Joseph Dye, H. H. Dukes, and their associates. They were all great teachers and few of us today can match their achievements!

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Physiologists at Med Labs 1946-61

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Medical Laboratories (Med Labs), a component of the Research and Engineering Command of the Army Chemical Corps located at Edgewood, MD, northeast of Baltimore, had as its primary mission search for improved methods for treating chemical warfare casualties. Recently Mary Ann Marrazzi wrote me about the career of her father Amedeo S. Marrazzi, whom I recruited to Med Labs in 1948 to reinforce our basic research into the mechanism of action of the nerve gases that Germany was prepared to use in World War II. Mary Ann has followed in her father's footsteps professionally and is now an Associate Professor, Pharmacology, Wayne State University. Her father's achievements have been described by Killam (6) and Luby (7), but little mention has been made of his eight years in Med Labs. This I will do together with a record of many of the other scientists who played major roles in the program of Med Labs.

Amedeo came with an M.D. from New York University College of Medicine and an appointment as Professor of Pharmacology at Wayne State University to become Chief of Toxicology at Med Labs. He soon built up a functional laboratory for research in the fields of neurophysiology and neuropharmacology. In 1948 he recruited E. Ross Hart and E. Eva King, pharmacologists, and in 1950 William A. Krivoy, pharmacologist, and Caroline tum-Suden, physiologist. Eva King left that year to complete work for her Ph.D. at the University of Illinois. In 1951, after Harold E. Himwich resigned, Amedeo succeeded him as Chief, Clinical Reseach Division. This gave him increased responsibility and added resources for research.

In late fall of each year there was a flurry of activity preparing abstracts for the meeting of the Federation of American Societies for Experimental Biology (FASEB). I was kept busy reading them and helping solve the problem of security clearance, often difficult, sometimes impossible. Med Labs always had many papers on the program not only in physiology but also in pharmacology, biochemistry, and pathology. Amedeo and his colleagues were quite successful in that drive to appear before peers with reports of their research. During Amedeo's eight years at Med Labs he was senior author or contributing author of 56 scientific papers including abstracts and chapters in books. Ross Hart was his chief co-author but King, Krivoy, and tum-Suden also shared authorship of his papers.

Amedeo's prodigious scientific productivity was achieved by excluding most social activities except perhaps establishing friendly relations with those in his laboratory. I gained a better insight into his life pattern when my wife Chloris and I were invited to dinner in his

home. It was clear at once that there was a tender attachment between Amedeo and his wife Rose. She was afflicted with multiple sclerosis and at that time, the early 1950's, she was confined to a wheel chair. Their lively son and daughter seemed to be celebrating the occasion; there was evidence of warm feelings for them by both parents. From then on I understood better how Amedeo's life was divided between his drive for a distinguished career and a deep love for his invalid wife and their two promising children.

I had wondered how Amedeo's early years influenced his professional years. Mary Ann Marrazzi supplied significant facts about those years. Amedeo was the only offspring of Italian immigrant parents. His father, a building contractor, taught his son the use of tools. Amedeo became skillful with his hands. But he disappointed his father by refusing to join him in the contracting business and instead entered New York College of Medicine. Then a romance began that continued through life. Rose, a brillant classmate, and Amedeo were married midway in medical school. This severed the tie between Amedeo and his parents, and Rose also was on her own. There were hard times: Amedeo drove a taxi at one period and in his fourth year taught biology at the City College of New York.

His daughter described how his skills acquired as a youth became useful in later years: "Dad learned to be handy in making and fixing things. He built a lot of his early electrophysiological recording equipment, often before it was commerically available. With Mom's illness he designed and rigged up special devices that allowed her to function better, devices that amazed many rehabilitation experts."

I have asked two who were his colleagues at Med Labs for their assessment of Amedeo's scientific achievements. William A. Krivoy, now Pharmacologist at the National Institute of Drug Abuse, Addiction Research Center, Lexington, KY, replied in part as follows: "Scientifically Amedeo was best known for his being one of the earlier investigators to recognize adrenaline as an inhibitor of synaptic transmission, and proposed this to be one physiological role of adrenaline. The original observations and ideas have now gained general acceptance, but were pooh-poohed for a number of years. Amedeo fought for the thesis. All resources he could muster were devoted to evidencing it. It became a cause célèbre, and the basis for a majority of his publications. His effort has been forgotten and receives only a fraction of the recognition it deserves."

Eva King Killam, Professor of Pharmacology at the University of California, Davis, and Editor-in-Chief of *The Journal of Pharmacology and Experimental Therapeutics* writes: "He was an innovator in early neurophysiological methodologies and their use to study drug action. He did work at the most advanced level of his time. He was very bright and quick to draw implications from data and to synthesize hypotheses from data, hypotheses which could be tested experimentally." She added: "I appreciated his honesty, his sense of responsibility for his family and, at least, his junior staff, and his always challenging conversation."

The commanding officer of Med Labs when Amedeo arrived in 1948 was John R. Wood, Colonel in the Army Medical Corps. I arrived at Med Labs early in 1946 to serve under Col. Wood as Scientific Director. I was impressed with his administrative skill and his knowledge of the characteristics of chemical warfare agents including the nerve gases. He had been excellently trained in biochemistry. There was great affection as well as respect for him. He was guided by an advisory board. Among the eminent members were A. McGehee Harvey, Chief of Medicine at Johns Hopkins, Carl F. Schmidt, physiologist and Professor of Pharmacology at the University of Pennsylvania School of Medicine, and Milton C. Winternitz, Professor of Pathology at Yale University School of Medicine. He had a standing arrangement with the Army Surgeon General for assignment of medical officers to Med Labs for their two-year tour of duty. They were selected because of research ability (more about them later).

Col. Wood had recruited Harold E. Himwich from Albany Medical College in 1946 to head the Clinical Research Division. Harold was a leader in a field important to Med Labs, neuropharmacology. His wife Williamina A. Himwich, known as Mina, was also recruited as a promising physiologist. They soon became our close friends; we enjoyed their hospitality in their Harford County home. Harold continued his studies of the central nervous system and guided research in the clinical problems likely to arise in case of the use of nerve gases in warfare. During his five years in Med Labs his authoritative book, *Brain Metabolism and Cerebral Disorders*, was completed and published by Williams and Wilkins, Baltimore, 1951.

He resigned in 1951 to organize and direct the Thudicum Psychiatric Research Laboratory, a brain research laboratory at the Galesburg (Illinois) State Research Hospital. Mina was in charge of biochemical research; also during that period she was an indexer for the American Physiological Society (APS). She prepared cumulative indexes for *The American Journal of Physiology* (volumes 121-167) and *Physiological Reviews* (volumes 16-31 and subsequently 32-46). Harold died March 5, 1975. After a job at the University of Nebraska, Mina retired to the Delmarva Peninsula. Becoming bored with retirement, she accepted a position with a hospital at Columbia in eastern Maryland.

One of the early physiologists recruited to Med Labs by Col. Wood in 1944 was Leigh E. Chadwick, a protege of Wallace O. Fenn of the University of Rochester. Leigh, a versatile scientist, took charge of the Entomology Laboratory. After I arrived in 1946 I became impressed with his erudition. Besides his Harvard Ph.D. he had postgraduate education in German from

Philipps University, Marburg, Germany, as well as M.A. degrees from Harvard University and the University of Pennsylvania. He had able scientists in his group including Charles C. Hassett, Ph.D. 1941 from Johns Hopkins University, who joined Chadwick in 1945 and stayed at Med Labs until his retirement, and Dietrich H. F. A. Bodenstein, an authority in the field of insect endocrinology, who was at Med Labs 1945-1958. Chadwick resigned in 1956 to accept a professorship at the University of Illinois. In 1966 he retired from there in poor health but was able to utilize his linguistic skill during retirement, completing the translation from German of Walter Linsenmaier's *Insects of the World*, published by McGraw-Hill, New York, 1972. Leigh died February 4, 1975, and his wife Maria, August 12, 1981.

William Harold Chambers, known to his friends as Harley, came from Cornell Medical College to Med Labs in 1947 to head the Toxicology Division. Later that year, incident to a reorganization he became Chief, Physiology Division. He and his wife Winona, called Nona, acquired a Harford County farm with a grand brick farmhouse. It was always a pleasure to have dinner with them and to hear Harley's report on the farm operations he directed. At the time he joined us, Harley was Executive Secretary of FASEB, during the hiatus between the death of Donald R. Hooker in 1946 and the appointment of Milton O. Lee in 1947. He resigned from Med Labs in 1961 with a tragic loss of memory. They settled at Bar Harbor, ME, where Harley lost ground and died April 10, 1966. Nona wrote recently about her life in Maine. For her a special treasure is the account of Harley's career by Wendell H. Griffith, a colleague of Harley during World War II (5).

In 1953 Chloris and I decided to leave the Government quarters on the Post and build our home off Joppa Road in Harford County. One of our neighbors was Caroline tum-Suden. She lived at the end of the country road in an attractive cottage surrounded by flowers. We frequently visited her and continued to do so after she and I retired. At our last visit not long before her death January 24, 1976, she was in pain from arthritis and reported concern about her heart. She had been a conscientious and skillful investigator. She once declared to me that she doubted she was earning her salary, a self-criticism unique in my experience. She made determined efforts to have a paper to present at APS meetings. She left no needy relatives and provided in her will a gift to APS that totaled $108,000 (1).

Two other physiologists who owned homes in Harford County were Francis N. Craig and Charles G. Wilber. Col. Wood had recruited Frank from New York University College of Medicine in 1946. He had earned his Ph.D. at Harvard in 1937 and had subsequent training in physiology there. With engineering advice from Paul D. Bales, he designed an environmental room for evaluating the adequacy of protective clothing for use in toxic environments. Frank retired in 1978 from his position as Chief, Medical Physiology Branch, and besides caring for his large garden has been tracing his New England roots. His wife Mary not only continues to be involved with "Planned Parenthood" in Baltimore but also has been taking flying lessons. We were entertained at their home a few years ago—a reunion of old-time friends.

Charlie Wilber had been Associate Professor of Physiology at St. Louis University before joining Med Labs in 1952 to head the Animal Ecology Branch. His reputation in the field of environmental physiology was already well established. He and Edward F. Adolph of the University of Rochester as associate editors joined me in planning and editing *Adaptation to the Environment*, published by APS in 1964 as Section 4 of the *Handbook of Physiology*. He left Med Labs in 1961 and since 1967 has been Professor of Zoology at Colorado State University, where his wife Claire has been granted an advanced degree in music. From time to time we have learned of the marriage of each of their six children.

We had many ties to Wallace O. Fenn, Professor and Chairman of Physiology at the University of Rochester. He sometimes participated in our symposia as the country's foremost leader in respiratory physiology. Besides Leigh Chadwick two others of his protègès were J. Henry Wills and Richard G. Horton. The latter had obtained his Ph.D. at Cornell in 1937 and was at the University of Rochester with Fenn in 1939-41. He had been recruited to Med Labs by Col. Wood in 1942 and became a mainstay in our research, basic and applied toxicology, staying until 1972, when he became a private consultant in toxicology.

Henry Wills received his Ph.D. in physiology at Rochester in 1941 and was in pharmacology there until 1946. After a year as Assistant Professor of Pharmacology at the University of Tennessee he came to Med Labs in 1947 to become our senior pharmacologist, staying until his appointment as Professor of Pharmacology at Albany Medical College in 1965. He had wide familiarity with the literature of physiology and pharmacology. I frequently called on him for advice.

Another member of the APS, Carl M. Herget, Ph.D. in Physics, Johns Hopkins University, 1940, joined Med Labs about 1947 to be Chief, Biophysics Division. Floyd A. Odell, Ph.D. in Biology, Yale, 1940, had been acting chief of the division and became assistant chief under Herget. Together they were a powerful team in exploring wound ballistics. Our friendship with Mary Winston Herget continued after their divorce; we still exchange Christmas cards. Carl retired from Med Labs shortly before his death in 1969.

I have mentioned Charles C. Hassett as a young physiologist who joined Chadwick in the Entomology Laboratory in 1945. After Chadwick resigned in 1956, Hassett took over as Chief of Entomology until 1960. When Henry Wills became Chief, Physiology Division, about 1960, Hassett was appointed assistant chief of that division. In October, 1962, he was assigned as an exchange scientist to The Netherlands' National Medical Biological Laboratory in Delft; the research program of that laboratory was closely related to that of Med Labs. He and his wife were able to take with them their two children as well as the family's bulldog. In exchange, a physiologist of the Delft laboratory, Dr. Egbert Deeter, brought his wife and three children to Edgewood for a year. Dr. Deeter was assigned to work with Frank Craig in studying and hopefully mitigating stresses imposed on soldiers wearing protective clothing designed for use in chemical warfare. Wills resigned in 1965; Hassett was acting chief of the division for a year. After that he held other administrative posts. He retired in 1975 and is enjoying a quiet life at his home in Towson, MD, near Baltimore.

Walter Fleischmann and his wife Susan shared professional education and early training in Vienna,

both earning Ph.D. degrees in Zoology there. Walter had earned an M.D. defree earlier. He was in Med Labs for only three years, 1946-1949, but during that time became recognized as a sound physiologist. He was genial and portly: he starred each year in our Christmas party as a realistic Santa Claus. They moved to Tennessee in 1957, where he became Chief of Laboratory Services at the Veterans Administration Center, Mountain Home, TN, until his retirement in 1965. Walter was on the list of Senior Physiologists with whom I corresponded for the Senior Physiologists Committee of APS. His piano and garden were great sources of pleasure.

Roger A. Hoffman completed his Ph.D. in physiology and endocrinology from Purdue University in 1956 and was immediately recruited by Wilber for his Animal Ecology Branch, later called Experimental Zoology Branch. Roger became a member of APS in 1961. I believe I joined Wilber in sponsoring him. Roger was broadly trained in the biological sciences and had a special interest in hibernation. Wilber and I asked him to write a chapter on hibernation for *Adaptation to the Environment*. He completed this when he was at Colgate University during a leave from Med Labs. He joined their faculty in 1965 and has been Professor of Biology, Colgate University, since 1970.

While this account has been concerned chiefly with physiologists, the other medical sciences were well represented at Med Labs. The dean of our biochemists, William H. Summerson, came from an associate professorship at Cornell Medical College in 1947 to head biochemical research. He moved to the Food and Drug Administration in 1966 and retired from it in 1969. One of his responsibilities at Med Labs was to investigate the properties of substances that penetrate the skin. In helping with this study under Summerson's skillful guidance, two young medical officers at Med Labs 1946-48 became interested in dermatology. One of them, Aaron B. Lerner, has been Professor of Dermatology at Yale University since 1957, and the other, Thomas B. Fitzpatrick, has been Professor of Dermatology at Harvard Medical School since 1959.

Many others of those young medical officers made significant medical contributions to our research. As described elsewhere (3) research contracts supported by Med Labs plus the talents of several medical officers led to the adoption of mouth-to-mouth resuscitation.

I am selecting one of those medical officers for special mention: John A. Clements, M.D., Cornell, 1947. After two more years there as a research assistant in physiology, he was called up for military duty in 1949 and was assigned to Med Labs. He and Margot were married that year; we soon began calling on them for entertainment, Margot singing and John the accompanist. John was one of the leaders in the research on methods of resuscitation. At the end of his military duty in 1951, I persuaded him to stay on as civilian member of our Clinical Investigation Branch. He was assigned as "contract officer" with the Harvard School of Public Health, where he provided a valuable link between Med Labs and scientists there, particularly James L. Whittenberger and Edward P. Radford of the Department of Physiology. John also became acquainted with Julius H. Comroe, Jr., Professor of Physiology and Pharmacology at the University of Pennsylvania Graduate School of Medicine. Soon Julius shared my high opinion of John and had him appointed to a concurrent position as Research Associate in Physiology 1952-58. John also came to the attention of David Grob, Associate Professor of Medicine at Johns Hopkins; John was appointed a Lecturer in Anesthesiology, 1955-61.

We arranged for John to spend 1952 at our counterpart laboratory, the Chemical Defence Experimental Station at Porton, England, where he and Margot formed lasting friendships. After his return he reestablished ties with Whittenberger and Radford; he found that he and Radford had a common interest in pulmonary surface effects. John tells me that his research on lung surfactant grew directly out of Radford's work on pulmonary surface effects. John was able to devote much of his time to gaining an understanding of the physical chemistry of surface tension, a knowledge of pertinent literature on the elasticity of the lungs and of interfacial forces. He became a member of APS in 1958. In 1961 he received the Research Development Achievement Award from the Army for his scientific contributions to the program of Med Labs.

When Comroe became President of APS in 1960, he exercised his prerogative as president, selecting John to give the sixth Bowditch Lecture at the Society's fall 1961 meeting at Bloomington, IN. John's scholarly lecture dealt with early studies of the physics and chemistry of surfaces that led to his own research on surface phenomena, particularly as related to pulmonary function. Julius Comroe had left Pennsylvania in 1957 to organize and direct the Cardiovascular Research Institute at the University of California School of Medicine in San Francisco. He recruited John to that Institute in 1961, where John has also been Professor of Pediatrics since 1964.

In 1980 I was the dinner guest of John W. Severinghaus, Professor of Anesthesiology in that medical center. We were entertained after dinner in Med Labs tradition, Margot singing and John accompaning her on the piano. Two other guests from days at Med Labs were Gustave and Betty Freeman. Gus had been Chief, Clinical Investigation Branch, 1951-57; he resigned to begin another career and has been Director of the Department of Medical Research of Stanford Research Institute, Menlo Park, CA, since 1958.

As mentioned above it was Col. Wood who made the original arrangement with the Army Surgeon General for assignment of young medical officers to Med Labs for their two-year tours of duty. When Col. Wood was reassigned in 1950, he was succeeded in turn by Cols. Milward W. Bayliss 1950-53, Norman W. Elton 1953-55, Albert Dreisbach, and Douglas Lindsey. All became my friends; a good relationship always evolved. Each one succeeded in having able young medical officers assigned to the laboratory.

Finally I mention two who were not members of APS but who played major roles in Med labs and with whom I have remained in contact. Francis N. Marzulli, toxicologist and applied physiologist at Med Labs 1947-63, lived on Joppa Road. He was involved in our selecting a nearby eight acres of woodland and meadow where we built a home in 1953. The only laboratory study in which I took part in more than 14 years in Med Labs involved Marzulli and medical officer John C. Seed. On Sundays we measured energy expended while riding bicycles equipped with tires that ranged from racing to balloon type (4). The Schwinn company provided the bicycles and tires. On the basis of our findings they

shifted their production away from balloon tires that had been promoted prior to 1950. Marzulli is now a consultant to the National Academy of Sciences–National Research Council. We often visit Francis and Florence at their home in Bethesda. John Seed left Med Labs in 1950 and is now a research associate in the Electrical Engineering Department of Princeton University and also engages in family practice in Princeton.

Another whom I wish to mention is Dorothy Ward, expert retriever of information and best friend of my secretary, Catherine Engel. Catherine was a family friend; in 1961 after my retirement she accompanied us on a trip to Europe. In her fourteen years as my secretary she kept me out of trouble in handling classified documents and carried out all her duties with skill, intelligence, and loyalty. Her one fault was cigarette smoking. Dorothy and I were unable to persuade her to stop. Years after my retirement she had lung cancer and then in 1971 a brain tumor. We always exchanged birthday greetings In 1971 her greeting came a month early, an arrangement of everlasting flowers. Dorothy wrote later that sending that was one of her last conscious acts before lapsing into a coma.

This has been a short chronicle of scientific achievements of my colleagues 1946-61 and of friendships, one ending with pathos. Those achievements formed the basis for my receiving two citations when I retired, one from the Department of the Army signed by Secretary Elvis J. Stahr, Jr., and one from the Department of Defense signed by Secretary Robert S. McNamara.

I appreciate the help of Mary Ann Marrazzi, Eva K. Killam, and William A. Krovoy and their permission to quote from their letters.

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Cover Update

Thanks to letters from H. M. Edinger of the New Jersey Medical School and D. L. Beckman of East Carolina University School of Medicine, we present more complete information on the cover of the October issue of *The Physiologist* (Vol. 25, No. 5, 1982).

Cover: With Carl J. Wiggers is David F. Opdyke, who was the first Chairman of the Physiology Department of the New Jersey Medical School. He served in that capacity for 18 years until his retirement in 1977 and continues to be active in research at the East Carolina University School of Medicine and at the Mount Desert Island Biological Laboratory.

News from Senior Physiologists

L. Joe Berry to Louise Marshall:

I was in the department of microbiology at Bryn Mawr from 1940 to 1970 and then moved to the University of Texas at Austin, from which I am comfortably retired. Along the way, and among other appointments, I was chairman of the NIH study section of bacteriology and microbiology (1964-1967) and advisor to the Lunar Receiving Laboratory for NASA. My specialties have been the host response to infection, stress physiology, ribosomal vaccines, and cellular immunity.

The University of Texas has a policy that is generous for faculty who reach retirement age. Retirement is voluntary at age 65-70 and compulsory at 70. However, even at age 70, faculty may continue on a part-time basis, i.e., one-third or one-half time. I was half-time for the 1980-81 year and will continue for 1981-82. I have two predoctoral students, one postdoc, and a full-time technician working in my laboratory supported by an NIH grant that runs through August 1983. I have retained my office and laboratory space in the department. In other words, I am a most fortunate man.

Dept. of Microbiology
University of Texas
Austin, TX 78712

Bill Archdeacon to E. Brown:

I spent two separate years in Malaysia teaching in their medical school, then one year in Libya, and five months in Rhodesia, now Zimbabwe. I enjoyed the foreign experience very much. Each country had a culture all its own. I learned to like all the countries and feel that Americans are missing something if they never go abroad.

I live in an apartment by myself and watch TV, read, and listen to music in addition to losing money in the stock market. I don't pretend to try to do research any longer and have no guilt feelings over this. I don't have to impress anybody about how I am fighting age.

P.O. Box 22324
Lexington, KY 40522

I. H. Page to E. B.:

What a nice idea for the APS to remember it has ancestors. I am one without the common sense not to write a book. So for the past year I have been mired down in putting "finishing touches" on a manuscript entitled, "The Mosaic Theory of Hypertension." The touches would be finished if my friends didn't seem to know so much and write so much. Much of the rest of my time is spent in getting old (81 years), playing tennis for which I write the rules, and also what is euphemistically called "jogging." I go to few meetings because some time ago I decided not to go unless I had something specific to do. Another reason for going to few meetings is that we live year-round in Hyannis Port, and except for Ted Kennedy et al. it is incredibly peaceful and dull. There is enough heat in the winter, coolth in the summer, and drinks at 5 p.m. Come see for yourself!

Box 516
Hyannis Port, MA 02647

Continued on page 480

Constituent Letters Are Important Keys to Legislative Decisions

The question of the value of constituent letters to elected officials can perhaps be answered best by examining some of the events that led to consideration by the Congress of enactment of an omnibus reform bill regarding the use of animals in research, testing, and experimentation.

The stimulant within the Congress for enactment of the "Humane Care and Development of Substitutes for Animals in Research Act" was not the result so much of the actual issues involved, but rather of the volume of mail received in Congressional offices citing alleged abuses of laboratory animals by scientists, researchers, and educators.

Congressional staffs have indicated that during the last 16 months the mail received by House members and the committees was at various times more than thirty- and fifty-to-one in favor of legislative initiatives that would restrict scientists, researchers, and educators in their use of animals. Similar ratios also have been cited by Senate staffs.

Such volumes of mail were largely responsible for:

- Oversight hearings by the House Subcommittee on Science, Research, and Technology in October 1981 to examine seven bills that were directed at both restricting the use of laboratory animals and promoting the development of alternative methods. All seven of these proposals had been dormant since their introduction at the beginning of the 97th Congress in January 1981.
- The introduction in April 1982 of an omnibus animal research reform bill (HR 6245) that would have diverted up to 50% of Federal research support funds for the purpose of developing alternative methods and would have limited the use of animals in programs of research, testing, and experimentation supported by Federal funds.
- Amendments to HR 6245 by the House Committee on Science and Technology in August 1982 that resulted in the development of the current proposal, HR 6928. The new modified bill eliminates the promotion of alternative methods from existing Federal funds for biomedical research, eases the proposed mandatory requirements for accreditation of research institutions, and provides some exemptions for entities included in the earlier versions of the previous bill.
- The successful blocking of an amendment by Reps. Edward R. Madigan (R-IL), James T. Broyhill (R-NC), and Phil Gramm (R-TX) that would have required a study to determine the possible impact of HR 6928 on both research and research institutions supported with Federal funds.

Letters from the memberships of the humane organizations and animal rights groups were largely responsible for the first two and the last of the examples cited. Letters from the research community played the key role in moving the full committee to eliminate the development of alternative methods from existing research funds in easing some of the requirements of mandatory accreditation.

The importance of constituent letters cannot be overemphasized, primarily because such letters serve as a barometer for elected officials. A general rule for many Congressional offices and the Administration is that for each letter received on a particular issue there are another 1,000 persons back home who probably agree with the letter but did not take the time to write. (The exception is the standardized form letter. Such letters are usually counted as only one when they are obviously part of an organized campaign of identically written letters.) The ratio for telephone calls—either to the elected official's office or the district office at home—is that for each call there are another 100 persons back home who also agree with the caller.

The importance of this barometer effect of constituent letters is significant in today's political world where the return to elected office is usually determined by a percentage point or two. Thus positions and voting records are determined largely on what the elected official hears from the constituents.

Aside from the barometer effect, constituent letters also represent one of the most effective means in establishing continuing relationships with elected officials. However, to be most effective you must know your elected official's policy positions and priorities as well as assignments to committees and subcommittees. This information is available from the newsletter elected officials regularly send to constituents who request them.

It also is important to know the names of the staff persons assigned to handle the issues in which you have an interest, because staff people can have a major influence in forming an elected official's viewpoint and positions. Such staff people usually carry the title of director, counsel, administrative assistant, or legislative assistant.

In writing or telephoning elected officials the keys to being effective are "be brief," "be specific," and "be knowledgeable." Be sure to express your opinions in identifying the issues and how such legislation, if enacted, would affect your institution. Also provide recommendations for change that do not conflict with the elected official's stated positions or policies.

It is of little value to write or telephone just to say that you oppose a particular bill without providing the reasons for your opposition and offering suggestions on how to help to improve the bill. It is also not necessary to state the case presented by the other side as the elected official already knows it.

Perhaps the toughest decision in writing to an elected official is knowing when to write. The effectiveness of proper timing of letters can best be demonstrated by the fourth example listed earlier, the Madigan-Broyhill-Gramm proposal that would have placed the animal reform legislation on hold until a study could be con-

ducted. The two days before the amendment was to be presented on the floor of the House of Representatives, the members of two humane organizations delivered letters to each of the 435 Representatives, protesting the proposed amendment because it would delay the possible enactment of HR 6928. The amendment was defeated by a two-to-one margin.

This example of how constituent letters can block a study of the issues coupled with the fact that the scientific community has been on the short end of thirty- and fifty-to-one ratios point out the need for all scientists, researchers, and educators to make their opinions and concerns known to elected officials. This need was further emphasized in recent weeks when it was reported to the American Physiological Society that *1*) a Congressional office from a western state has received only one letter from a researcher and *2*) another Congressional office representing a large densely populated eastern city area had not received any letters from researchers. Both offices also said that they each had received more than 400 letters since October 1981 from members of humane organizations and animals rights groups pushing for the passage of the "Humane Care and Development of Substitutes for Animals in Research Act." The question from both offices to APS was: Why are you concerned when the researchers from our district have not written. Obviously, they (researchers) must be for this legislation too.

The need for constituent letters from both sides of all legislative issues is important so as to present a balanced view before legislative decisions are made. While the overall affects of legislative proposals are pointed out by the Washington representatives of the involved associations and societies, the final decision, however, usually rests on the mail. Twenty minutes of your time to write and a twenty-cent stamp can be an important key in legislative decisions that could affect you for the next twenty years.

William Samuels, CAE

Senior Physiologists

Continued from page 478

James J. Irving to Arthur B. Otis:

Thank you so much for writing and for your birthday wishes. I do not feel 80—in fact am quite surprised to be so old.

When I retired from Harvard in 1978, I was appointed to a post in the NIH Emeritus Professor, whereby one is employed for a period to do a specific piece of research or some similar activity. I was at the National Institute for Aging in Baltimore from 1978 to 1981, studying the effects of aging on Bone Formation, using a bone implantation method. I've got some interesting results, and I was sorry when the job finally terminated.

My wife and I decided to return to the Boston area, where we had lived for 20 years and had lots of friends. I am now virtually completely retired. I do some editorial work and have a desk at the Forsyth Dental Center. I would like to be a bit more occupied but have not so far found retirement boring. In fact, it's rather a pleasant sensation to have no definite schedule. Last year I was a session chairman at two conferences in my field; so I still have some scientific value.

Forsyth Dental Center
Boston, MA 02115

James A. Shannon to Arthur:

Tom Kennedy and I are trying to pull together much of the NIH historical development 1950-1970. He is now with the Association of American Medical Colleges but was with me at Goldwater Memorial 1942-1946 and then at NIH 1949-1970.

My wife died in the spring of 1977. I am living in Portland, doing what many people at my age do when there is not much to bother them: garden, keep house, and serve as a consultant (R. J. Reynolds Industries).

There is much more to write about, but the above will indicate a fairly active time since retirement, a pleasant life really.

8302 SW Homewood St.
Portland, OR 97225

William F. Windle to Roy O. Greep:

Thank you for your warm greeting on my 84th birthday. I have retired finally after more than one false start, the first of which was in Philadelphia 32 years ago. But after leaving the Institute of Rehabilitation of NYU in 1970, I came to my alma mater, Denison University, for a last fling at research on neural regeneration until I was overtaken by paralysis agitans. My last contributions are in the book, *Stephen Walter Ranson, Ground Breaking Neuroscientist,* which I edited and the Brain Research Institute of UCLA published last year.

229 S. Cherry St.
Granville, OH 43023

APS 128th Business Meeting

Time: 4:40 P.M., Thursday, October 14, 1982
Place: Town and Country Hotel, San Diego, CA

I. Call to Order

The 128th Business Meeting was called to order by the President, W. C. Randall, who welcomed the members. The ballot for election of new members and a proposed amendment to the Bylaws were distributed with the agenda.

Dr. Randall was happy to report that the registration has reached 1,350, exceeding the budgeted 1,200. In addition to the financial success, the sessions have been well attended. Dr. Randall took this opportunity to express the Society's appreciation to the Local Committee for the excellent arrangements.

II. Report on Membership

The President-Elect, A. P. Fishman, presented the report on the current status of the Society membership and deaths since the Spring Meeting.

A. Summary of Membership Status. As of September 7, 1982, the APS membership reached 6,077, of which 4,456 are Regular, 553 Emeritus, 11 Honorary, 94 Corresponding, 703 Associate, and 260 Student members.

B. Deaths Reported Since Last Meeting. The names of those members who deaths have been reported since the previous meeting were read by Dr. Fishman, who asked the audience to stand for a moment of silence in tribute to them. (p. 488).

It was noted by Dr. Randall that the voluntary contributions of members, including Emeritus members, has reached $10,000. These monies enable the Society to undertake projects which otherwise would be impossible. A list of these contributions appear in the October issue of *The Physiologist*. On behalf of Council and the Society as a whole, Dr. Randall expressed his thanks and gratitude.

III. Election of Members

A. Appointment of Tellers. The tellers appointed by the President were J. P. Filkins, S. Lipsius, J. M. Loeb, and M. M. Sayeed, who collected the ballots for the election of new members.

B. Election of Members. Dr. Reynolds announced that all candidates nominated were elected to membership. (p. 485)

IV. Amendment to the Bylaws

A proposal to amend the Bylaws providing for amendments by mail ballot was offered at the Cincinnati Business Meeting. In referring to the handout that was approved by Council, Dr. Randall announced that, in compliance with the Bylaws, the proposed amendment was published in the June issue of *The Physiologist*.

It was moved and seconded that "If a proposed amendment to the Bylaws receives a majority vote of the regular members present and voting at the Business Meeting but fails of a two-thirds majority necessary for passage, such proposed amendment must be submitted to the regular membership by mail ballot. A two-thirds majority of the regular members responding within thirty (30) days after submission shall result in passage of the amendment."

In responding to a question from the floor, Dr. Reynolds said that on two or three occasions a vote had failed for lack of a two-thirds vote. There was a suggestion to increase the majority vote to 80% instead of two-thirds. Another member said that because so few members attend the Fall Business Meeting, the intent of the original proposal was to have all Bylaw amendments submitted to the members for vote by mail ballot. This has not been accomplished in the document before the membership.

Dr. Fishman commented that Council recognizes that the Fall Business Meeting is not well attended and has had discussions as to how this might be changed. One possibility being pursued by Council is to schedule a brief Business Meeting in the morning followed by a plenary session with a very distinguished speaker.

As the discussion progressed, it became very clear that the membership was not satisfied with the proposed amendment as presented by Council. Therefore, **a motion to table the original motion was passed with six members voting in the negative.**

V. Actions of Council

Dr. Randall reported that a significant action of Council was the decision to obtain liability insurance covering individuals conducting volunteer work for the Society, e.g., members of the Editorial Boards and Committees who expose themselves to legal suits. In recent years, a number of associations and societies have obtained such insurance. It is important for the Society to offer this type of protection for everyone conducting Society business.

The report of the Finance Committee was received by the Chairman, Robert Forster, who indicated that the Society finances are in satisfactory condition. There is a balanced budget which does not involve any increase in dues.

Council received the report of the Publications Committee Chairman, Howard Morgan. The publications are in a very vigorous state and continuing to grow at the rate of about 10% a year of published papers which are of excellent quality. Particularly noted was the inauguration of a new series of books entitled "People and Ideas." The initiation of this series was with a reprinting of "Circulation of the Blood: Men and Ideas," by Fishman and Richards. The original volume published in 1964 is now a collector's item. These books will be devoted to the development of ideas in physiology from an historical viewpoint and are considered an important element of the forthcoming Centennial of the Society culminating in 1987.

The Program Committee report (p. 483) was presented to Council by the Chairman, Michael Jackson. An important component of this report is the

fact the present structure of the Program Advisory Committee is working well and all specialty groups in the Society have direct access to programming of scientific sessions.

The report (p. 483) of the Chairman of the Public Affairs Committee, John Shepherd, was accepted by Council with great satisfaction. This newly structured committee provides representation from each state to deal with specific legislative questions, issues and problems at the national, state, and local levels. The Committee has been successful in providing factual information which has had a beneficial influence on the legislative process at both national and state levels. Mr. William Samuels, the APS Public Affairs Consultant, was introduced by Dr. Randall.

In responding to questions from the floor, Mr. Samuels informed the audience of the status of the Humane Care and Substitutes for Animals in Research Act (HR 6928). It is on the calendar for consideration during either the lame-duck session scheduled to begin on November 29 or as a first priority for the 98th Congress when it convenes in January. Mr. Samuels will continue to keep the membership apprised of the progress of this and other bills through the pages of *The Physiologist*.

A member expressed the opinion that the American Medical Association (AMA) should be more concerned about the pending legislation on the use of animals for research. Since the ability of cardiologists, surgeons, and so forth to help their patients is totally dependent on research, it was suggested that members of the Society seek the support of their colleagues in clinical departments to encourage the AMA to take a stand on the issue and support the Society's efforts.

A report was presented by the FASEB Executive Director, Robert Krauss, on the progress of the new FASEB Summer Conferences, which were initiated this year. These were widely recognized as being highly successful and will be continued in the future with the Society playing an appropriate role in the organization of several of these conferences. The announcement of the forthcoming summer conference will be published in the *Federation Proceedings,* as well as *The Physiologist.*

A representative from the American Association for the Accreditation of Laboratory Animal Care (AAALAC) informed Council of its activities. In view of the likelihood that future legislation may require such accreditation of facilities conducting government sponsored research, it was felt that Council should be completely aware of the procedures and implications of such accreditation procedures.

Council was pleased to have a session with Professor Cesar Tim-Iaria, President of the Latin American Physiological Association. Several steps were initiated which, hopefully, will result in better physiological communication between the Americas. These contacts were initially made by David Bohr during his presidency.

Plans for the XXIXth International Congress of Physiological Sciences, to be held in Sydney, Australia, August 28-September 3, 1983, were described to Council by Dr. Eugenie Lumbers, who is representing the Congress Organizing Committee. Council also heard about the plans for travel awards for American Physiologists to attend the Congress.

VI. New Business

A. Travel Award Applications. Dr. Reynolds announced that the date for receipt of the Travel Award applications has been extended, and he proposes to communicate with the Chairmen of Departments of Physiology, who are members of APS, informing them of the extended deadline. Individuals who have not submitted applications were urged to do so immediately.

B. Invitation of the XXIXth Congress of IUPS, Sydney. Dr. Eugenie Lumbers, representative of the IUPS Congress Organizing Committee, expressed her appreciation for the support her colleagues have received from the American Physiological Society in promoting and encouraging U.S. participation in the Congress.

She announced that the Congress will open with a plenary session at 3:00 P.M. on Sunday, August 28, 1983, in the Concert Hall of the Sydney Opera House. On the same evening, there will be a "Welcome to Sydney" reception, a Congress reception on Thursday, September 1, and another plenary session on Saturday morning, September 3. All members are invited to a Congress concert by the Sydney Symphony Orchestra at the Opera House on Monday evening, August 29, for which there is a special application on the registration form. All scientific sessions will be held at the University of New South Wales, with 40 invited lectures, 97 symposia which are mostly grouped into themes, free communications in the form of posters, and also scientific film presentations. Also, 43 satellite symposia will be held in Australia. The deadline for receipt of abstracts is January 31. Many pre- and post-tours are scheduled throughout the Congress. A number of Sydney hotels have been booked at special convention rates. College accommodations are also available on a single occupany basis at the University of New South Wales and the University of Sydney. Accommodations cannot be guaranteed for members who have not paid their deposits by July 1, 1983. Second circulars are presently being mailed to those individuals who responded to the first circular. In closing, Dr. Lumbers thanked the APS for the opportunity to address the assembly and for its most gracious hospitality.

With no other business, the meeting was adjourned at 5:30 P.M., October 14, 1982.

Alfred P. Fishman, President-Elect

Future Meetings

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

*Campus meeting

Committee Reports

Porter Development Committee

The Porter Development Committee is now supporting two postdoctoral fellows and two predoctoral fellows. They are Dr. Jose E. Garcia-Arraras, who is continuing his fellowship in the laboratory of Dr. Nicole Le Dourain at the Institut d'Embryologie in the Centre National de la Recherche Scientific at Nogent-sur-Marne, France; Dr. Nelson Escobales, who is a graduate of the Department of Physiology and Biophysics at the University of Puerto Rico and is now a postdoctoral fellow in the laboratory of Dr. Mitzi Canessa in the Department of Physiology and Biophysics at the Harvard Medical School; Ms. Jean A. King, who is a candidate for the Ph.D. in the Department of Biological Sciences at Hunter College in the laboratory of Dr. James H. Wyche; and Ms. Darlene K. Racker, who is a candidate for the Ph.D. degree in the Department of Physiology and Biophysics at Chicago Medical School. The Committee has also continued funding for the Atlanta and New Orleans consortia and has also provided support for 15 undergraduates in predominantly black schools in the New Orleans area to attend the FASEB meeting in April.

We again express our appreciation to the Harvard Apparatus Foundation for its continuing support of the Porter Development Program. For the year of 1982, a grant of $75,500 was made to the American Physiological Society.

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

Program Committee Report

The Program Executive Committee approved the following symposia for presentation at the APS Fall Meeting, 21-24 August 1983, in Honolulu:

Factors influencing vasopressin in body fluids. Sponsored by Section on Water and Electrolyte Homeostasis. Organized by J. Claybaugh.

Prostaglandins, leukotrienes and lung fluid balance. Sponsored by Section on Respiratory Physiology. Organized by A. B. Malik.

Neurohumoral regulation of circulation. Sponsored by Section on Cardiovascular Physiology. Organized by V. J. Bishop.

Autonomic control of coronary tone. Sponsored by Section on Cardiovascular Physiology. Organized by P. M. Vanhoutte.

Underwater physiology. Sponsored by Section on Environmental, Thermal and Exercise Physiology. Organized by Y.-C. Lin.

Physiology of sea birds. Sponsored by Section on Comparative Physiology Organized by H. Rahn and C. C. Whiton.

H^+ transport in epithelia. Organized by F. C. Rector, Jr., and J. G. Forte. This symposium will consist of 5 or 6 sessions including invited oral presentations and poster discussions and continues a series of triannual symposia on this topic.

The intent of these newly instituted Caroline tum-Suden travel awards is to provide support for distinguished investigators to participate in APS symposia at the spring or fall meetings. Nominations are made by symposium organizers, endorsed by the program representative of the section sponsoring the symposium, and reviewed by the Program Executive Committee. Up to four awards may be made each year, subject to the availability of funds.

For 1983 awards are to be offered to the following speakers in symposia to be presented at the Spring Meeting in Chicago:

S. R. Bloom speaking in the symposium on Neuroendocrine Control of Insulin Secretion, chaired by D. Porte.

G. Elzinga speaking in the symposium on Information Retrievable from Pressure-Volume Relationship, chaired by K. Sagawa.

P. E. Hartman speaking in the symposium on Nutrition and Physiological Factors Influencing Lactation, chaired by D. E. Bauman.

The concept of thematic planning in the organization of the spring meetings of FASEB is alive and well. The intention is to encourage an interdisciplinary focus on specific topics under the FASEB umbrella. Each year FASEB member societies are assigned the responsibility of coordinating the organization of symposia, minisymposia, and contributed paper sessions relating to particular themes. For the 1983 spring meeting, APS is responsible for a Neuroendocrinology theme, and Susan Smith is coordinating this program. In 1984 the APS theme topic will be Regulatory Mechanisms, and this will be coordinated by Gene Yates. Your opinions on thematic planning in general and suggestions for appropriate topics for future themes should be sent to me or the program representative of your section.

Michael J. Jackson, Chairman

Public Affairs
April–August 1982

The Public Affairs Committee (PAC) has focused its efforts since April primarily on three areas: the "Humane Care and Development of Substitutes for Animals in Research Act" (HR 6928, formerly HR 6245); appropriations for US Department of Agriculture's Animal and Plant Health Inspection Service (APHIS); and California's repeal of its pound release law (SB 1438).

A summary of the PAC activities follows.

HR 6928

An omnibus laboratory animal bill was introduced in the House on April 29 by Rep. Doug Walgren (D-PA) and was reported upon favorably by the Subcommittee on Science, Research, and Technology on June 9. Among the Society's concerns with the Subcommittees version of the bill was the provision in Title 1 that established a mechanism for second-chance funding for only those grant proposals that made reference to development of alternative methods but were not funded after having been approved by peer review.

More than 50 letters and telephone calls were generated by the Public Affairs Advisory Committee (PAAC) members who contacted the chairman of the Committee on Science and Technology and their own representatives about this concern. This effort by

"No Shows"

At the San Diego meeting, the Program Advisory Committee received several complaints about authors who failed to show up to present their scheduled papers. Such absences have always been a problem but may occur more frequently in future because of reduced travel funds. At its meeting in Chicago this Spring, the Program Executive Committee plans to discuss "no shows" and invites written suggestions on how to effectively handle this problem.

PAAC members was undoubtedly an important factor in the Society's successful effort to have this provision removed from the bill.

(Six days prior to the August 3 markup of the bill by the full Committee, the Committee chairman invited APS, the National Society for Medical Research, the Association of American Medical Colleges, and the National Association of State Colleges and Land Grant Universities to meet with the Committee staff directors for the purpose of preparing an amendment that would eliminate second-chance funding and still encourage development of alternative methods. The amendment proposed by this group was introduced at the markup by Rep. Walgren and Rep. Margaret Heckler (R-MA) and was accepted unanimously by the Committee.)

After the Committee markup an effort was undertaken to have the Committee on Energy and Commerce and its Subcommittee on Health and the Environment waive the right of review so that the bill could go directly to the House floor. The Subcommittee on Health and the Environment has jurisdiction on all legislation involving biomedical research.

PAAC members were asked to contact both the Subcommittee Chairman Henry Waxman (D-CA) and Committee Chairman John Dingell (D-MI) and their own representatives and request that oversight hearings be held regarding the institutional cost for both administering the bill and for accreditation and to review the proposed minimum requirements for the accreditation of research facilities (more than 100 animals for rodent species, more than 10 animals of nonrodent species, one or more nonhuman primates).

It has been estimated that the institutional costs for administering the bill and for accreditation will total at least $1,150,000,000 over the next 10 years, the life-span of the bill. As a means to offset some of this expense the Society is proposing that two of the accreditation minimums be raised to minimums of more than 500 animals of rodent species and more than 100 animals of nonrodent species.

This bill still is under consideration by the Subcommittee on Health and the Environment.

APHIS

APS took the lead in developing and presenting joint statements before the agriculture, budget, and appropriations committees in both the Senate and the House. Joining APS in presenting testimony were the Federation of American Societies for Experimental Biology, the Association of American Medical Colleges, the National Society for Medical Research, and the American Institute for Biological Sciences.

The primary concern voiced by these groups is the proposal by the Administration that would transfer the authority to inspect research facilities from APHIS to state and local groups, private industry, humane organizations, and individuals. The Administration would accomplish this by reducing current APHIS appropriations from $4,900,000 to $1,500,000.

This appropriation has been recommended for funding at the higher level by both the House and the Senate Appropriations Committees.

SB 1438

In a coordinated effort with California PAAC member Edward Rhode, W. F. Ganong, and Stephan Arditti, University of California legislative representative in Sacramento, APS provided information to the members of the California Assembly's Health Committee and Ways and Means Committee regarding the probable cost to California physiologists should researchers be barred from securing animals from the pounds in that State. The bill, approved earlier by the State Senate, was rejected by the Assembly largely on the grounds of the additional costs the proposed law would place on academic research institutions in the state. Much of this expense would have to be made up with additional state appropriations.

Other Activities

The PAC provided information to agencies in Chicago, Jacksonville, and Tampa regarding proposed ordinances in those cities that would prohibit pounds from releasing animals to academic institutions for the purposes of research and teaching.

John T. Shepherd, Chairman.

Publications Committee

Physiological Reviews: A Look Back and A Look Ahead

The Publications Committee is pleased to announce the completion of the latest in a series of cumulative indexes to the Society's journals. A 15-year cumulative index to *Physiological Reviews* was distributed, with the October issue, to all 1982 subscribers to the journal. (Nonsubscribers may purchase a copy for $5.00.)

The 180-page index covers volumes 47–*61* (1967–1981). It is composed of an author index and a subject index. The author index includes authors' names for each article, complete article title, volume number, and initial page number of each article. Coauthors are listed alphabetically with *see* references to the first author. The subject index main headings are printed in boldface and secondary and tertiary headings in regular type. Cross-references (*see* and *see also*) are included.

As we look back at ways to improve the usefulness of what has been published in *Physiological Reviews*, we also look ahead to exciting new reviews scheduled for future issues. S. G. Schultz and his Editorial Board from throughout the world have secured a superb selection of reviews from leading scientists. The following list contains an exquisite selection of article, for the first part of 1983, that we shall all want to read this coming year.

Coronary Physiology. E. O. Feigl, University of Washington

Gas Exchange and Control of Breathing in Reptiles. M. L. Glass and S. C. Wood, Max-Planck-Institut für experimentelle Medizin and University of New Mexico.

Physiologically Instructive Genetic Variants Involving the Human Red Cell Membrane. J. C. Parker and L. R. Berkowitz, University of North Carolina

What, if Anything, is SI? Organization of "First Somatosensory Area" of Cortex. J. H. Kaas, Vanderbilt University.

Body Energy Balance and Food Intake: a Neuroendocrine Regulatory Mechanism. J. Le Magnen, College de France, Paris

Role of Precursor Availability in Control of Monoamine Biosynthesis in the Brain. J. D. Fernstrom, Massachusetts Institute of Technology.

Transduction in Invertebrate Photoreceptors: Role of Pigment Bistability. P. Hillman, S. Hochstein, and B. Minke, Hebrew University of Jerusalem.

Motor Unit and Muscle Activity in Voluntary Motor Control. H.-J. Freund, Universitaet Duesseldorf.

Development of Respiratory Control. A. H. Jansen and V. Chernick, University of Manitoba.

Mitochondrial Metabolism of Glutamine and Glutamate and its Physiological Significance. Z. Kovacevic and J. D. McGivan, University of Novi Sad, Yugoslavia and University of Bristol.

Turnover and Precursor-Production Relationships of Nonlipid Metabolites. G. Hetenyi, Jr., G. Perez, and M. Vranic, University of Ottawa and University of Toronto.

H. E. Morgan, Chairman.

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Honorary	11
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Associate	703
Student	260
Total	6,077

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Deaths Reported Since the 1982 Spring Meeting

Bale, W. F.
Atlanta, GA
6/28/82

Bremer, F.
Brussels, Belgium
4/07/82

Da Costa, E.
Chicago, IL
6/20/82

Goetzl, F.
Berkeley, CA
11/26/81

Holmes, J. H.
Denver, CO
4/05/82

Knowlton, G. C.
Dacula, GA
3/02/82

Levine, H.
New Britain, CT
11/16/81

Parkins, W. M.
Philadelphia, PA
6/28/82

Pinkston, J. O.
Staunton, VA
6/29/82

Schaefer, K. E.
Old Lyme, CT
6/04/82

Scott, J. B.
East Lansing, MI
1/02/82

Seif, S. M.
Pittsburgh, PA
6/82

Sekelj, P.
Montreal, PQ, Canada
8/23/82

Sendroy, J., Jr.
San Diego, CA
1/07/82

Shimizu, C. S. N.
Los Angeles, CA
2/14/82

Smith, D. C.
Raleigh, NC
2/09/82

Steinbach, H. B.
Woods Hole, MA
12/21/82

Wiedeman, M. P.
Philadelphia, PA
4/18/82

Zawoiski, E. J.
Philadelphia, PA
3/29/82

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 July 1 are considered for nomination by the Council at the Fall Meeting. Applications received between July 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:

Article III, Section 3 - Corresponding Members. Any person who has conducted and published meritorious research in physiology, who is presently engaged in physiological work and who resides outside of North America shall be eligible for proposal for corresponding membership in the Society.

Duties and Privileges:

1. Serve on Society Committees, Boards and Task Forces.
2. Serve as one sponsor of new Corresponding Members (One regular member must be sponsor of a new Corresponding Member).
3. Orally present or co-author a contributed paper and sponsor a non-member authored paper at the Fall scientific meeting.
4. Orally present or co-author one contributed scientific paper at the annual Federation meeting or sponsor one paper.
5. Receive The Physiologist.
6. Receive Federation Proceedings, Public Affairs Newsletters and annual Membership Directory.
7. Subscribe to handbooks and periodicals published by the Society at membership rates.
8. Register to attend scientific meetings of the Federation and the APS Fall meeting at member rates.

FOR ASSOCIATE MEMBERSHIP

Bylaws of the Society:

Article III, Section 5 - Associate Members. Persons who are engaged in research in physiology or related fields and/or teaching physiology shall be eligible for proposal for associate membership in the Society provided they are residents of North America. Associate members may later be proposed for regular membership.

Duties and Privileges:

Same as for Regular Members except for the privilege of:

1. Holding Executive Office, or membership on certain committees.
2. Voting at Society Meetings.
3. Sponsoring New Members.
4. Receiving the Daggs Award.
5. Selection as Bowditch Lecturer.

FOR STUDENT MEMBERSHIP

Not all questions on the application form may be appropriate – Please place NA next to any such question.

Bylaws of the Society:

Article III, Section 7 - Student Members. Any student who is actively engaged in physiological work as attested to by two regular members of the Society and who is a resident of North America. No individual may remain in this category for more than five years, without reapplying.

Duties and Privileges:

1. Present one contributed paper at the Fall Scientific meeting with the endorsement of the student's advisor.
2. Receive The Physiologist.
3. Subscribe to Handbooks and Periodicals at member rates.
4. Register to attend scientific meetings of the Federation and the APS Fall meeting at student rates.

Submit original and 7 copies of application and supporting documents.

APPLICANT'S LAST NAME _____

Date _____

THE AMERICAN PHYSIOLOGICAL SOCIETY
9650 Rockville Pike, Bethesda, MD 20814

MEMBERSHIP APPLICATION FOR:

REGULAR ☐
CORRESPONDING ☐
ASSOCIATE ☐
STUDENT ☐

CURRENT MEMBERSHIP CATEGORY; YEAR ELECTED _____

See Instructions

Name of Applicant: _____
First Middle Last

Mailing Address _____ Birth Date: _____

_____ Citizenship: _____

_____ Country of Permanent Residence:* _____

_____ Telephone No.: _____

* Alien residents of Canada and Mexico see General Instructions. Alien residents of U.S. enter Alien Registration Receipt Card number _____.

1. EDUCATIONAL HISTORY

Dates	Degree	Institution	Major Field	Advisor

Doctoral Dissertation Title:
(if any)

Postdoctoral Research Topic:

2. OCCUPATIONAL HISTORY

Present Position:

Prior Positions:

Dates	Title	Institution	Department	Supervisor

SPONSORS

#1. Name: _____ #2. Name: _____

Mailing Address: _____ Mailing Address: _____

_____ _____

_____ _____

_____ _____

Telephone No. Zip Code Telephone No. Zip Code

I have read the guidelines for applicants and sponsors and this application and attest that the applicant is qualified for membership.

#1 Signature _____ #2 Signature _____

Each sponsor must submit an original and 7 copies of a confidential letter of recommendation to the Society, under separate cover.

APPLICANT'S LAST NAME _____

3. **DESCRIBE YOUR PHYSIOLOGICAL TEACHING** – What percent of your time/effort is spent in teaching Physiology?_____

Describe in the space provided your teaching of physiology including course descriptions (content, format); supervision of pre-doctoral and post-doctoral students; special contributions (films, textbooks, etc.).

4. **INTEREST IN THE SOCIETY** – List any APS Meetings attended by date and check the appropriate box for any papers.

SPRING (FASEB)			FALL (APS)		
Date	Presented	Coauthor	Date	Presented	Coauthor
_____	☐	☐	_____	☐	☐
_____	☐	☐	_____	☐	☐
_____	☐	☐	_____	☐	☐
_____	☐	☐	_____	☐	☐
_____	☐	☐	_____	☐	☐

List other scientific societies of which candidate is a member:

In the space provided state your interest in wanting to join the Society:

5. **SPECIAL CONSIDERATION** – Include any other contributions (Administrative, university, national service, awards and honors) that may be important to physiology.

6. **DESCRIBE YOUR RESEARCH** – What percent of your time/effort is spent in research?_____

Describe the fundamental physiologic questions in your research and how you have answered these questions. Limit the paragraph to the space provided.

7. **BIBLIOGRAPHY** – Attach a list of your publications under the following categories:
   1. Complete physiological papers, published or accepted for publication.
   2. Physiological abstracts (limit to ½ page).
   3. Other papers not primarily physiological (limit to ½ page).

The entire bibliography should not exceed 2 pages. Give complete titles and journal references with inclusive pagination. Use the bibliographic form found in the Society's journals. List authors in the order in which they appear in the publication.

DO NOT INCLUDE A CURRICULUM VITAE

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Permeant Ions, Impermeant Ions, Electrogenic Pumps, Cell Volume, and the Resting Membrane Potential

CHARLES EDWARDS
Department of Biological Sciences
State University of New York at Albany
Albany, New York 12222

After a number of years of teaching the ionic basis of the membrane potential, I have found that students often have difficulty in understanding the processes responsible for the potential. The descriptions in most textbooks are not very satisfactory and in some cases are, I think, in error. Therefore I have written the following outline which combines the known results in a simple way and may give more insight into the processes underlying the potential.

Analysis of the ion contents of cells and the solutions in which cells reside reveals several general properties of the distributions of most major ions. The potassium ion (K^+) is distributed so that the concentration within the cell is many times greater than that in the bathing fluid. The concentrations within the cell of both chloride ion (Cl^-) and sodium ion (Na^+) are always less than those in the bathing fluid. The exact values of the concentrations are somewhat variable for different cells, but these inequalities seem to be generally true.

The laws of chemistry and physics require that in a solution the concentration of positively charged ions equals the concentration of negatively charged ions. In a typical bath solution there is a high concentration of Na^+ and Cl^- and a low concentration of K^+, so that to a first approximation this rule holds. There are of course other ions, both negative and positive, in most bathing solutions, but the concentrations are usually small compared with that of NaCl, and so they have been ignored. However, it may be seen that there is a deficiency in the description of the internal contents; the K^+ level is high and the Cl^- is low, and so there must be other negatively charged ions (anions) within the cell to balance the positive charges. In fact most cells contain negatively charged proteins as well as various phosphorylated compounds that participate in metabolism. Two very familiar and common examples of the latter are adenosine triphosphate (ATP) and creatine phosphate, both of which have several negative charges at the pH of the cell interior. Further, there is probably a reason why in evolution these compounds became impermeant and therefore locked within the cell. These phosphorylated compounds are necessary for the formation and utilization of chemical energy by the cell, and if they were lost as they were formed, the cell would not survive for long. However, their retention poses a problem about the osmotic balance of the cell, and this will be considered later.

One other general property of the cell is the presence of a difference in potential across the cell membrane. The inside of the cell is negative with respect to the bathing solution.

If two solutions of KCl of different concentrations (say 1 and 10 mM) are separated by a membrane permeable to only one of the ions a potential difference will appear between the two solutions. Consider the membrane to be permeable only to K^+; then K^+ will tend to move, by diffusion, from the side of high concentration (10 mM) to the side of low concentration (1 mM). However, the number of ions that can move is limited (Fig. 1); as soon as a K^+ moves, a charge imbalance is set

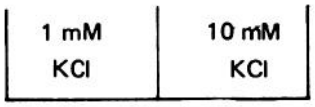


Figure 1

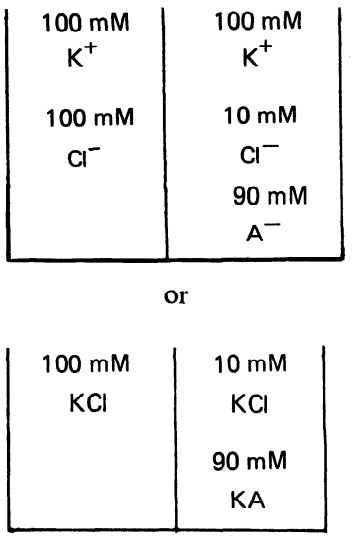
up, since the side from which the K^+ moved becomes negative and the side to which the K^+ moved becomes positive. This positive potential tends to oppose the further movement of the positively charged potassium ions. In time the diffusional force driving K^+ from the side of high concentration to the side of low concentration is exactly equal and opposite to the electrical force tending to oppose the movement of K^+; the net movement of K^+ will then cease. Note that the movements of ions across the membrane due to diffusion continue, but that for each ion the movements are equal and opposite. Equating the electrical force (E) to the diffusional force gives the following equation

$$E = \frac{RT}{zF} \ln \frac{[K^+]_1}{[K^+]_2} \qquad (1)$$

where R is the gas constant, T is the absolute temperature, z is the valence, and F is the Faraday constant. For the example illustrated in Fig. 1, $E = 58$ mV and the side with 1 mM KCl is positive with respect to the other side. If the membrane were permeable to Cl^- instead of to K^+, the same equation is applicable; however, for Cl^- z is -1, and so the sign of the potential is now negative and the direction is reversed. This equation, called the Nernst equation, describes the potential difference set up by the presence of two solutions of unequal concentration under conditions where the movement of one of the two ions is constrained. Note that the amount of ion that must move to set up the potential is too small to be measured chemically, so that if one were to analyze the contents of the solutions before and after the contact, no differences would be found. However, some ions must move for an electrical potential to develop, and this can be estimated by use of the equation for the charge on a capacitor: $Q = CV$, where Q is the charge, C is the capacitance of the membrane, and V is the potential difference. For a typical muscle fiber $C = 1.6 \times 10^{-8}$ F ($C_m = 10^{-6}$ F/cm^2, the fiber is a cylinder, diameter = 50 μm, length = 1 cm, and so area = 1.6×10^{-2} cm^2), $V = 90$ mV, and so $Q = 1.4 \times 10^{-9}$ coulomb or 1.4×10^{-14} molar equivalents, since there are 96,500 coulombs/mol.

Consider the situation pictured in Fig. 2, where there is an impermeant ion, A^-, on one side of the membrane, which in this example is permeable to both K^+ and Cl^-. There is a gradient in the Cl^- concentration so that it moves by diffusion from the side of high concentration to the side of low concentration. As it moves, it leaves unpaired K^+ and thereby sets up a potential, so that the side to which it moves becomes negative. This difference in potential causes the movement of K^+, and this occurs in parallel with the movement of Cl^-, so that the two ions move together. It is assumed for now that water does not move with the ions; actually water *will* move with the ions, and this problem will be dealt with below. Initially, Cl^- is moving down a concentration gradient and K^+ is moving between two sides with no concentration difference, and so no energy is required. In time, a measurable amount of KCl will move, and so the Cl^- gradient will decrease and a K^+ gradient will develop. The movement will continue as long as the energy given up by the movement of Cl^- is greater than the energy required to move K^+, i.e., as long as the Cl^- concentration ratio exceeds the K^+ concentration ratio. When these

Figure 2



ratios become equal, the net movement of KCl will cease; this condition can be written as

$$[K^+]_1/[K^+]_2 = [Cl^-]_2/[Cl^-]_1 \qquad (2)$$

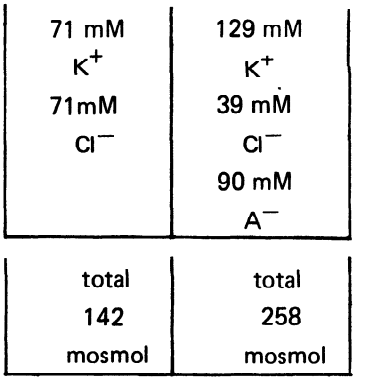
or

$$[K^+]_1[Cl^-]_1 = [K^+]_2[Cl^-]_2$$

The distribution of other permeant ions should also agree with the ration given in *Eq. 2*. With the number given in Fig. 2, the final concentration will have the approximate values given in Fig. 3. Either of these ratios can be put into *Eq. 1* above to calculate the resting membrane potential.

Let us turn next to the osmotic problems caused by the impermeant ions within the cell. If the number of particles on each side is summed, it is seen that the totals are unequal. If the numbers of particles on the two sides are unequal, then the concentration of water on the two sides are unequal and water will move down its concentration gradient, i.e., from the side of high concentration (and low number of solute particles) to the side of low water concentration (with the high number of solute particles). The movement of water in this direction will tend to equalize the concentration of water on the two sides. The situation just described is a Donnan

Figure 3



equilibrium; in the presence of impermeant ions, there will be a potential difference and also an osmotic gradient.

The basis of the resting membrane potential in living cells is a Donnan equilibrium, and so there arises the problem of the control of the inherent osmotic imbalance. There are two ways to block the movement of water. The application of an appropriate pressure to the side of low water concentration will block the movement of water; this amount of pressure is, by definition, the difference in osmotic pressure between the two sides. Some plant cells use this mechanism, because the rigid cellulose wall blocks the osmotic movement of water.

Alternatively, the addition of an impermeant substance to the other side to balance the concentrations of particles on the two sides will serve the block the movement of water. Thus, even though some of this substance can appear on the side with the high number of particles, the concentration on the other side should be sufficiently greater so that the particle totals on the two sides are equal. This is the mechanism used by animal cells, and the substance used to balance the osmotic difference is Na^+. The osmotic imbalance resulting from the presence of internal impermeant anions is balanced by the internal Na^+ concentration's being lower than its external concentration. Since the cell membrane is, in fact, somewhat permeable to Na^+ and there are impermeant ions present within the cell, the Na^+ level within the cell should be higher than that outside; in fact the inside-to-outside concentration ratio of Na^+ ($[Na^+]_i/[Na^+]_o$) should be the same as that for K^+, as given in *Eq. 2*. However, the cell membrane has the ability to keep the Na^+ concentration within the cell low in the face of conditions which would make it high. The mechanism responsible for this is called the Na^+ pump. The movement of Na^+ out of the cell requires energy, because Na^+ is moved from a region of low concentration to one of high concentration and because positive ions are moved to a region of positive potential (since the inside of the cell is negative with respect to the outside, the outside is positive with respect to the inside). However, the Na^+ pump also moves K^+ into the cell; the Na^+ and K^+ movements are coupled, but they are not matched 1:1. A 1:1 coupling would eliminate the electrical work of the pump but not the work required to overcome the concentration gradient. The partial matching of the movements of the ions reduces the amount of energy required for the electrical work. The incomplete matching means that there is a net movement of positive ions out of the cell, and this will contribute to the resting potential (it will make the inside more negative). The pump is therefore said to be electrogenic. If the Na^+ pump is blocked as it can be by the addition of ouabain, there will be a small change in the membrane potential (it will become less negative) in those cells in which the pump is electrogenic and the magnitude of the change in potential is determined by the electrogenic and the magnitude of the change in potential is determined by the electrogenic contribution of the pump.

The concentration gradient produced by the Na^+ pump is exactly that required to counteract the osmotic imbalance, i.e., the concentration of Na^+ is higher on the side with the low number of particles. The principal consequence of the block of the Na^+ pump is swelling of the cell, because as the internal Na^+ concentration increases, the number of particles within the cell increases and the entry of water leads to swelling of the cell. A consequence of the movement of K^+ by the pump is that the internal concentration of K^+ is greater than the level described by the amount of impermeant anion and the conditions for the Donnan equilibrium.

The so-called nonelectrogenic part of the resting membrane potential may be calculated from the Goldman-Hodgkin-Katz equation

$$E = \frac{RT}{F} \ln \frac{P_{K^+}[K^+]_o + P_{Na^+}[Na^+]_o + P_{Cl^-}[Cl^-]_i}{P_{K^+}[K^+]_i + P_{Na^+}[Na^+]_i + P_{Cl^-}[Cl^-]_o} \quad (3)$$

where the P is the relative permeability of the membrane to the ion denoted. In effect, this equation sums the Nernst potentials for the ions, weighting the contribution of each ion by the permeability of the membrane to that ion. The permeability to K^+ is usually at least 10 times greater than that to Na^+, and so the membrane potential is close to the Nernst potential for K^+. The permeability to Cl^- is usually similar to that for K^+, and so the Nernst potential for Cl^- is close to the resting potential. In the giant axon of the squid there appears to be also a Cl^- pump, so that the internal Cl^- level exceeds that expected from *Eq. 2*

In summary, the resting membrane potential is largely due to the presence of impermeant anions within the cell, leading to a high concentration of K^+ and a low concentration of Cl^- within the cell. This distribution of ions produces an osmotic imbalance; in animal cells this is overcome by the Na^+ pump, which uses energy to keep the Na^+ concentration within the cell low in the face of conditions that would make it high. The movement of Na^+ out of the cell by the pump is coupled with the movement of K^+ into the cell, and so the concentration of K^+ within the cell is somewhat greater than that expected from the Donnan equation. This is the reason why in some cells the K^+ equilibrium potential (as calculated from the K^+ concentration ratio) is more negative than the resting potential. Furthermore, if the Na^+ and K^+ movements are not coupled 1:1, then the pump is electrogenic, so that the membrane potential may be more negative than predicted by the Donnan equilibrium.

Suggested Readings

1. Aidley, D. J. *The Physiology of Excitable Cells* (2nd ed.). New York: Cambridge, 1978.
2. Conway, E. J. Nature and significance of concentration relations of potassium and sodium in skeletal muscle. *Physiol. Rev.* 37: 84-132, 1957.
3. Hodgkin, A. L. The ionic basis of electrical activity in nerve and muscle. *Biol. Rev.* 26: 339-409, 1951.
4. Katz, B. *Nerve, Muscle and Synapse.* New York: McGraw, 1966.
5. Thomas, R. C. Electrogenic sodium pump in nerve and muscle cells. *Physiol. Rev.* 52: 563-594, 1972.
6. Tosteson, D. C. Regulation of cell volume by sodium and potassium transport. In: *The Cellular Functions of Membrane Transport,* edited by J. F. Hoffman. Englewood Cliffs, NJ: Prentice-Hall, 1964, p. 3-22.

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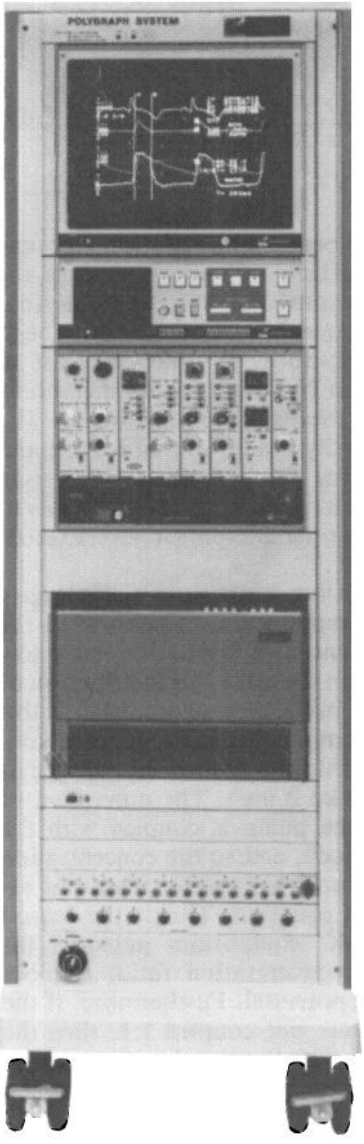


■RM-6000

The main system RM-6000 can be equipped with a microcomputer-assisted color monitor. Which displays up to eight parameters with the digital values in corresponding colors. The microcomputer facilitates the calculation of time, amplitude, integrated and averaged values, and permits direct readouts of information on one display.

Accuracy in measurement

The sensitivities of the recorder and the monitor are standardized at 10mm/1V, with their inputs connected directly to the outputs of the plug-in units.
The ink-writing recorder with position-feedback penmotors ensures ±0.5% linearity, while the ink-jet recorder provides for superior frequency response up to 1kHz. Also, ±2.5% linearity is ensured for the monitor.

Ease of operation

The amplifier console employs a centralized control system. Which provides for the simultaneous application of individual calibration signals to plug-in units, and the instantaneous stabilization of monitor channels with a touch of a button.
Further, the program board in the console permits easy interconnections of system components, eliminating external patch cord connections around the rack.

Versatility of system composition

The modular construction permits you to configure a polygraph system to your exacting present needs with the potential for future expansion. The available modules include monitors, recorders and amplifier consoles which accommodate up to eight plug-in units which may be selected from approx. 40 modules for measuring the parameters listed below.

■Mini-polygraph RM-6100

The main frame can be equipped with an ink-writing or heated-stylus recording system. It will accept plug-in units for your specific needs. Selectability of the recording system and the plug-in units permits you to configure a mini-giant to serve you efficiently and economically.

Measuring Parameters:

Apex Cardiogram
Blood Flows
- Mean flow
- Minute volume
- Pulsatile flow
- Stroke power

Blood Pressures
- Arterial
- Intraventricular
- Mean
- Pulse
- Venous

Cardiomuscular Displacement
Cardiomuscular Tension
Cardiac Outputs
- Dye dilution—both cuvette and earpiece methods
- Impedance plethysmogram
- Thermodilution

Cystometry
Displacement
Electrocardiograms (ECG)
- Standard 12-lead
- Telemetry system

Electrocorticogram
Electroencephalograms (EEG)
- Depth electrode derivation
- Evoked EEG response
- Needle electrode derivation
- Surface electrode derivation
- Telemetry system

Electromyograms (EMG)
- Evoked EMG
- Integration of EMG
- Needle electrode derivation
- Surface electrode derivation
- Telemetry system

Electronystagmogram (ENG)
Force
Galvanic Skin Response
Heart Rate
His-bundle electrogram
Internal Pressures
- Esophagus
- Intracranial
- Urethral
- Others

Minor Tremor
Muscular Displacement
Muscular Tension
Phonocardiograms
- Acceleration method
- Air-conductive method

Plethysmograms
- Body
- Impedance
- Photoelectric

Pneumotachograms
- Flow velocity
- Flow volume
- Intra-esophagus pressure

Pulse Waves
- Carotid artery pulse
- Jugular venous pulse

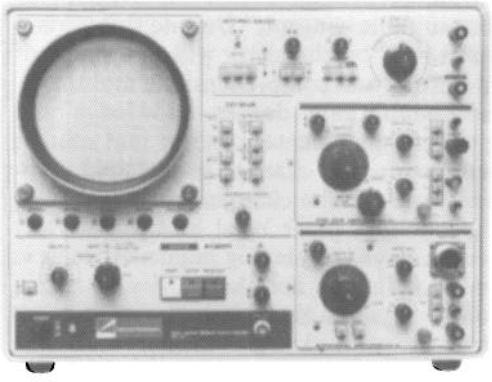
Respiratory Curves
- Thermistor sensor
- Elastic rubber tubing

Sphygmogram
Temperatures
- Body cavity
- Body surface
- Fluid/solution/liquid

Urethral Pressure Profile (UPP)

reliability, modularity, flexibility, expandability and cost effectiveness, plus operational simplicity

■Related Instruments



Dual-beam Memory Oscilloscope VC-10
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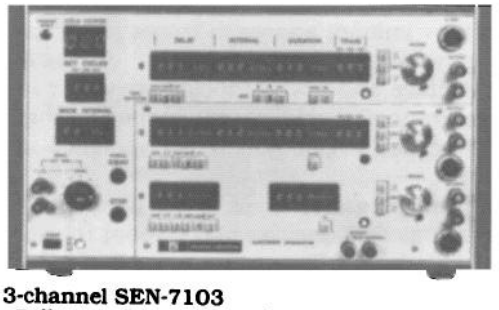
The 2-channel memory allows:
- Direct readout of stored data on an analog recorder without additional interface
- Display of a Lissajous graph or X-Y signals
- Simultaneous observation of past and current waveforms
- Analysis of pretrigger vital information
- Interface compatible with RS-232.

Electronic Stimulators SEN-3201/7103
Digital thumbwheel switches are used for easy setting of single or paired pulse time and required number for train output. Accuracy is ensured by a crystal-controlled oscillator. The output voltage can be set to max. 10V through the vernier dial. Modulation is also provided for composing complex waveforms.

Single-channel SEN-3201
- An additional unit permits the mixture of positive and negative stimuli.



3-channel SEN-7103
- Different stimulus waveforms can be set independently for the three channels.
- Compound waveform can be drawn on 1st channel.

Ink-writing Recorders WI-600 series
(2, 4 and 8 channels)
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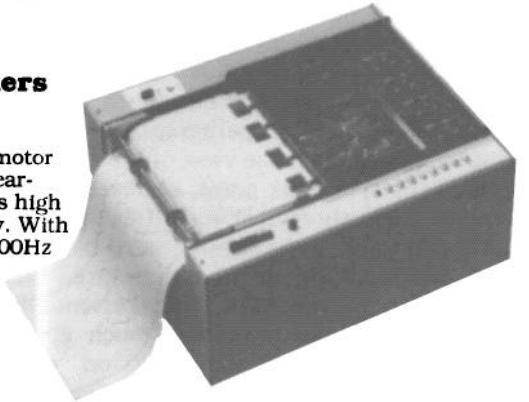
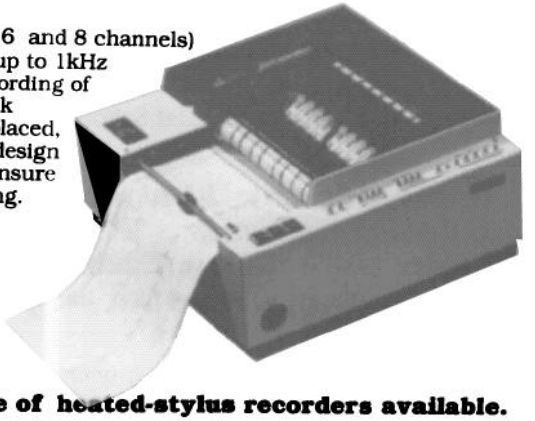


Ink-jet Recorders RIJ-2100 series (4, 6 and 8 channels)
High frequency response up to 1kHz allows for high fidelity recording of His-bundle studies. The ink cartridge can be easily replaced, while the special ink and design features of the jet nozzle ensure operation free from clogging.



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Book Reviews

Thirst. Problems in the Behavioral Sciences.
B. J. Rolls and E. T. Rolls

New York: Cambridge, 1982, 194 pp., illus., index, $29.50 (hardback), $10.95 (paperback)

Thirst by Rolls and Rolls is a difficult book to review, perhaps because as the authors point out in their forward it is aimed at "students of psychology, physiology, medicine, biology and zoology." A book aimed at such a diverse audience has a hard task in pleasing all. The first two chapters relating to the physiology of fluid and electrolyte balance are written for a beginning student and hold little interest for workers in the field. The followig chapters are of more interest for researchers, dealing with the origins of thirst, the neural and pharmacological control of drinking, and other specific problems. The authors have read and presented much of the literature on the subject. Each aspect of thirst is covered well in individual chapters, but for the most part the writing seems directed at workers in the field rather than students. Thus one can get an excellent review of the literature. A nice touch added at the end of each chapter is a short paragraph in which the literature is summarized, as is the view of the authors as it relates to each topic. A weak point, however, is that the review is not sufficiently critical, and often the viewpoint of the authors appears to be substantiated by a biased reading and interpretation of the literature. One omission should be mentioned. The book is essentially a review of thirst in mammalian species; much good and informative work has been done on nonmammalian vertebrates that bears directly on the general problem of thirst. It would have been more helpful if some of these data had been included.

Richard L. Malvin
University of Michigan Medical School.

Membrane Fluidity: Biophysical Techniques and Cellular Regulation.
M. Kates and A. Kuksis (Editors)

Clinton, NJ: Humana Press, 1980, 445pp., illus., index, $54.50

Membrane Fluidity provides an overview of an area that is playing an increasingly important role in cellular function. The title is somewhat illusory in the sense that not only is the problem of membrane fluidity considered from several different aspects, but correlation of changes in phospholipid composition of membrane with physiological events (parts II, III, and IV) represents a key aspect of this volume. This book is a compilation of papers presented at a Satellite Symposium of the XIth International Congress of Biochemistry held in Toronto, Canada, in July, 1979. Thus the work presented is at least three years old. A primary aim was to emphasize the factors controlling membrane fluidity. Toward this end, part I considers new approaches employed to measure lipid composition and fluidity. Included among these procedures is a consideration of the development of capillary chromatography and ion mass spectrometry. These chapters are for the specialist. Part IV, which considers the homeostatic regulation of membrane fluidity, is a rather diffuse section covering a wide range of topics from the control of membrane lipid fluidity in fungi to the regulation of phospholipid *N*-methylation in hepatocytes. While Professor Lands provides a lucid theoretical definition of "membrane fluidity," the Editors aver in the preface that one of the highlights of the symposium was the general recognition that ..."membrane fluidity requires a revision in its working definition, or perhaps even a replacement by some other more suitable concept." Despite this caveat, those interested in lipid biochemistry will find many of the chapters interesting and comprehensible, and the interested reader should gain deeper knowledge and understanding of the fundamental concept that cellular function is accompanied by changes in the lipid composition of membranes. These changes, particularly involving the phospholipid polar head group and fatty acyl groups, are portrayed as playing important roles in modifying membrane fluidity and the activity of certain membrane-bound enzymes. Such knowledge will, of course, provide us with keener insight into the biochemical mechanisms associated with changes in the properties of cellular membranes.

Ronald P. Rubin
Medical College of Virginia

Fundamental Cardiovascular and Pulmonary Physiology.
J. F. Green

Philadelphia, PA: Lea & Febiger, 1982, 347 pp., illus., index, $20.00

This is yet another volume to add to the list of cardiovascular monographs that have recently appeared. It is significantly different from the others only in that it also deals with the respiratory system. Although its subtitle, *An Integrated Approach for Medicine* (prominently displayed on the cover and mentioned in advertising for the volume), promises what would surely be a useful, and perhaps unique, approach to the presentation of basic physiology, that promise is explicitly negated in the Preface and never appears anywhere in the volume. "Integration" is evident only in the fact that two functionally related organ systems are included in the same volume.

That disappointment aside, there are a number of pertinent observations that one can make about the actual content of this book. Throughout, it displays a quantitative orientation. It is richly illustrated with diagrams of model (physical) systems and graphic displays of quantitative arguments. Although these are sometimes helpful, more commonly they are sufficiently complicated so that they are likely to hinder rather than assist the student in coming to grips with difficult relationships.

In general, the inclusion of individual topics in the areas of cardiovascular and respiratory physiology is what one would expect. However, the weight given to these topics is skewed heavily toward the more quantitatively oriented areas. And even here, the emphasis is often odd. For example, a very much simplified model

of the Hodgkin-Huxley formulation is developed at some length (to no obvious benefit to the student, who is likely to have been exposed to a more relevant model elsewhere), but significant features of myocardial membranes, such as calcium currents and the pacemaker potential, receive very skimpy coverage. Homeostatic regulation of blood pressure and ventilation is discussed, but little is said about the baroreceptors and chemoreceptors themselves. The regional circulations (coronary, cerebral, skeletal muscle, etc.) are described in a cursory way, and the whole area of gas transport is dealt with in such a condensed manner that important features of the mechanisms involved are likely to be overlooked by the student. The depth of coverage of individual topics is thus uneven and often inappropriate.

Finally, three brief chapters on "Disturbances" fail to systematically develop examples of pathophysiology in ways that would reinforce concepts of normal physiology.

This is, on the whole, not a bad book, but it is difficult to determine the audience for which it is most appropriate. Its usefulness in a medical physiology course is limited by its uneven attention to important topics and its tendency to "muddy the water" with potentially confusing mathematical development. It is clearly more appropriate as a text for physiology graduate students or biomedical engineering students, who would be better able to handle the more quantitative presentation and for whom it is more appropriate. Last, but certainly not least, lecturers may very well find useful ideas for the development of the physics of the cardiovascular system that can be incorporated in their own teaching.

Joel A. Michael
Rush Medical College, Chicago

Corrected Book Reviews

Physiololgist 25(5) 450-451, 1982

Excitable Cells in Tissue Culture.
P. G. Nelson and M. Lieberman (Editors)

New York, Plenum, 1981, 422 pp., illus., index, $42.50

This multiauthored book presents a much needed collection of materials on an important and fast-moving research area. As such, it seems to be written for those active in excitable cell research, but the book is very readable and could serve as a text for an advanced graduate course. The stated aim of the book is not that of an exhaustive review; rather, it emphasizes systems most pertinent to the study of the unique properties of membranes in excitable cells: their passive electrical properties, ionic channels, neuropharmacology, and to a lesser extent, the formation of specialized cell-to-cell connections. The chapters have been written by a series of contributors expert in different areas. This imparts a highly specialized and authoritative flavor to each article. Chapters are well referenced up to about 1979, with scattered and somewhat limited citations to articles after that time.

The book divides naturally into four major sections. The first section discusses peripheral and central neuronal systems, the second reviews biophysical techniques used in tissue culture systems, the third deals with research in clonal systems, and the final section deals with the various forms of muscle cells.

In the first chapter, Burton and Bunge review work on autonomic neurons as representative of the peripheral nervous system. The history of autonomic neuron cultures, and particularly their utilization and response to neurotransmitters, is well reviewed. The bulk of the material centers around reports on the behavior of rat superior cervical ganglion cells in culture. Nelson and colleagues review dissociated cell cultures of central nervous system tissues with an emphasis on use of such cultures in defining central synaptic transmission. While an appendix gives "how-to" descriptions on the preparation of tissue cultures from rat cerebellum, mouse spinal cord, and rat celebral cortex, the discussion within the chapter itself is confined almost exclusively to chick and rodent spinal cord and dorsal root ganglion cultures. Macdonald and Barker discuss in detailed fashion the pharmacology of central synaptic transmission, again considering only spinal cord neuronal preparations. γ-Aminobutyric acid (GABA), glycine, β-alanine, and glutamate are the transmitters emphasized. A possible drawback of this first section is that spinal cord neuronal preparations, taken as models of central neurons, still are tissues that may be too "peripheral" for the dedicated "centralists" among us.

The next two chapters on electrophysiological techniques are good for both the novice and the experienced worker. Smith and colleagues present a good overview on the use of voltage clamp methodology in elucidating the time and voltage dependence of ionic currents across the cell membrane. Cultured muscle cells and spinal cord neurons are compared, illustrating that different electrode and current driver systems are needed for different cell types. While carefully presenting the limitations, the authors demonstrate very nicely where voltage-clamp techniques can be used to a great advantage. Lecar and Sachs describe membrane noise analysis; although a little more difficult for the novice to read, the article presents a good overview on how channel noise can be measured and interpreted. Current fluctuations due to opening and closing of single channels and currents summed from simultaneous fluctuations of many channels and the distinction between channel noise and other sources of electrical noise in the system are presented clearly. This leads nicely into understanding the new and powerful "patch-clamp" techniques, which can be used to observe fluctuations in a single channel while controlling membrane potential.

The section on clonal cell systems is also very worthwhile. These cells differ from others discussed in the book in that they are permanent cell lines dividing continuously in tissue culture and, as such, have had to arise from tumor or embryonic explnts. These chapters detail the advantages of such tissue culture systems for excitable cell studies and point out extensive possiblities for their use. A nice example is the use of artificial fusion techniques to produce large cells highly suitable for microelectrode manipulations in electrophysiological studies. The advantages (and caveats) implicit in using tissue culture systems to provide parallels to differentiating excitable cells are discussed. Kimhi reviews extensively the biology of neuroblastoma cultured cells and, to a lesser extent, pheochromocytoma cultured cells. Spector covers electrophysiological studies in clonal nerve cell lines. Catterall describes data in

neuroblastoma cells, pointing to a two-state allosteric model of sodium channels in which alkaloid neurotoxins activate the channel and increase sodium flux by binding preferentially to the activated state; scorpion toxin binding at a second site reduces the energy required for activation, as for heterotropic cooperativity in allosteric enzymes. Channel inhibitors like tetrodotoxin bind at a third site. Sodium channels in skeletal and cardiac muscle have similar behavior but differ quantitatively.

The last section concerns muscle cells. Kidokoro traces the development of tetrodotoxin-sensitive sodium channels and action potentials in myoblasts, multinucleate myotubes, and adult skeletal muscle cells. Myoblasts and myotubes exhibit calcium currents that give their action potentials a similarity to those in cardiac muscles but later disappear. Purves enumerates the technical problems in making electrophysiological observations in cultures of smooth muscle cells and the variability among cell types. Calcium exchange in myocardial cell cultures is reviewed by Langer, with an emphasis on the role of the components of the cell surface coat. Lieberman and colleagues review their timely and original efforts on the uses of chick heart cell cultures grown into linear strands or spherical clusters for electrophysiological and tracer studies. These have given improve precision, for example, in characterizing sodium currents, a technical feat.

In summary, the book is highly readable. It well merits purchasing by libraries and by investigators in the field. It suggests broadened approaches for those in tissue culture research and new substrata for those in electrophysiological research.

James B. Bassingthwaighte
Helen C. Kiefer
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Structure and Function in Man. S. W. Jacob, C. A. Francone, and W. J. Lossow

Philadelphia, PA: Saunders, 1982, 697 pp. (book), 276 pp. (lab. manual)., illus., index, $26.95 (book), $11.95 (lab. manual)

Jacob, Francone, and Lossow successfully present a textbook and laboratory manual that integrate anatomy and physiology. Both books are coordinated in a logical and organized sequence as shown by their coverage of four units emphasizing physiology: 1) a general introduction on the body as a whole, the cell, and tissues; 2) the framework of the body including the skin, skeletal, articular, and muscular systems; 3) integration and metabolism with sections on fluids and electrolytes, special senses, nervous, circulatory, lymphatic, respiratory, digestive, urinary, and endocrine systems; and 4) the reproductive system. The authors state in the preface that many of the chapters have been either partially or completely revised since the last edition. Each textbook chapter begins with a list of behavioral objectives followed by the organ anatomy in which important terms are in boldface print. Thereafter an extensive description of the physiological system or organ ensues. Of particular importance are the clinical pathologies that are discussed for most of the physiological systems. The reader will also appreciate the detailed summary outline and the review questions at the end of each chapter, which afford the student the opportunity of testing his comprehension of the subject matter.

There are many other points in the book's favor. Both the illustrations and text are clearly and accurately labeled, thereby enhancing visual understanding and facilitating learning. After each of the major headings in dark or red bold type the various figures and tables are noted as referring to the underlying text. Also, there are numerous illustrations (525), tables, anatomic diagrams, schematic representations, and charts throughout the text that summarize and organize previously mentioned anatomic relationships. For example, in the unit on muscles, various groups of muscles are arranged in columnar form that includes names, origins, insertions, functions, and nerve innervations. Another tremendous aid to the reader consists of many color-coded figures depicting arteries, veins, nerves, and muscles. Additionally, the appendix includes several useful sections: prefixes, suffixes, combining forms, metric units and US equivalents, suggested additional reading, and a glossary of terms.

There is one shortcoming. In general the laboratory manual lacks the textbook's depth and detail. In my opinion, many experiments, although supplemental to the textbook, are too superficial and do not reflect the caliber of the textbook. I found both the textbook and laboratory manual to be generally well written. However, the format, terminology, and depth make it more suitable for an elementary course in anatomy and physiology. I would suggest that these books be used together for the beginning student preparing for a health-related career.

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