THE PHYSIOLOGIST

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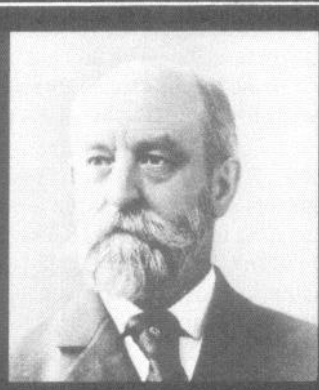
Cover: See 28th Bowditch Lecture, p. 333

Bowditch Lectureship

The annual Bowditch Lectureship in honor of the first elected President of the American Physiological Society, Henry Pickering Bowditch, was established in 1956. The lecturer is selected by the President of the Society from among the members who have done outstanding work and are under 40 years of age. Funds for an honorarium are given by the Society. The lecture is given as a formal presentation at the Fall Meeting of the Society. The first Bowditch Lecture, titled "Role of the red blood corpuscles in the regulation of renal blood flow and glomerular filtration rate," was given in 1956 by John R. Pappenheimer of Harvard Medical School. At the present time, the source of funds is the income from investment of an unrestricted bequest from former Society member Caroline tum Suden.

Bowditch Lecturers

1956	John R. Pappenheimer	1970	Donald Kennedy
1957	Bodil Schmidt-Nielsen	1971	J. Alan Herd
1958	Arthur B. DuBois	1972	Felix Strumwasser
1959	Lloyd M. Beidler	1973	Rodolfo R. Llinas
1960	Carl W. Gottschalk	1974	Clay M. Armstrong
1961	John A. Clements	1975	Thomas G. Coleman
1962	T. Hastings Wilson	1976	Jared M. Diamond
1963	Eugene M. Renkin	1977	Franklyn G. Knox
1964	Daniel L. Gilbert	1978	Joseph B. Martin
1965	Ernst Knobil	1979	Joseph H. Szurszewski
1966	David H. Hubel	1980	Fred J. Karsch
1967	Peter F. Curran	1981	Barry K. Gilbert
1968	Eugene Braunwald	1982	Kent Hermsmeyer
1969	John Urquhart III	1983	David R. Kostreva



The 28th Annual BOWDITCH LECTURE

Functional Mapping of Cardiovascular Reflexes and the Heart Using 2-[^{14}C]Deoxyglucose

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Dr. Randall, distinguished members of the Council, members and guests of the Society, I want to thank you for the privilege and honor of giving the 1983 Bowditch Lecture here in beautiful Hawaii. After Dr. Randall asked me to give this lecture, I read about Dr. Bowditch and his work, and I learned that our first president like our last was very interested in the study of both the heart and the nervous system, an area of physiology which Dr. Randall has expanded greatly for all of us and whose enthusiasm for this area of research has been a stimulus to me personally.

Before I begin, I would like to publicly acknowledge several individuals who have played a vital role in the accomplishment of the studies that I will relate to you in the next few minutes. First of all, I want to thank Dr. John P. Kampine, who as my mentor introduced me to the excitement of physiological research and the perseverance that it requires, and as my present chairman he has always supported my ideas with encouragement and financial backing. Other members of our Anesthesia Research Laboratory at the Wood VA Medical Center whose interaction has been vital include Dr. Robert Coon, Dr. Zeljko Bosnjak, Dr. Jeanne Seagard, Dr. Stephen Abram, and Mr. Norman Herman. I am also grateful to Dr. Edward Zuperku, Drs. Neil and Gretchen Mandel, Mr. Fran Hopp, and two undergraduate students, Miss Penny Rheingans and Mr. Brendon Conlon whose talents with computer technology are unmatched. A special thanks is also due to Mr. James Wood and Mrs. Monica Olsen for their superb technical skills. But most importantly, I am thankful to God for helping me to become a physiologist and allowing me to study a small part of His creation.

Since the early 1900s (36) radiolabeled materials have been used to gain new information in physiology (21, 97), biochemistry (65, 87), pharmacology (4, 59), anatomy (76), and diagnostic medicine. About seven years ago, Dr. Louis Sokoloff and his colleagues at the National Institute of Health (NIH) attempted to develop a new technique for measuring cerebral blood flow; however, this technique proved to be more useful for measuring cerebral glucose metabolism (90, 92). This technique is based on the following principles. Under normal conditions glucose is the primary metabolic substrate needed for brain metabolism. Circulating plasma glucose is transported across the blood-brain barrier and phosphorylated by the hexokinase enzyme. It then passes down the glycolytic pathway and within a few minutes is converted to carbon dioxide and water. Deoxyglucose follows the same transport and metabolic pathway and is phosphorylated by the hexokinase enzyme; however, it remains trapped as deoxyglucose 6-phosphate and is not metabolized any further because of either the absence of or inadequate supply of deoxyglucose-6-phosphatase activity in the brain. Therefore the attachment of a radiolabel like ^{14}C or ^{3}H on to the deoxyglucose provides us with a marker that can be used with autoradiography or scintillation counting to detect regions of brain that are using the most glucose during a period of time. Sokoloff went on to develop the quantitative autoradiographic technique which allows us to determine precisely the number of micromoles of glucose utilized per 100 grams of brain tissue per minute. But what is really being measured with this technique? In brain it is probably the Na^+-K^+-ATPase (Na^+ pump) (70, 91). Since most of the energy expended by neural tissue is related to the maintenance of ionic gradients, it is proposed that the majority of glucose utilization occurs at synapses and cell bodies (70). Glucose is known to be an important metabolic substrate in other tissues like cardiac and smooth muscle where it is required for work-related energy needs of those tissues.

Our interest in this technique stems from our work with cardiopulmonary afferents and their reflex effects. Beginning in 1973, as a graduate student I began studying the characteristics of right atrial and right ventricular cardiac receptors with sympathetic afferents in dogs (58) and monkeys (102). During the study of right-heart receptors, nonadapting pulmonary stretch receptors with sympathetic afferents were found coursing through the white rami (57). Some of the reflex effects

of the cardiopulmonary sympathetic afferents were studied in dogs and monkeys. Pressor responses before and after buffer nerve denervation were studied in dogs in response to electrical stimulation of slow conducting fibers in the ansa subclavia (51). Depressor responses could also be elicited with cardiopulmonary sympathetic afferent stimulation of faster conducting fibers (52). Sympathetic afferent stimulation was also shown to reflexly inhibit respiratory drive in both dogs and monkeys (53). A cardiac nerve-evoked potential mapping study to determine the distribution and fiber type of the upper thoracic ventral roots was accomplished in dogs (56). The excitation charactertistics of vagal and sympathetic cardiac, ventricular, papillary muscle, aortic, pericardial, and pulmonary vascular receptors were also studied in dogs (80). The reflex effects of some of the vagal cardiac afferents on respiratory drive and blood pressure were also studied in sympathectomized dogs on cardiopulmonary bypass (54). The reflex effects of cardiac vagal afferents on renal efferent nerve activity were also studied in dogs on cardiopulmonary bypass (98). Changes in cardiac sympathetic and vagal afferent and efferent nerve activity during cardiac tamponade was also studied in dogs (15), as was the nonvagally mediated bradycardia that occurs during cardiac tamponade or severe hemmorhage (50). With prolonged cardiac tamponade it was observed that all the animals eventually develop electromechanical dissociation; however, the onset of dissociation can be delayed by sympathectomy or β-adrenergic blockade (49). Other observations made during the tamponade studies led to the investigation of the reflex effects of hepatic baroreceptors on renal and cardiac sympathetic efferent nerve activity. The hepatic receptors reflexly cause a marked increase in sympathetic efferent nerve activity (48). Renal vascular receptors that respond to increases in renal venous pressure reflexly inhibit sympathetic efferent nerve activity to both the kidney and the heart (55). Receptors have also been located in the spleen of the dog. These receptors increase their firing frequency during manual compression of the spleen. Increases in splenic arterial pressure have no effect on splenic afferent nerve activity. Electrical stimulation of the splenic afferents produce reflex increases in cardiac and renal sympathetic efferent nerve activity (35). It has been the results of these studies that have stimulated our interest in the central integration of the cardiovascular reflexes.

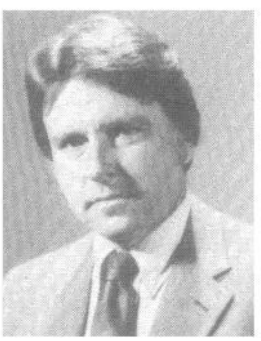
The importance of the medulla in the regulation of the cardiovascular system first became evident with the studies of Dittmar (26) in the early 1870s. These studies were extended by Ranson and Billingsley (84), in 1916, by their demonstration of pressor and depressor responses resulting from stimulation of various portions of the medulla. The pressor and depressor areas of the brain stem were further studied by Alexander (3) in the mid-1940s.

With the advent of recording technology during the 1930s, a number of milestones in cardiovascular and respiratory neural control were attained beginning with the first recordings of afferent impulses in the carotid sinus nerve by Bronk and Stella (12) in 1932. The following year Adrian (2) first recorded afferent nerve activity from pulmonary stretch receptors with vagal afferents. Then in 1936, Gesell and colleagues (31) were first to record central nervous system (CNS) respiratory activity near the obex. Since these early studies, a number of investigators have used CNS stimulation, lesioning, and recording techniques to localize the cardiovascular and respiratory centers. More recently, with the development of the horseradish peroxidase (HRP) technique by LaVail and LaVail (61), the neuronal connections of various medullary and pontine nuclei have been studied by Berger (9), Kalia and Mesulam (40, 41), and Lowey and Burton (67).

Since the stimulation studies of Ranson and Billingsley (84) revealed the pressor and depressor areas of the medulla, other investigators have defined these areas more specifically. Pressor responses have been reported from the stimulation of the lateral reticular formation in the rostral two-thirds of the medulla (99), periventricular gray (99), posteromedial hypothalamus (14), medial septum and median forebrain bundle (14), cerebellar fastigial nucleus (29, 69, 73), medullary raphe (1), dorsolateral sulcus of the spinal cord (17), and cerebral cortex (38). Depressor responses have been reported from stimulation of the medial reticular formation in the caudal half of the medulla (99), dorsolateral funiculus of the spinal cord (17), dorsal motor nucleus of Xth nerve (30), anterior hypothalamus and preoptic region (37), spinal trigeminal complex (60), paramedian reticular area of the medulla (74), medullary raphe (1), and the cingulate gyrus (66).

Decreases in heart rate have been reported from stimulation of the paramedian nucleus (14), nucleus ambiguus (14, 30), nucleus tractus solitarius (14), external cuneate nucleus (18), spinal trigeminal complex (60), the dorsal motor nucleus of Xth nerve (32), and the dorsal nucleus medulla oblongata centralis (96). Increases in heart rate have been reported from stimulation of the lateral reticular nucleus (34), dorsolateral pressor area (3), and posteromedial hypothalamus (14).

The central integration of the carotid sinus reflex has been studied and reviewed by many investigators including Spyer (93). In addition the IXth nerve degeneration studies of Cottle (22) and Ingram and Dawkins (39) have resulted in the conclusion that the IXth nerve pro-



David R. Kostreva was born in Milwaukee, Wisconsin, in 1945. He served with the US Army in Vietnam from 1968 to 1969 and was awarded the Bronze Star, Purple Heart, and two Air Medals. He received a B.A. degree from the University of Wisconsin, Milwaukee in 1972, and a Ph.D. in Physiology from the Medical College of Wisconsin in 1976. He was a postdoctoral fellow of the American Heart Association from 1976 to 1977 and held a National Institutes of Health (NIH) postdoctoral fellowship from 1977 to 1978. He then received a Young Cardiovascular Investigator Award from NIH in 1978. He has been an Associate Professor in the Departments of Anethesiology and Physiology of the Medical College of Wisconsin since 1981 and is currently the recipient of a Research Career Development Award from the National Heart, Lung, and Blood Institute of NIH. He is a member of the American Physiological Society, the Society for Neuroscience, Sigma Xi, and the Society for Experimental Biology and Medicine. He has served on two NIH study sections and has reviewed manuscripts for a number of journals. His family consists of his wife Bonnie and their children David, Daniel and Cherie.

jects primarily to the intermediate zone of the nucleus tractus solitari (NTS) just rostral to the obex. Miura and Reis (74) have suggested that the afferent information projected to the paramedian reticular nucleus is by myelinated fibers in the IXth nerve, whereas nonmyelinated IXth nerve afferents project to the intermedite portions of the NTS. Lipski et al. (63) have provided some evidence that the parahypoglossal area and nucleus ambiguus may also be involved in the carotid sinus reflex. Supramedullary areas such as the pons (72) and hypothalamus (14) have also been shown to modulate the carotid sinus reflex. Using HRP Berger (9) has recently studied the distribution of the carotid sinus afferent and efferent neurons in the cat. Afferent cell bodies were found in the petrosal ganglion, and efferent cell bodies were located in the nucleus parvocellularis and retrofacial nucleus. Although specific areas of the CNS have been shown to mediate or modify portions of the carotid sinus reflex, the complete functional reflex loop has not been demonstrated.

The central integration of the carotid body chemoreceptors with afferents that course along with the carotid sinus nerve have been studied by only a few investigators, including Cottle (22), Kerr (44), Davies and Edwards (25), Miura and Reis (74), and Lipski et al. (64). Most of these studies indicate that the chemoreceptor afferents project to the medial part of the NTS in the region of the obex. Since both the carotid sinus and the carotid body afferents project to the brain stem in the carotid sinus and IXth nerves, the degeneration, stimulation, and HRP studies that have been done on the IXth nerve have not been able to distinguish between baroreceptor and chemoreceptor projections in the brain stem. However, some of the microelectrode recording studies from medullary sites have localized some of the chemoreceptor endings.

The central integration of the aortic baroreceptors with vagal afferents has been studied (18). Crill and Reis (24) indicate that the aortic depressor afferents project to the caudal portion of the NTS. In comparison, the carotid sinus afferents project to the more rostral portions of the NTS and reticular formation. More recent studies by Donoghue et al. (27) and Katz and Karten (42) also suggest that the aortic afferents project to the NTS. The reflex decrease in heart rate produced by activation of the aortic depressor nerve has been shown to be mediated by the nucleus ambiguus (19), whereas the decrease in heart rate produced by the carotid sinus reflex is mediated by the external cuneate nuclei. Apart from these studies, the complete reflex loop of the vagal aortic afferents has not been determined and remains to be investigated.

Cardiac receptors with vagal afferents and sympathetic afferents have been studied by many investigators over the past 15 years. However, little is known about the central integration of the cardiac vagal or sympathetic afferents. Only a few studies on cardiac vagal afferent projections to the medulla can be found in the literature; they include studies by Baertschi (8), Donoghue (28), Keith (43), Kidd (45), Lee (62), and their co-workers. In addition a lesioning study by Burkhart, Funnell, and Ledsome (13) suggests that left atrial vagal afferents project to the intermediate portion of the NTS. The Xth nerve degeneration studies of Cottle (22) demonstrated that vagal afferents project primarily to the caudal half of the NTS. Although several sites in the medulla are associated with physiological and electrical stimulation of cardiac vagal afferent and efferent fibers, including the dorsomedial area of the NTS, the area postrema, medial reticular tissue adjacent to the paramedian reticular nucleus and raphe nucleus, dorsal motor nucleus of Xth nerve and parahypoglossal area, Kidd (45) states in his review, "although there are a large number of investigations of sites within the medulla from which cardiac and vasomotor changes may be evoked by electrical stimulation, there is no evidence which allows assessment of these to reflex pathways involving cardiac receptors." Although vagal and sympathetic cardiac receptors can both reflexly cause systemic pressor or depressor effects, the central integration, functional CNS neuroanatomy, and neuroanatomical similarities and differences between the vagal and sympathetic cardiac reflexes as well as the differences between the cardiac and carotid sinus and/or aortic baroreceptor CNS reflex pathways are not known. Some of these results are summarized in Figure 1, which shows the majority of visceral afferent information projecting to the NTS region of the medulla in the cat, dog, and monkey. Figure 2 is a summary of the efferent projections from the NTS to other parts of the CNS.

Methods

The method that we chose to study the central projections of the cardiovascular reflexes was the 2-[^{14}C]-deoxyglucose technique of Sokoloff and colleagues (90, 92). We chose this particular technique because, first of all, it had not been used previously to study specific cardiovascular reflexes and, second, it is a technique that would allow us to obtain a great deal of information concerning the entire brain during the activation of a single reflex in a relatively small number of animals.

The general protocol employed is shown in Figure 3. We have used three species of animals thus far—dogs, cats, and rats. All of the animals are fasted for approximately 18 h prior to the experiments. A blood glucose measurement is made prior to anesthesia to ensure that the animals are indeed fasted. Their glucose values should be very close to those previously reported for fasted animals. The animals are then anesthetized with pentobarbital sodium (35 mg/kg iv), intubated, and placed on positive-pressure ventilation. An arterial blood sample is then analyzed using a Radiometer blood gas analyzer, and the ventilation is then altered to ensure that the P_{CO_2}, pH, and P_{O_2} are within ranges predetermined as acceptable for the study. It is important to note that carbon dioxide has an inhibitory effect on glucose utilization by brain tissue (71). The appropriate physiological parameters are then monitored; these may include systemic arterial blood pressure, electrocardiogram, heart chamber pressure, nerve activity, and so forth. The neural reflex to be studied is then identified physiologically, and several practice runs are performed to ensure that the appropriate physiological responses can be repeatedly evoked. A single bolus of 2-[^{14}C]deoxyglucose (American Radiolabeled Chemical, St. Louis, MO) suspended in saline is then injected intravenously at a dose of 100 μCi/kg. The reflex to be studied is then periodically stimulated as frequently as possible during the next 45 min. During this same period, 16 paired blood samples are taken for measure-

ment of glucose and scintillation counting. Forty-five minutes after injection of the deoxyglucose, the brain and other tissues of interest are removed as rapidly as possible and placed in isopentane that has been cooled to −40 °C for approximately 20 min. The tissues are then frozen-sectioned at 20-μm increments by use of a cryostat. These 20-μm sections are then placed on glass coverslips on a warming stand. Each section is numbered and then covered with film (Kodak MR-1) and placed in an X-ray cassette for 12 days. The autoradiographs are then developed as X-rays and "densitometerized" by use of a computerized scanner. The paired glucose and scintillation counts, lumped constant for the species that was used, and the densitometerized values of the ^{14}C standards that were placed on each film are then programmed into the computer to enable conversion of the densitometerized image into one that represents glucose utilization.

Brain Mapping

The first study we conducted with this technique was to stimulate the left cut central end of the vagus in an anesthetized dog, with the contralateral vagus sectioned. The results are shown in the next few figures. Figure 4 is an example of an autoradiograph from one of these dog medullas with left vagal afferent stimulation. The increased density of the image over the left NTS indicates increased glucose utilization by that portion of the brain. The portion of the left NTS that appears to be most metabolically active is the medial subnuclei of the left NTS. The contralateral NTS shows no change in glucose utilization compared with adjacent brain tissue. A few other structures are also activated by the vagal afferent stimulation. These include the inferior olivary nuclei and the external cuneate nuclei. The histology of the same section is shown below, and a corresponding section from a control animal is shown on

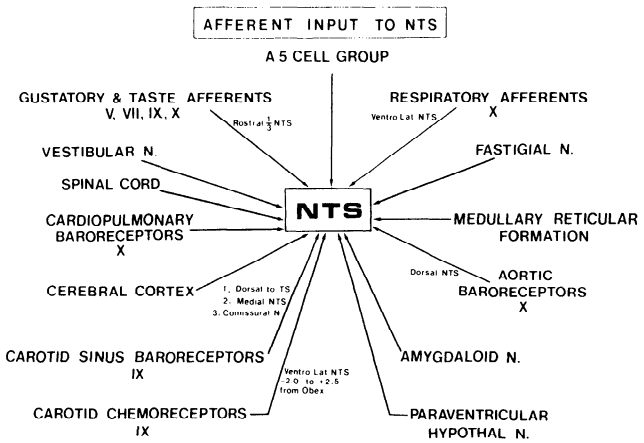


Figure 1
Summary of visceral and central afferent inputs to nucleus tractus solitarii (NTS).

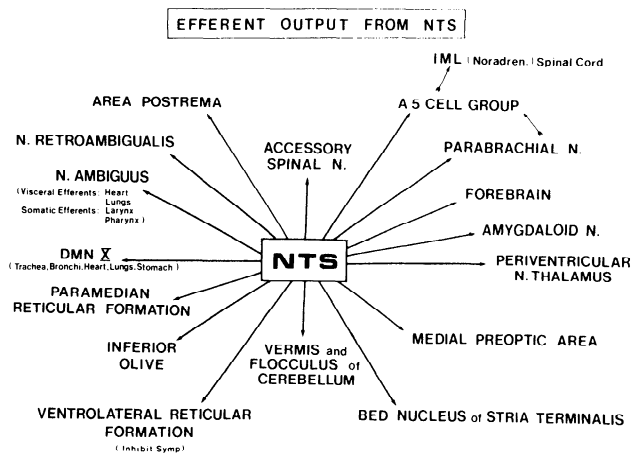


Figure 2
Summary of efferent projections from nucleus tractus solitarii (NTS).

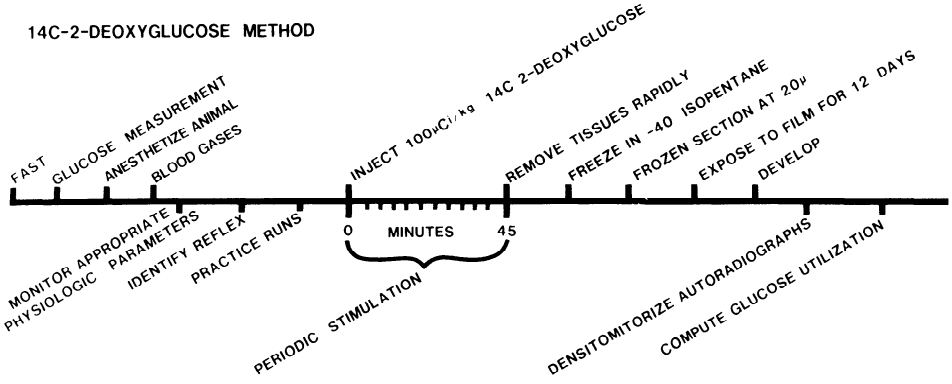


Figure 3
Outline of 2-[^{14}C]deoxyglucose technique.

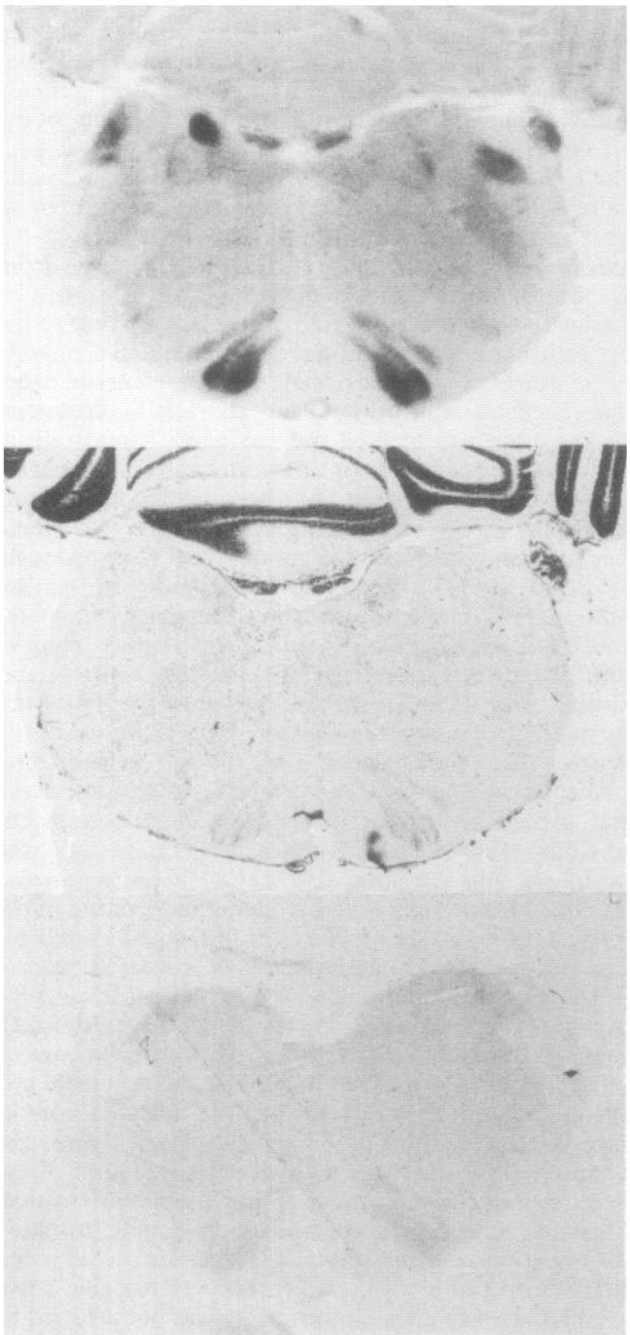


Figure 4
Photographs of original autoradiographs taken from a dog medulla with left vagal afferent stimulation shown in *top panel*. *Middle panel* is corresponding histological section of top panel autoradiograph stained with cresyl violet. *Botton panel* is an autoradiograph taken from same area of medulla from nonstimulated control dog.

the bottom of the figure. However, quantitation of these autoradiographs is impossible by visual inspection alone. Computer analysis of the autoradiograph is shown in Figure 5. The image in the lower left of the figure is a medullary section taken from a control dog that was anesthetized but not denervated or stimulated. The other three sections are taken from another dog that was anesthetized and in which the left vagus was cut and the central end stimulated afferently. The colors of the images correspond to different levels of glucose utilization, as indicated by the color key on the right-hand side of the figure. Figure 6 is an example of the detailed type of analysis of the autoradiographs that has been programmed specifically for these studies. An area of interest, such as the NTS, can be outlined using a computer-controlled cursor. Once the origin of the encircled area has been retraced, the computer then displays the total number of points enclosed, the area in square millimeters, the minimum and maximum glucose utilization level, the mean glucose utilization value, as well as the standard deviation and standard error. This type of analysis allows statistical comparisons of nuclei and subnuclei in the same animal as well as between animals. Figure 7 demonstrates the value of this type of analysis. The medullary sections shown are from another dog with vagal afferent stimulation. As indicated in the table on the left side of the figure, one can see the differences in glucose utilization of the left NTS compared with that of the right NTS, as well as a comparison with the NTS from a control nonstimulated animal. In addition since serial sections are examined in these studies, one can also determine the longitudinal glucose utilization of various nuclei within the CNS, as shown on the lower left of this figure. This is representative of the dogs with left vagal afferent stimulation. Glucose utilization by the ipsilateral NTS began 1.5 mm caudal to the obex and ended approximately 1 mm rostral to the obex. The maximum glucose utilization occurred between 0.5 and 0.8 mm rostral to the obex.

The carotid sinus afferent projections were also studied in both anesthetized dogs and cats. The carotid sinus nerve was then cut, and the central end was stimulated electrically. The contralateral carotid sinus nerve was sectioned. Stimulation parameters were altered to produce a typical baroreceptor reflex response, i.e., bradycardia and hypotension. An example of the pattern of glucose utilization that is seen in the cat medulla is shown in Figure 8. In this animal only a depressor response was observed, suggesting that the chemoreceptors which course through the same nerve probably were not activated, since they would have produced a pressor response, which in fact was observed if the stimulation parameters were altered. Areas of increased glucose utilization include the ipsilateral dorsolateral NTS, the external cuneate nuclei bilaterally, and the medial subnuclei of the NTS in the more rostral sections. In the animals that were stimulated the increased longitudinal glucose utilization began 540 μm rostral to the obex and projected approximately 2 mm rostral to the obex. Stimulation of the left carotid sinus nerve in the dog resulted in a different pattern of glucose utilization. The dorsolateral NTS was activated bilaterally with the ipsilateral NTS having a greater increase in activity. This is definitely different from the ipsilateral distribution seen in the cat.

In another study the left T_3 white rami communicantes were sectioned, and the cut central end was stimulated electrically. This type of stimulation would emulate the activation of some of the cardiopulmonary sympathetic afferents. Regions of the medulla that increased glucose utilization with sympathetic afferent stimulation include the ipsilateral lateral NTS, portions of the external cuneate nuclei, and portions of the inferior olivary nuclei. Vagal, sympathetic, and carotid sinus afferents all appear to project to the NTS region; however, different portions of the NTS are activated with different afferent input. Other regions of the medulla that show increases in glucose utilization in-

clude the external cuneate nuclei, which are not very active in control nonstimulated animals, and the inferior olivary nuclei. Only a few studies have suggested a possible role for these other nuclei in central integration of the cardiovascular reflexes (19, 89). Other regions of the brain that were examined included the pons, where carotid sinus afferent stimulation increased glucose utilization of the parabrachial regions, and the paraventricular nuclei of the hypothalamus. Sympathetic afferent stimulation increased the glucose utilization of the preoptic and paraventricular nuclei. The only regions of the cortex that showed increases in glucose utilization were those found within the insular cortex of dogs during carotid sinus afferent nerve stimulation.

Mapping of Sympathetic Ganglia

Since all neural tissue uses glucose as its primary metabolic substrate and Yarowsky and Ingvar (101) showed that specific changes in glucose utilization could be measured in rat cervical sympathetic ganglia with changes in neural input, which was confirmed by Saji and Obata (88) in cultured ganglionic cells, a study was designed to look at cardiovascular reflexes mediated by the stellate and middle cervical ganglia of the dog. Many investigators have clearly demonstrated that the sympathetic ganglia can mediate visceral reflexes without connection with the CNS or spinal cord (5–7, 10, 10a, 11, 100).

Drew Armour from Dalhousie University, Zeljko Bosnjak, and I designed an experiment to determine if cardiopulmonary afferent stimulation to a decentralized ganglion preparation in an anesthetized dog could produce measurable changes in glucose utilization of the middle cervical ganglion, stellate ganglion, and the heart. In this study the vagal trunk was transected above the level of the middle cervical ganglion, all rami connections with the stellate ganglion were cut, the vagal trunk below the middle cervical ganglion but above the heart was cut, and the central end was positioned on stimulating electrodes. The cardiac nerves arising from the middle cervical ganglion and the ansae and stellate ganglia were left intact. Electrical stimulation of the vagal trunk to the decentralized ganglia resulted in marked increases in glucose utilization of both the middle cervical ganglia and stellate ganglia as shown in Figures 9 and 10. On the left side of Figure 9, three control left stellate ganglia are shown. On the right are shown three reflexly stimulated decentralized stellate ganglia. Although the stimulated ganglia have a general increase in glucose utilization, there are specific regions within these ganglia that are extremely active as indicated by the glucose measurement for the controls versus the reflexly stimulated ganglia. The increase in glucose utilization was more uniformly distributed in the middle cervical ganglia than in the stellate ganglia as shown in Figure 10. These data indicate that both the middle cervical and the stellate ganglia are activated with cardiopulmonary afferent stimulation to a decentralized ganglion preparation.

Mapping of the Heart

The hearts from these animals were also sectioned transversely and the autoradiographs were scanned. The results are shown in Figure 11. On the left side of the figure is a section taken from an in vivo nonstimulated dog heart that was beating normally and generating a normal systemic pressure. The heart section on the right side is taken from one of the animals with the decentralized ganglia during cardiopulmonary afferent stimulation. It is evident that the glucose utilization of the reflexly stimulated heart increased substantially in regions of the left ventricular endocardial and myocardial layers. The right ventricle was not effected. The large area in white within the endocardium is a papillary muscle in cross section. Sections taken through the region of the apex were not significantly different from those from the control animal. The results from this study are quite similar to those obtained in a separate study where the left ventrolateral cardiac nerve was stimulated directly to the heart. In this study small dogs were anesthetized, and the chest was opened and the left ventrolateral cardiac nerve was located and sectioned. The cut distal end was then positioned on electrodes and stimulated efferently toward the heart. A representative example of the results of this study are given in Figure 12, where they are compared with the results from the previously described study with reflex stimulation of cardiopulmonary afferents to a decentralized ganglia preparation. The pattern of glucose utilization is quite similar in both the direct stimulation of the left ventrolateral cardiac nerve as shown on the left side of the figure and the indirect stimulation as shown on the right side of the figure. These data suggest that the left ventrolateral cardiac nerve may have been the efferent cardiac nerve that carried the reflex information described in the previous study. These studies also point out the usefulness and potential for the 2-[^{14}C]deoxyglucose technique for mapping the functional innervation of the heart. This is further emphasized in Figures 13 and 14. The regions of the heart that have increased glucose utilization with the right recurrent cardiac nerve stimulation are shown in Figure 13. In this study small dogs were anesthetized, and the right recurrent cardiac nerve was located and sectioned and the cut distal end was stimulated efferently toward the heart. A control heart section is shown on the left side of the figure, and a section from the heart with direct stimulation of the right recurrent cardiac nerve is shown on the right side. Areas of increased glucose utilization include primarily the myocardial layers of the left ventricle. These data differ from those with left ventrolateral cardiac nerve stimulation in that the endocardium was not effected by right recurrent cardiac nerve stimulation. The data obtained from these direct cardiac efferent stimulation studies are in agreement with the results reported by Randall et al. (81–83, 94) for dogs in which strain gauges were sewn onto the inner and outer surfaces of the heart and specific cardiac nerves were stimulated efferently.

Figure 14 is a representative transverse section taken from an animal that was given a spinal anesthetic. A control section is shown on the left side, and a section from an animal with spinal anesthesia is shown on the right. These animals were lightly anesthetized with pentobarbital sodium and allowed to breathe spontaneously. Small doses of spinal anesthetic were then given repeatedly through a lumbar needle until the animal stopped breathing spontaneously; this indicated that the spinal cord was anesthetized up to the level of the phrenic motor nucleus at C_3–C_5. Both heart rate and blood pressure decreased significantly below control

levels. Saline was given intravenously to raise blood pressure to within the same range as that maintained in the control animals. In spite of the decreased work of the heart because of the lowered blood pressure and heart rate, the glucose utilization of the left ventricle was significantly greater than that seen in the control animals. Several explanations may account for this difference. First of all, Klassen et al. (46) have shown that endocardial blood flows increase significantly in dogs given epidural anesthesia. Therefore an increase in flow and availability of the labeled glucose could account for the increased uptake. But, in addition, the energy requirements of the endocardium and myocardium could have increased, although this explanation is the least likely, since heart rate and pressure were below control levels. And third, a shift in the substrate requirements could have occurred; thereby the left ventricle may have utilized more glucose than fatty acids with spinal anesthesia. This latter explanation is not possible to test using the deoxyglucose technique alone.

One of the difficulties with using the 2-[^{14}C]deoxyglucose technique in the heart is that glucose is not the only substrate that cardiac muscle requires. As reviewed by Opie (77–79) and others (75, 95), cardiac muscle substrates include free fatty acids, glucose, lactate, and amino acids. In addition, the fasting state of the animal determines the relative utilization of the various substrates. For instance, in fasted animals free fatty acids may account for 60% of cardiac metabolism while glucose accounts for 28% and lactate 11%. In 3-h fasted animals, free fatty acids may account for only 34% of cardiac metabolism while glucose accounts for 60%. After a meal, free fatty acids may contribute very little to cardiac metabolism while glucose may account for 100% of cardiac metabolism (78).

Mapping of the Aorta

Vascular smooth muscle metabolism also requires glucose as one of its metabolic substrates, although fatty acids, amino acids, and ketone bodies also contribute to the metabolic requirements of vascular smooth muscle (20, 33, 68). The relative importance of these substrates is currently in question. For many years glucose was thought to be the primary metabolic substrate; however, recent evidence suggests that fatty acids may be more important (16, 23). During the course of our experiments on the glucose utilization of the heart we sectioned portions of the aortic arch. The initial results were surprising in that the relative glucose utilization of many of these aortic sections was greater than that measured in the beating heart. We therefore began to section representative regions of the aortic arch, thoracic aorta, abdominal aorta, carotid arteries, femoral arteries, subclavian arteries, renal arteries, coronary arteries, and cerebral arteries. Figure 15 is a representation of the relative glucose utilization that can be obtained from transverse sections of major arteries in anesthetized nonstimulated control dogs. It is quite evident that the arch of the aorta has the greatest glucose utilization of all vessels shown. In addition, comparison of the scanned autoradiographs with the corresponding stained section of artery indicate that the glucose utilization of the vascular smooth muscle within a given cross section is not uniform, but there appear to be regions within the arterial wall that require more glucose than other portions of that same vessel. This is depicted in Figure 15 in the femoral artery section shown on the bottom of the figure.

Examination of coronary arteries from control nonstimulated animals demonstrated, first of all, that glucose utilization could be measured in vessels of this size and that the relative glucose utilization had considerable variability even within vessels of the same heart. However, glucose utilization of coronary arteries increases with an increase in cardiac work as shown in Figure 16. The three coronary arteries depicted on the right side of the figure are from an animal that was reflexly activated with fastigial nucleus stimulation, i.e., the fastigial pressor response. Systemic blood pressure increased approximately 50 mmHg with each stimulation. The relative glucose utilization of these arteries is considerably increased compared with that seen in coronary arteries taken from a nonstimulated control animal as shown on the left side of the figure.

Glucose utilization of cerebral arteries was also studied in anesthetized cats. Two groups of cats were placed on positive-pressure ventilation with 100% oxygen. In one group the arterial carbon dioxide levels were maintained in the range of 20–25 Torr. The other group was also initially placed on 100% oxygen, and then carbon dioxide was added to the inspiratory gas mixture so that the arterial carbon dioxide levels were elevated to a range of 55–60 Torr. The animals were then allowed to maintain these blood gas levels for 45 min after the injection of the 2-[^{14}C] deoxyglucose. The brains were removed, frozen, and sectioned, and the major cerebral arteries were scanned and analyzed. Some of the results are summarized in Figure 17. The four anterior spinal arteries shown in this figure are from four separate animals. The two on the left are from the group with the low arterial carbon dioxide, and the two cerebral vessels on the right are from the group with high arterial carbon dioxide. It is clear that the arteries exposed to low carbon dioxide have an approximately 20-fold increase in relative glucose utilization compared with the arteries from the group exposed to high arterial carbon dioxide. Identical results were obtained from measurements made in the posterior cerebral arteries in these same animals. These results suggest the usefulness of the 2-[^{14}C]deoxyglucose technique for studying the cerebral vasculature, especially since it may be possible to use this technique to determine if vasodilatation or vasoconstriction had been taking place during the course of the experiment. This application also has potential for other vascular beds, especially in the study of neural control of the circulation. Since carbon dioxide has been shown to be a glucose utilization inhibitor in brain, this study suggests that the same may be true for the cerebral vascular wall, which may be one of the mechanisms of cerebral vasodilatation with elevated carbon dioxide levels.

Some of the major veins were also examined from a variety of control animals. These included the inferior vena cava, the portal vein, and the subclavian veins. The general observation was that very little glucose is used by these vessels. This is probably due to the much smaller mass of vascular smooth muscle found within the veins.

Mapping of Vascular Mechanoreceptors

One of the unexpected findings in the vascular studies that holds great promise is the localization of the carotid sinus baroreceptors using the 2-[^{14}C]deoxyglucose technique. An example is shown in Figure 18. Shown in this figure are longitudinal sections of the carotid artery at the bifurcation of the internal and external carotid arteries. The four serial sections are from the same animal. There is a significantly elevated glucose utilization throughout the carotid sinus bulb where the carotid sinus baroreceptors are located. Rees (85) has demonstrated histologically that the baroreceptors are distributed throughout the sinus bulb. The same sections that were used to make the autoradiographs were stained with Protargol stain, which is a modified silver stain that preferentially stains nerve terminals and cell bodies. The histological results correlate with the glucose utilization data, demonstrating that increased glucose utilization occurred only where there was histologically identifiable neural structures. This application of this technique may be useful in localizing receptors in other vascular beds including the possible localization of cardiac receptors.

Mapping of Visceral Organs

Other organs have also been sectioned and scanned from various animal studies. Adrenal glands can readily be visualized with this technique. The adrenal medulla has the same glucose utilization range as that seen in the control sympathetic ganglia. The adrenal cortex appears to be two to three times as active metabolically as the medulla in most of the adrenals examined. Liver and spleen have also been examined. Both of the organs have relatively little glucose utilization as measured by this technique. This may be due to the increased levels of nonspecific phosphatases, which would not allow the maintenance of deoxyglucose 6-phosphate. Arteries were quite active in the liver, and the lymphatic nodules of the spleen were also very active in terms of glucose utilization. Two major components of the respiratory system were also examined with this technique. These were the trachea and the lung. The areas that were most active included the smooth muscle of the trachea and the secretory layers of the pulmonary airways within the lung.

Mapping of the Kidney

Figure 19 depicts the pattern of glucose utilization within the kidney of the rat shown on the left and the kidney of the dog shown on the right. There are apparent differences between the medulla and cortex in both of these species, the medulla utilizing more glucose than the cortex. This has been corroborated by other methodologies (47, 86), where the medulla of the kidney has been shown to be glycolytic and the cortex more involved in gluconeogenesis. Several additional studies were done on the rat kidney by Norman Herman, a graduate student, and myself. In anesthetized rats, one kidney was denervated and the other left intact. Glucose utilization of the cortex of the denervated kidney was markedly decreased. Electrical stimulation of one renal nerve efferently in the rat resulted in decreases in glucose utilization of the medulla in the animals studied without effect on the cortex. Although the physiological implications of these changes in renal glucose utilization are not presently apparent, the changes that can be elicited with neural stimulation and denervation warrant further analysis of this technique, since it is really measuring changes in end-organ function.

Mapping of the Gastrointestinal Tract

The major segments of the gastrointestinal tract have also been sectioned and scanned as shown in Figure 20. This animal, like all the others, had been fasted for 18 h. The fast coupled with the anesthetic result in the absence of peristaltic movements of the upper gastrointestinal tract. This is reflected by the low-level glucose utilization of the smooth muscle layers and secretory cell layers of the esophagus in the upper left corner designated by the letter "E," the stomach "S," and the duodenum "D" in the upper right. The section in the lower left is from the jejunum "J" and the two on the lower right are from the ileum "I" and colon "C," respectively. The secretory layers of the ileum and colon are quite active. This was probably due to the fecal material found in the lumen at these levels.

In closing, I would like to point out some of the positive and negative aspects of this technology. In brain, spinal cord, and ganglia, with this technique, no information is given about tracts, only cell bodies and nerve terminals. However, the information that is obtained is related to brain function and not just to anatomy or connectivity of brain structures. In heart muscle, glucose is not the primary metabolic substrate, and a lack of oxygen or fasting state can cause a major shift in substrate utilization from fatty acids to glucose and reverse. Therefore, a labeled fatty acid technique is needed so that both glucose utilization and fatty acid utilization by cardiac muscle can be measured. This is an area that we are presently pursuing in our laboratory. In smooth muscle, the same problems apply as in cardiac muscle. Another major difficulty with the application of the 2-[^{14}C]deoxyglucose technique to the heart and smooth muscle is that the lumped constants have not been calculated for these tissues; therefore, at best the measurements using the lumped constants for brain are relative and they may or may not be absolute.

The length of the experiment may also be a limiting factor in that it requires a minimum of 30–45 min for the appropriate blood measurements to be made for the quantitative technique to be valid. The cost of the experiments can also be a limiting factor that is determined by the size of the animal model and the number of tissues to be studied.

But in conclusion, I believe that with the development of new labeled precursors and substrates, our knowledge of organ physiolgy and structure-function relationships will be greatly expanded by using these quantitative autoradiographic techniques so that we will be able to understand more fully the physiological processes involved in both healthy and diseased tissues.

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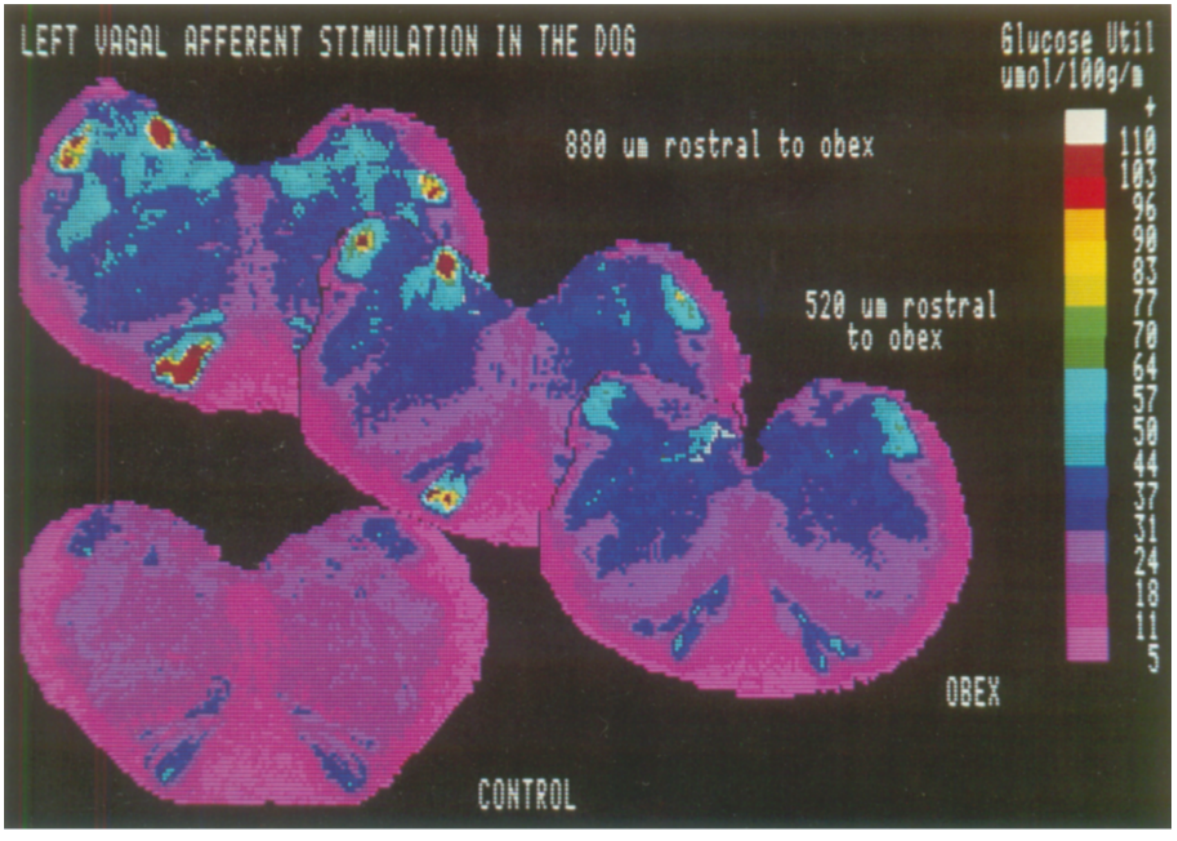

Figure 5 — Computerized scan of the autoradiographs shown in Figure 4. The colors represent different levels of glucose utilization as indicated on the color key shown on the right side. The values are glucose utilization in micromoles of glucose utilized per 100 grams of brain tissue per minute. Also shown are the position of the sections in microns relative to the obex.

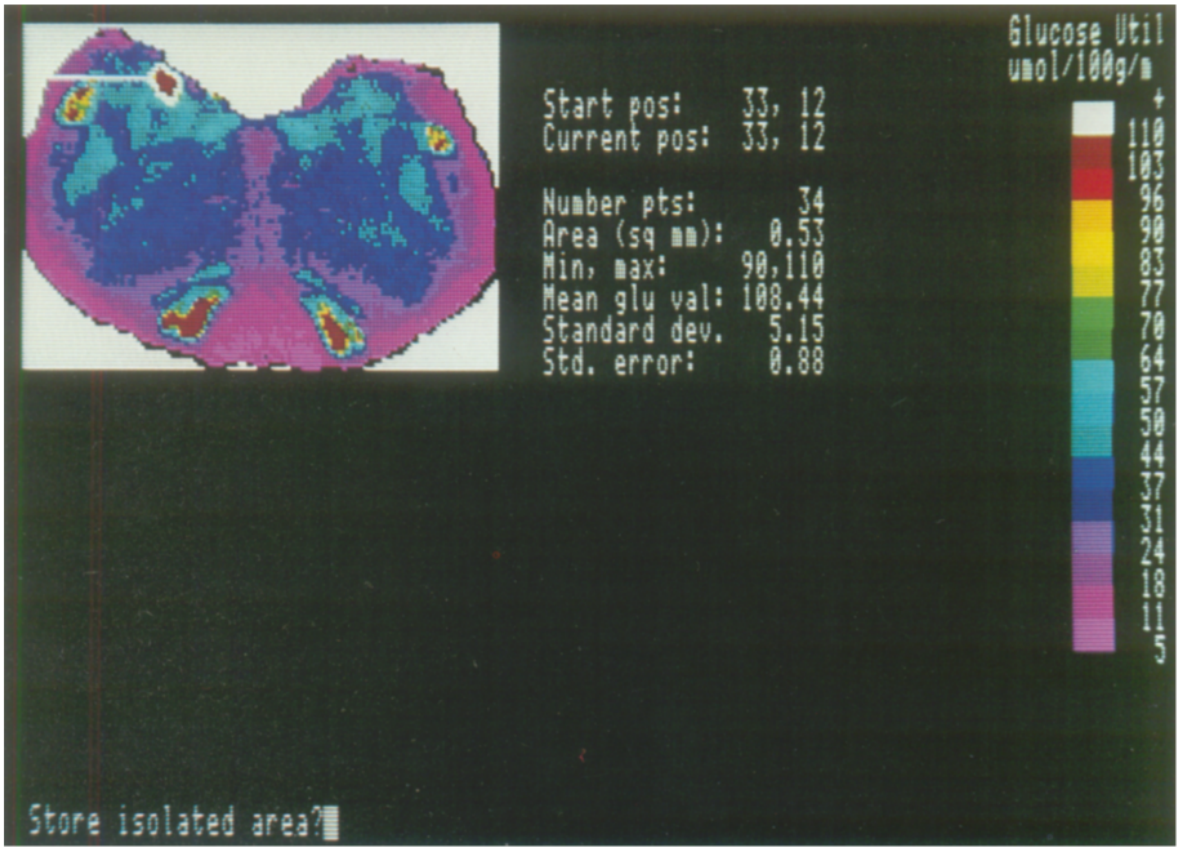

Figure 6 — Depiction of the area analysis program used to calculate the mean glucose value of any area or shape within a scanned section of tissue. Abbreviations are as follows: pos = position; pts = points of data; min = minimum; max = maximum; glu = glucose; dev = deviation; std = standard; umol = micromoles; g = grams; m = minute.

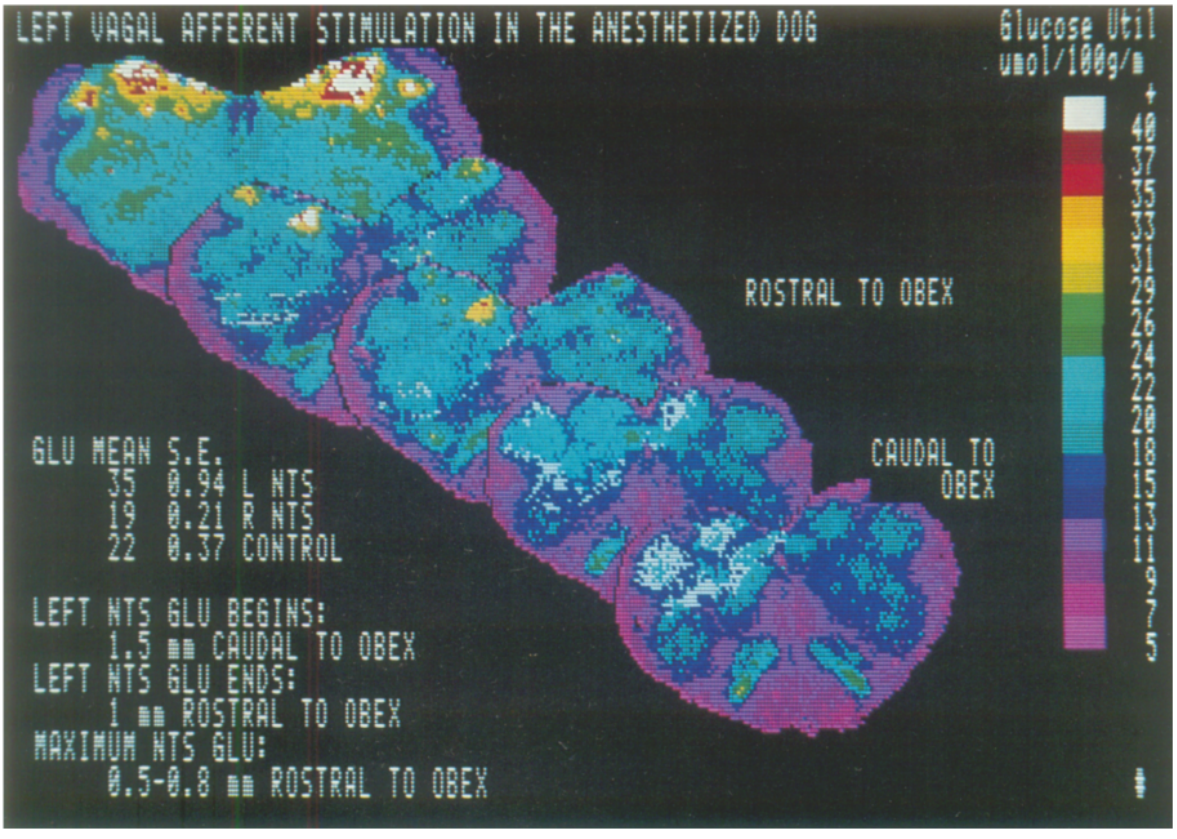

Figure 7 — Glucose utilization of medulla of anesthetized dog with vagal afferent stimulation. S.E. = standard error; NTS = nucleus tractus solitarii.

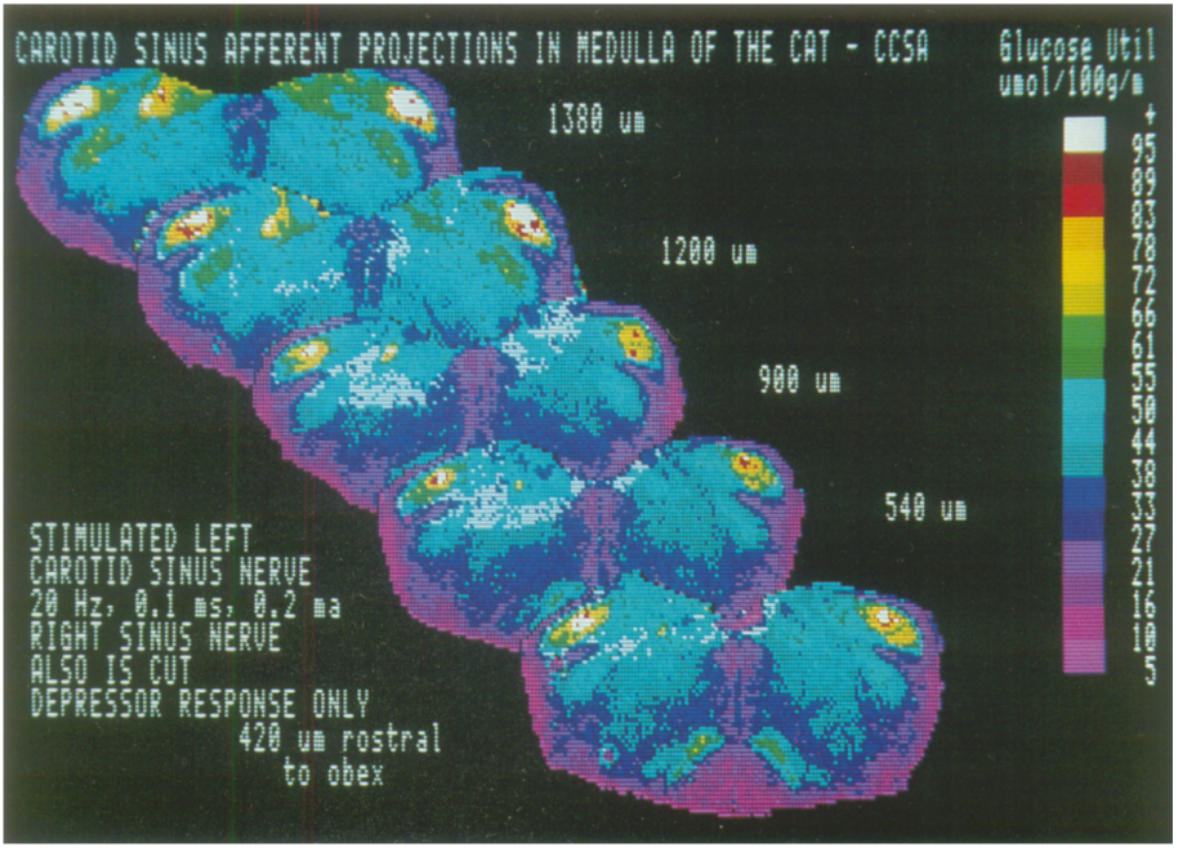

Figure 8 — Glucose utilization of medulla of an anesthetized cat during left carotid sinus afferent nerve stimulation.

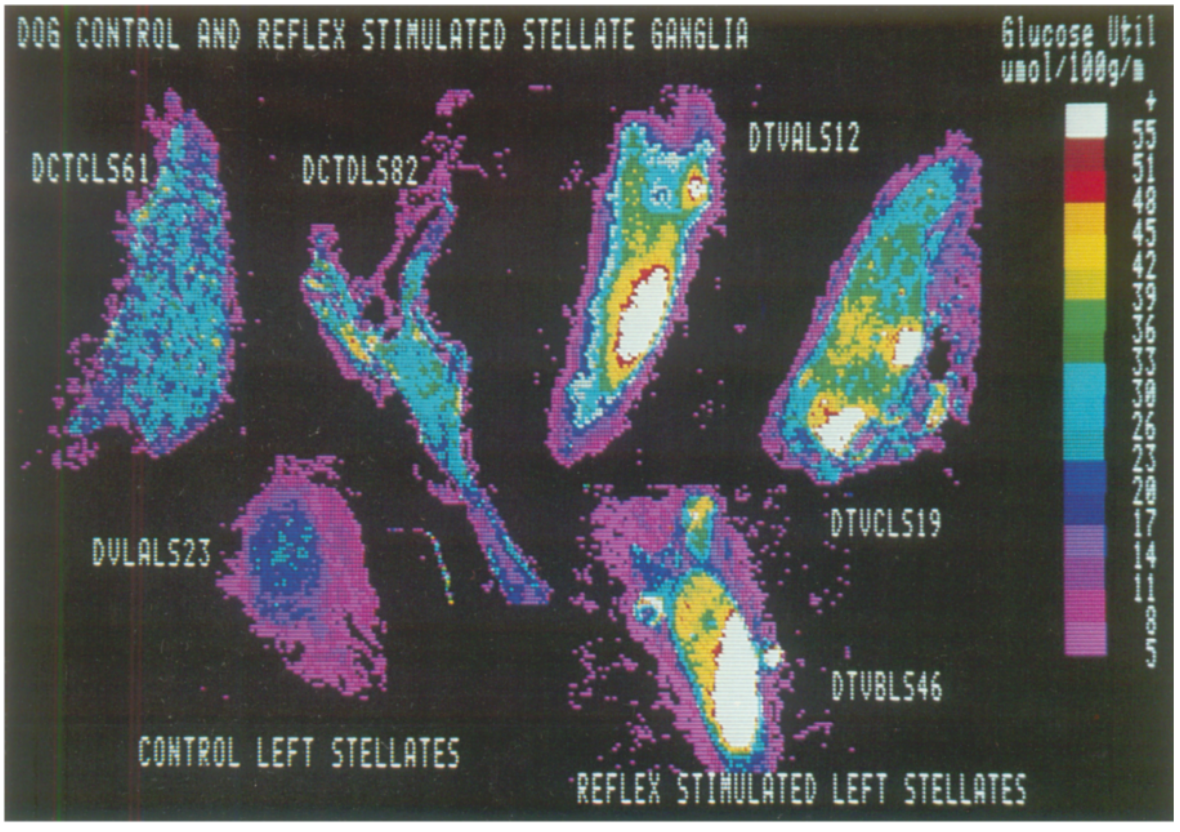

Figure 9 — Glucose utilization of the stellate ganglia in control and reflexly stimulated ganglia in the dog.

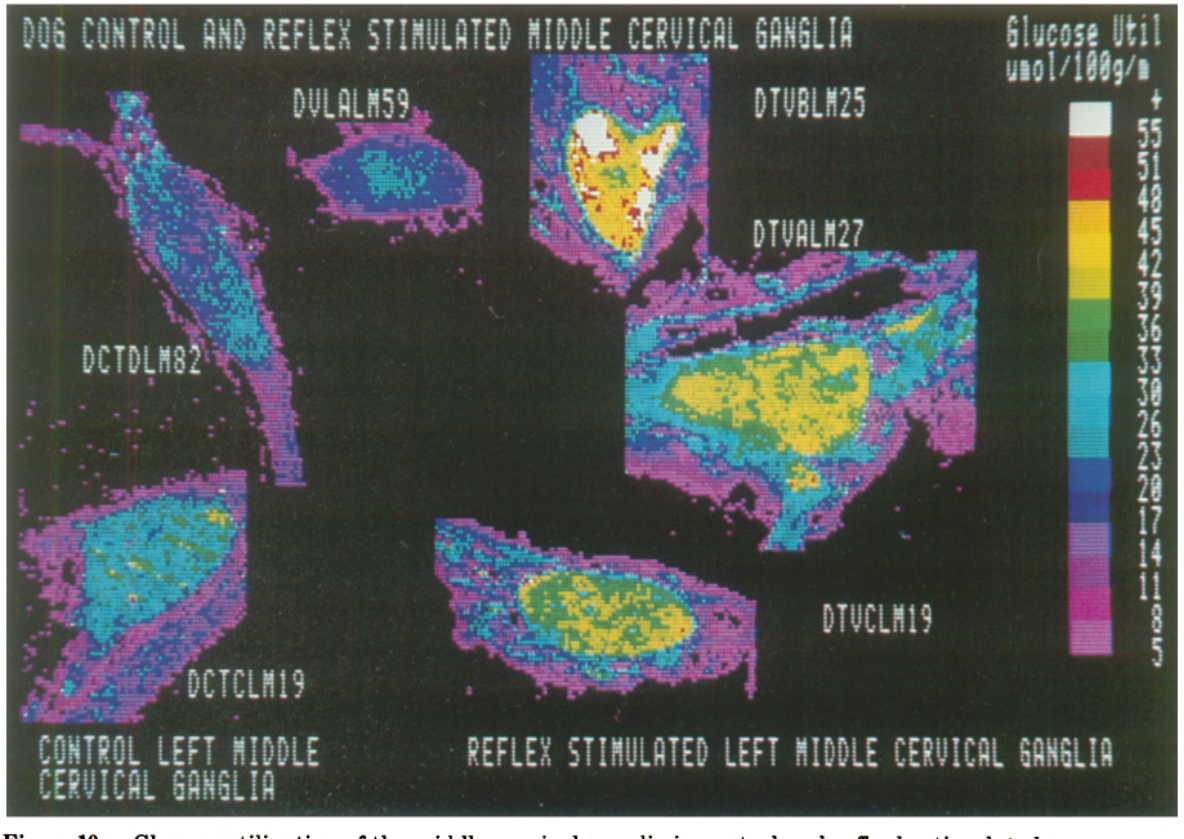

Figure 10 — Glucose utilization of the middle cervical ganglia in control and reflexly stimulated ganglia in the dog.

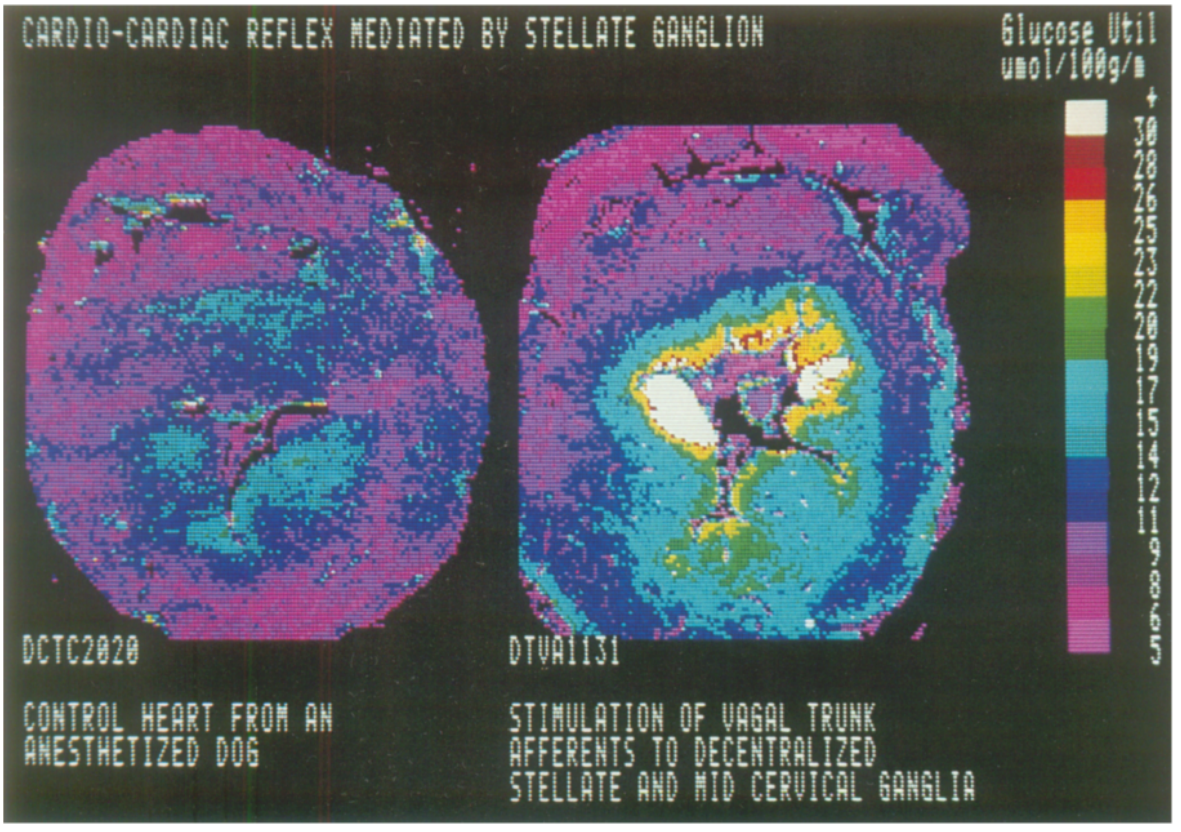

Figure 11 — Relative changes in glucose utilization of the heart in control versus reflexly stimulated anesthetized dogs.

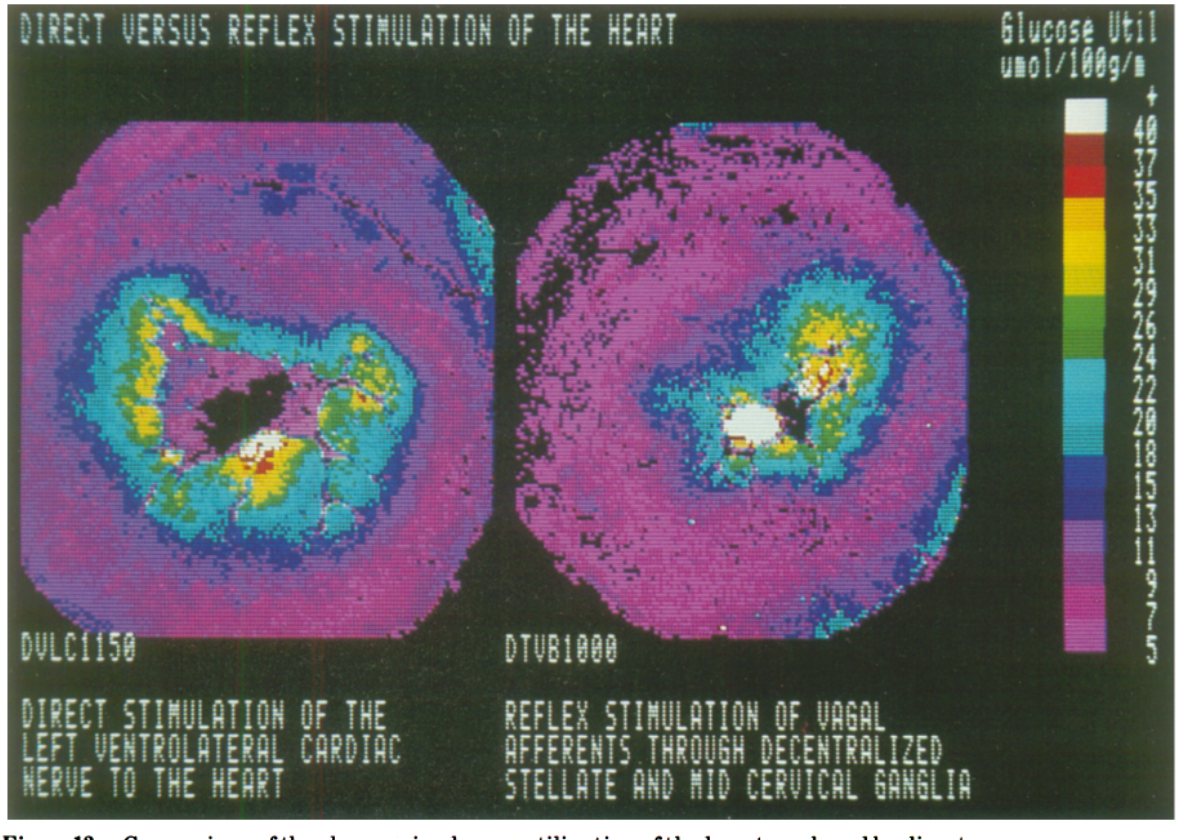

Figure 12 — Comparison of the changes in glucose utilization of the heart produced by direct versus reflex neural stimulation in anesthetized dogs.

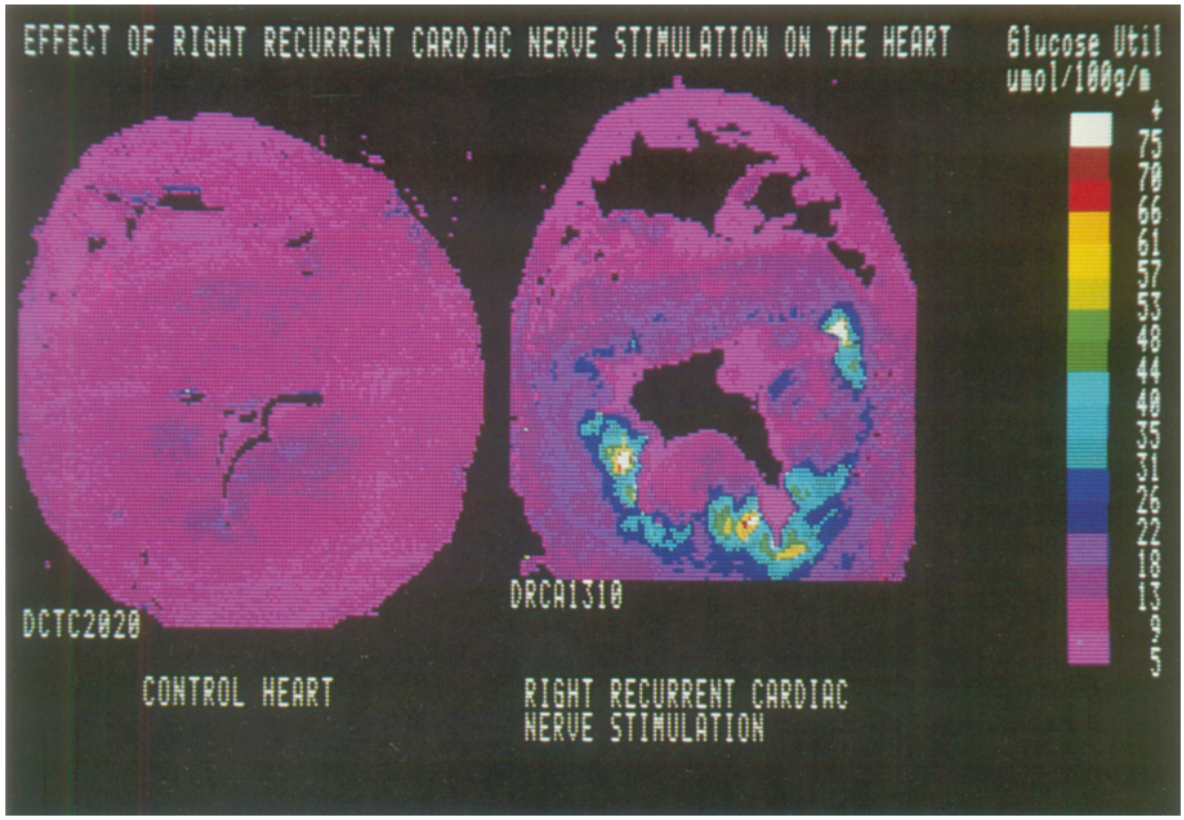

Figure 13 — Effect of right recurrent cardiac nerve stimulation on the glucose utilization of the dog heart.

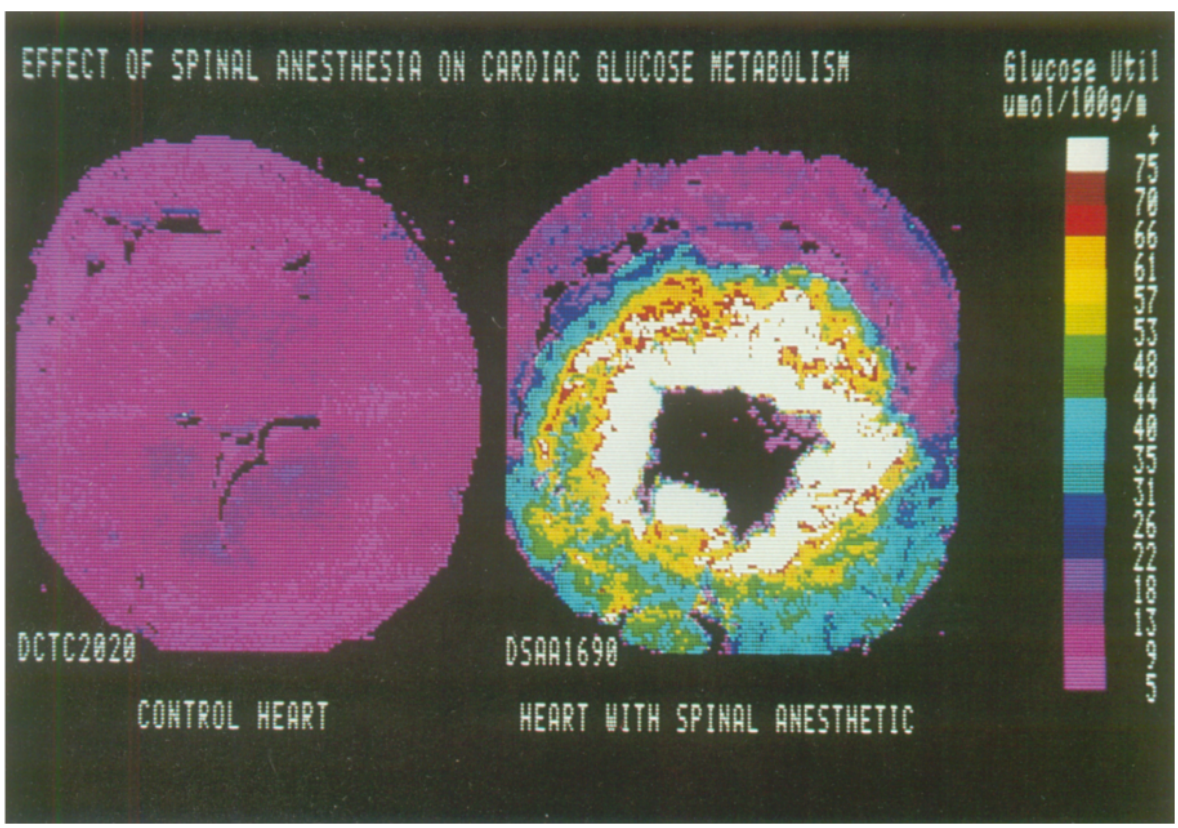

Figure 14 — Effect of spinal anesthesia on glucose utilization of the dog heart.

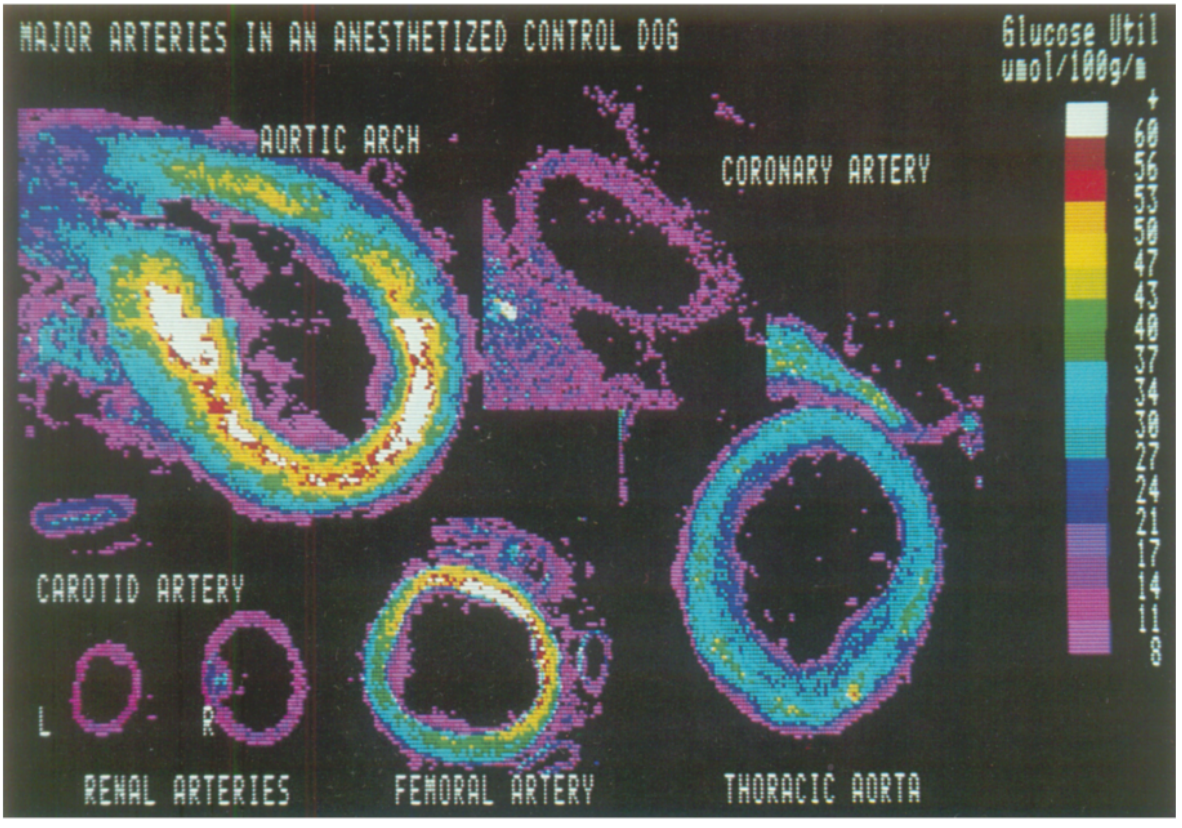

Figure 15 — Glucose utilization of major arteries in the anesthetized dog.

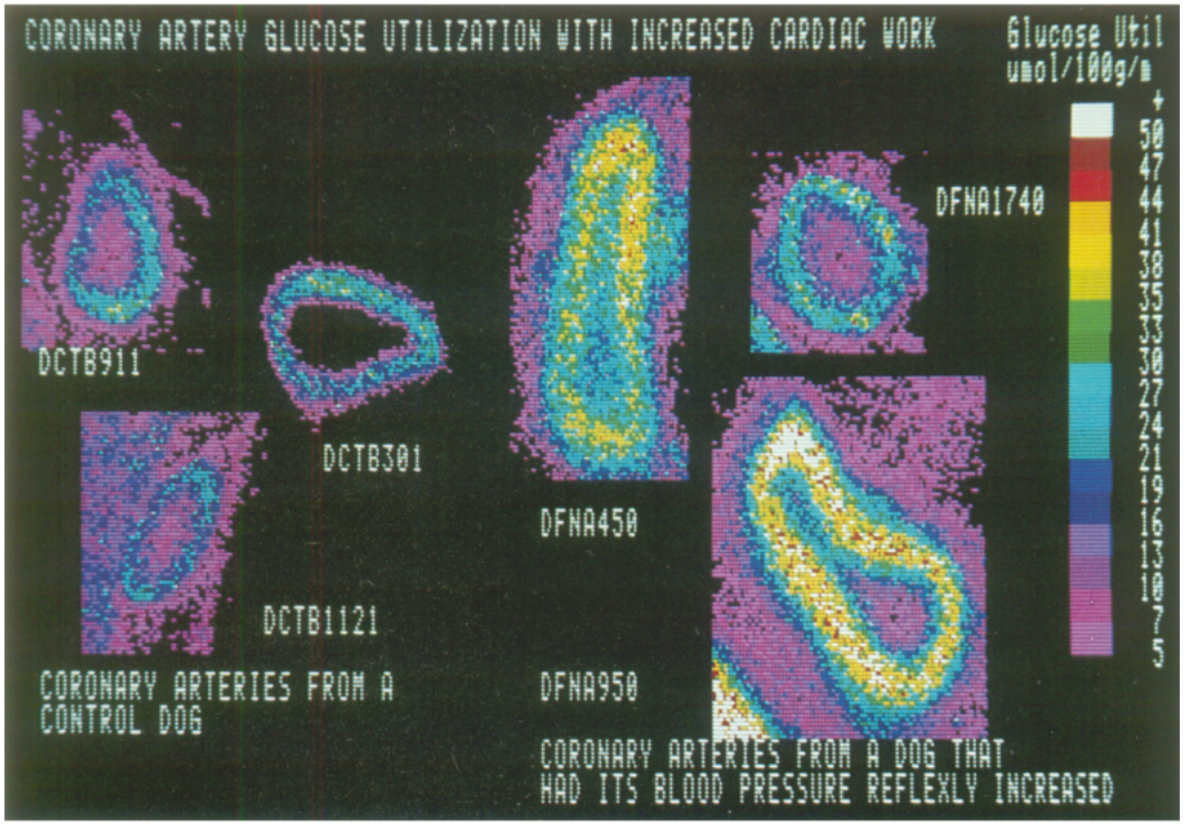

Figure 16 — Effect of increased cardiac work on the glucose utilization of coronary arteries in the anesthetized dog.

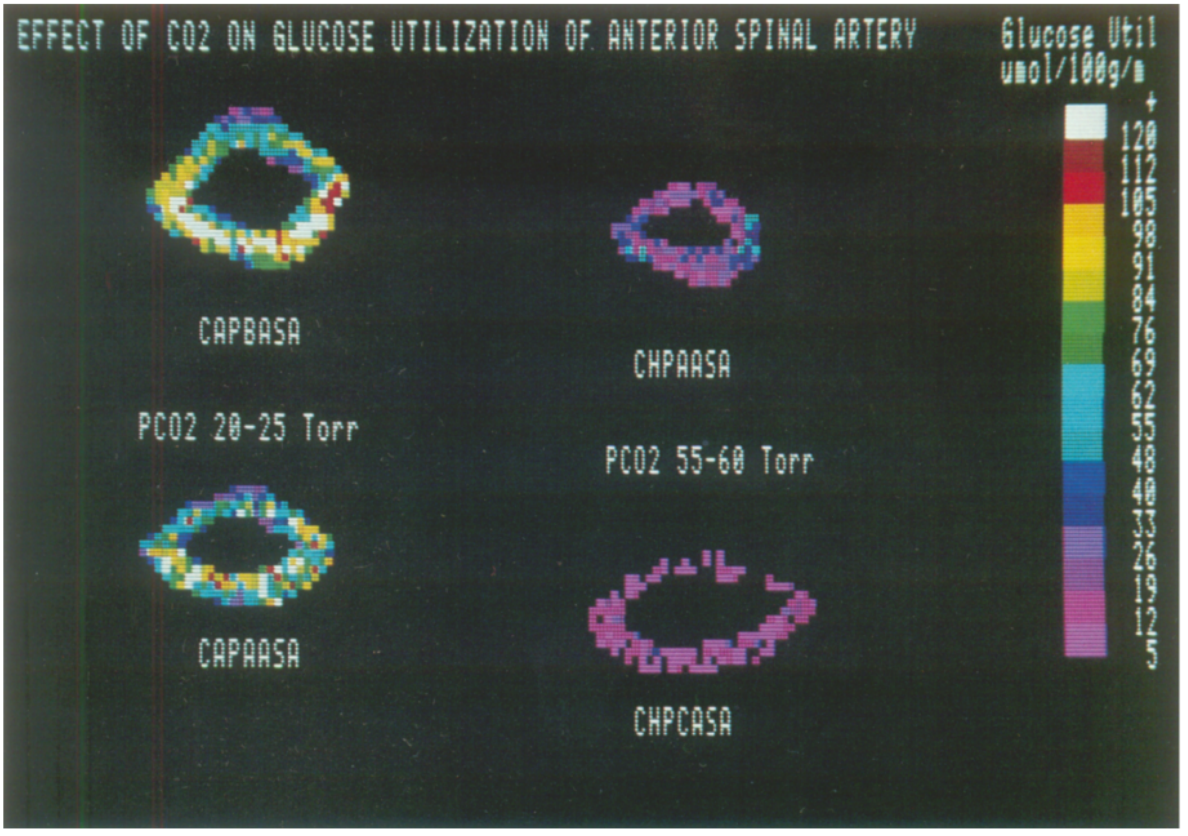

Figure 17 — Effect of changes in arterial carbon dioxide level on glucose utilization of cerebral arteries in the cat.

Figure 18 — Localization of carotid sinus baroreceptors and innervation in the dog.

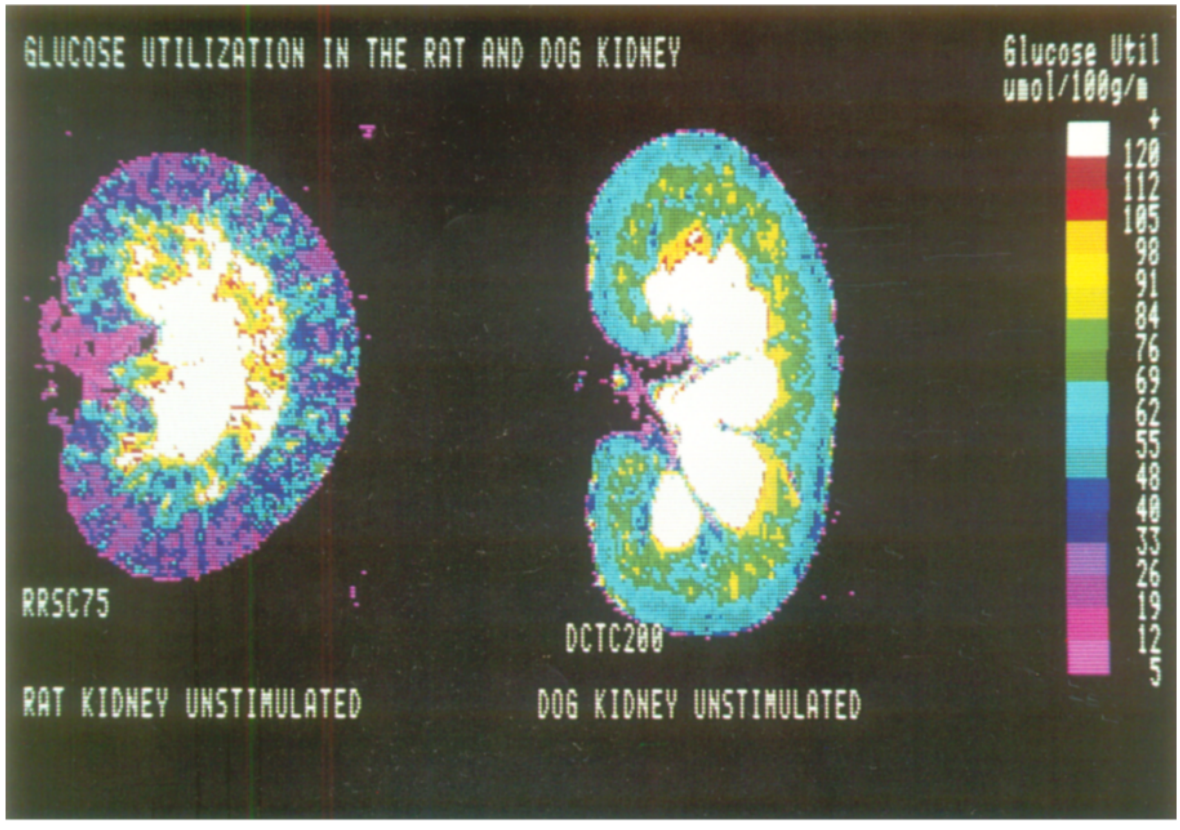

Figure 19 — Comparison of glucose utilization of the rat and dog kidney.

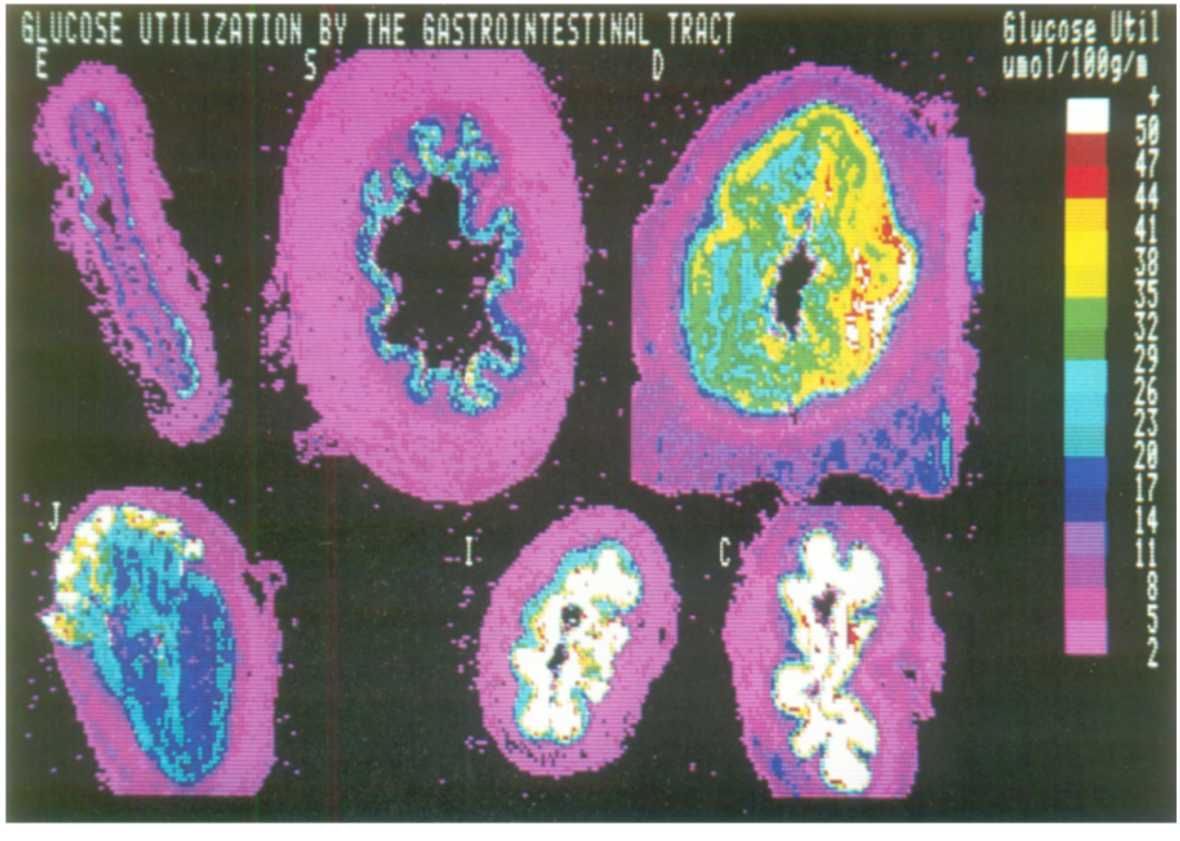

Figure 20 — Glucose utilization by major divisions of the gastrointestinal tract of the fasted and anesthetized dog.

Past President's Address

Crises in Physiological Research

WALTER C. RANDALL
Department of Physiology
Loyola University Medical Center
Maywood, Illinois 60153

You will properly indict me for being presumptious at many points in this address, including the selection of a title, and I enter this circumstance deliberately. I **intend** to rattle each of your individual cages vigorously during the next 30 minutes; but before I begin, let me say that one of the remarkable bonuses associated with the Presidency of the American Physiological Society is a vast expansion in insight and appreciation for problems and opportunities facing research and education in Physiology today. The APS office is, quite appropriately, a focal point for concerns of members. Most questions are handled efficiently and beautifully by Dr. Reynolds and his staff, but there are plenty left over for the President and Council. I have found the challenges to be very interesting and worthwhile, and I thank you for giving me the opportunity to recognize and respond to them, and I thank Council, Orr, and his superb staff for carrying me across the rough stretches. But among the challenges are some concerns and frustrations that I would like to pass along to you, the members of APS. I believe they deserve your attention.

Sources of Future Physiologists

As an educator and scientist, one of my primary preoccupations over the years has been with the problem of recruiting the best and brightest young people into physiological teaching and research. This has undoubtedly been influenced by my fortunate exposure across the years to a stimulating and insightful group of associates, including mentors, teachers, colleagues, and students. Where else can we live and work and have genuine renewal of excitement and inspiration each day that we come to our laboratories? I have never dared tell my Dean that I would want to teach and do research in Physiology even though he couldn't pay me. But there **are** some clouds on the horizon.

I have felt in the past few years that our profession has not consistently attracted the brightest and most creative college graduates. This isn't a concern for **numbers** of students but rather for **quality** of applicants. To acquire some first-hand information, during my President-elect tour, I asked the college science teacher what advice he gave to his brightest science majors about graduate school, and I then asked those same science majors, "What kind of picture does your science professors paint regarding a career in Physiology?"

Out of these conversations came the following impressions. *1*) There is lack of real knowledge about Physiology as a career choice. *2*) There exists an image of relatively low financial rewards in comparison to other professions. *3*) Little understanding of biomedical research and who does it. *4*) Conviction that research is difficult to get into and that it is poorly supported. *5*) That teaching is a dull and unrewarding way of life. *6*) In terms of investment of time, energy, and money, research and teaching are greatly overpriced. *7*) Medicine and other professions offer far greater security and status for the same investment of time in training. There were many variations around these central themes, but this list provides you and me with much to think about. Have we made Physiology as attractive to our successors as it has been to us and as it really is for the future?

It cannot be mere coincidence that almost every news magazine and editorial page during the past year or two has alluded to problems in education, starting with elementary levels right up through secondary schools and colleges. The great outcry for improved science and engineering education that occurred after Russia launched Sputnik I in 1957 has long since faded. A Chicago Tribune editorialist stated (2/2/82) "The weaknesses of the American educational system have become a national malady that gnaws at our economic strength, and our competitive edge in technology. The distressing fact is that the overwhelming majority of our population lives in a state of debilitating scientific illiteracy."

President Reagan's science advisor, Dr. George Keyworth, has pointed out that "Our survival and future progress depends upon the growth of knowledge and its wisest application." Yet the Reagan administration has virtually dismantled our education and training programs. It has embarked on a program of "economies" that has drastically curtailed research, turned the best minds of a generation away from academic careers, and closed the doors to first-rate young people who can not pay today's tuition and who will not opt for academic careers. A shocking aspect of the problem is that those around the President do not appear to understand the implication of their cuts. David Stockman himself recently conceded in the revealing statement, "we didn't think it all the way through." It appears the Reagan administration is determined to test the old adage . . . "If you think education is expensive, try ignorance."

Public Knowledge and Concern for Research

Most of you have encountered an era of anti-intellectualism in your daily rounds. Some senators publicly taunt scientists by awarding the "golden fleece" periodically to those investigators studying problems that do not have immediate and obvious "payoff potential." Americans fail to reward excellence

Fall Meeting of the American Physiological Society, 1982.

in intellectual endeavor, even many of your graduate departments argue that understanding of foreign language is a waste of time. The greatest use of small computers seems to be in pursuit of Pac Man, and far greater adulation and reward is given to star athletes (regardless of whether they can read or write) than is given scholarly achievement. There is desperate need for education of a public which appreciates and supports research and education.

Animal Rights Legislation

Virtually everyone in this audience is **aware** of an ever-increasing emotional clamor being generated by well-financed animal rights groups aided and abetted by publicity-seeking celebrities and sensationalizing editorialists. Their approaches are far more effective than the simple-minded antivivisectionists used to be. Their appeal is elaborately publicized, highly sophisticated, and quickly bought by legislators looking for a **cause** that will win votes. Never mind logic—will it win votes, seems to be their concern. Senators and congressmen will show you hundreds—nay thousands—of letters supporting their animal rights bills to every one that you and I in the medical or scientific community submit. Some such letters even seriously suggest using the elderly and/or prisoners for research purposes.

Do you remember Julius Comroe's Past President's speech (1961, unpublished) or his subsequent publication of Retrospectroscope (5)? Recall his cardiac surgeon standing at the peak of the mountain of success in thoracic surgery. He asked the question, "How did the surgeon get to the top of the mountain?" (Figure 1). But Julius's primary point was that laborious steps up the mountain were carved out, one at a time, by thousands of small contributions in basic science (Figure 2). He emphasized that most of those steps were **not** planned integral parts of a grand overall applied research project, programmed by government administrators or even an in-group of knowledgeable scientists or physicians. We owe much to Julius for these perceptive warnings (5–7).

I wish to emphasize a **third dimension** in the clinician's dramatic climb up the mountain. Open-heart surgery topped the list of Comroe's most important advances in clinical medicine. To the public, it is **the** dramatic achievement, "the pinnacle of surgery." I have arranged some of Dr. Comroe's key discoveries around cardiac surgery and highlighted the subsequent emergence of aortocoronary bypass (Figure 3). Note, these are major fields of knowledge that had to be developed, not individual papers. As you examine each individual field, ask yourself, "How many of these key developments depended upon animal based experiments?"

Again, selecting cardiac surgery as our prototype, let us climb the back of Comroe's mountain and pay particular attention to the fundamental basic experiments required before the surgeon could stand at the top.

Some of you are aware that I stand among those who have reason to applaud the skills and life-saving expertise of the cardiologist and the cardiac surgeon, and I do so without reservation. I am aware, however, that 80% of what benefited me only last year was simply unknown to medicine some 5–15 years ago. Every single bit of that progress was based on research. It mustn't bother us that aortocoronary bypass may not remain at the top very long. It is our responsibility to push the clinician upward with still greater triumphs as efficatiously as possible.

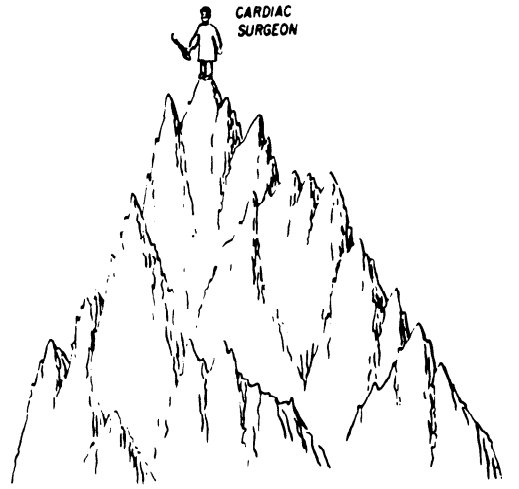

Figure 1
How did the cardiac surgeon reach the peak of the mountain of success in cardiac surgery? Did he take "One giant leap to the pinnacle?" (From Comroe and Dripps, with permission of the author and *Circ. Res.* 35: 661, 1974.)

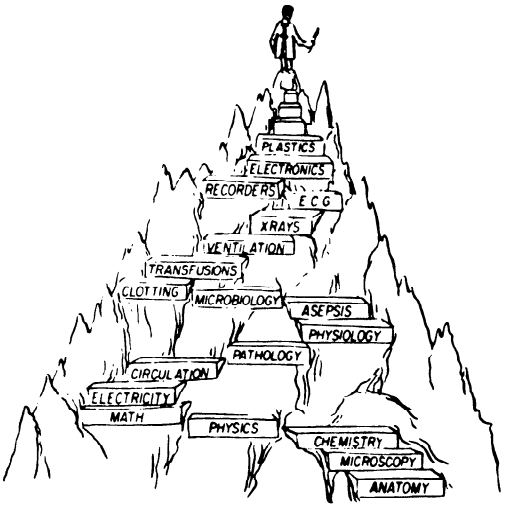

Figure 2
"Or did he climb the steps up the back of the mountain" carved out of thousands of individual advances in knowledge through basic research? (From Comroe and Dripps, with permission of the author and *Circ. Res.* 35: 661, 1974.)

Comroe's compilation of the top 10 clinical advances in cardiovascular-pulmonary medicine and surgery between 1945 and 1975 (8) thoroughly documents the investment of scientific manpower, ideation, time, effort, money, facilities, and animal life that have been committed to the surgeon's trip up the mountain. I have traced the references cited in just a few of his tables. Almost invariably, the model was whole animal in the early thrusts of the problem; only as the work progressed, could it be applied to human subjects. Selecting a single mountain peak, that of aortocoronary bypass, what **were** some of the key experiments which lifted the cardiac surgeon to the peak?

Climbing Mt. Coronary Bypass

I have plagiarized Julius's idea of the surgeon's mountain-top achievement and looked up the experimental models on which each key research advance was

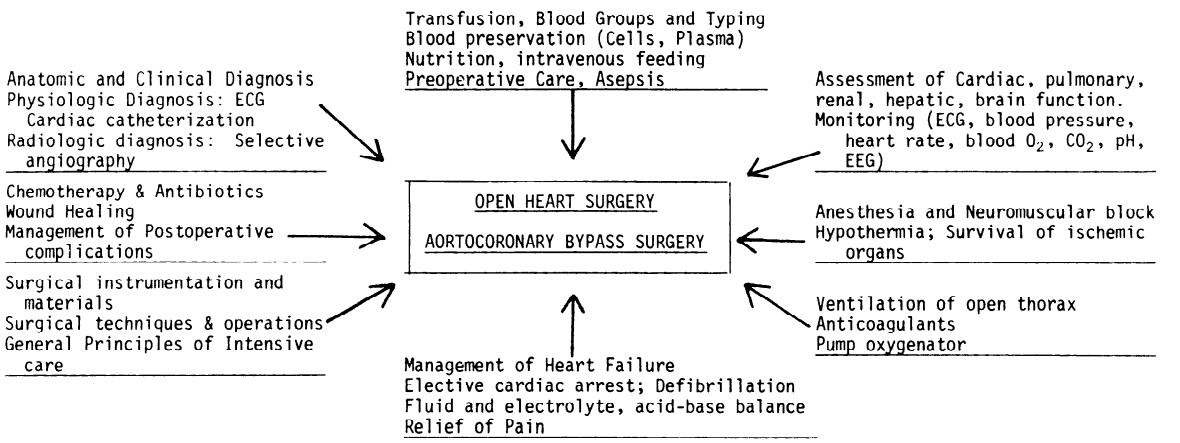

Figure 3
Areas of knowledge that had to be developed before modern treatments of the heart and cardiovascular system could become possible, with particular attention to aortocoronary bypass procedures. (Based on Comroe's research upon heart research.)

originally performed. In the foothills of the mountain, there was a great deal of variability in kinds of animals required, a great deal of comparative physiology. As problems became more specialized, individual lines of research were characterized by more restricted choices of animal species. And toward the top of the mountain, of course, man appears more prominently.

In Figure 4 a firm base was established in the observations of William Harvey (1628) and his comparative animal studies of the circulation (15). We step over numerous tentative ventures before 1733 when Stephen Hales introduced a long tube down the neck vessels into the beating heart of a horse to first record blood pressure. The next essential accomplishment in climbing this particular peak was the measurement of temperature and later the measurement of pressure in animal hearts by Claude Bernard (1844-47). The double-lumen catheter was invented and first used to quantitatively measure differential pressures in horse and dog hearts by Chaveau and Marey (1861-63). Fick was more of a physicist than laboratory experimentalist and in a publication less than one page in length (13) described a way to estimate cardiac output (the Fick Principle, 1870). It was Grehant and Quinquad who actually demonstrated the procedure in living dog models (1886); Zuntz first described systolic ejection and respiratory gas transport in the horse (1898). Hurter (1912) in Germany, made the first arterial puncture in man, and this was repeated in USA by Stadie in 1919. Montanari (1928) worked a probe into the right ventricle of experimental animals, and this was followed the next year (1929) by Werner Forssmann's catheterization of his own right heart by use of a urinary catheter and a mirror. He then walked up a flight of stairs to the fluoroscope to verify its position. His primary objective was to be able to inject drugs directly into the heart. Benatt (2) states that Forssmann's first attempt was in the cadavar and finding how easy it was to advance the catheter into the right heart decided to perform the procedure on himself. Benatt also learned that Bleichroeder had catheterized the right heart of the living dog as early as 1905 but considered the experiment of no practical value and did not then publish the results. Forssmann himself met with such bitter criticism from his professional colleagues that he was totally discouraged in his studies. However, Klein (1930) soon estimated cardiac output using the Forssmann catheter, and a few others tenatively probed the idea of ventricular angiography before Cournand and Ranges described the direct application of the technique to human patients in 1941. There followed one of the richest periods of cardiovascular research in history with the studies by Cournand, Richards, Lauson, Riley, et al. (9). Virtually every application to the human subject was carefully and prayerfully tested in cats, rabbits, dogs, chimps, monkeys, and other mammals before testing in man.

But the story doesn't stop there. In 1931, John Gibbon, a surgeon, watched a patient die from pulmonary embolization and realized that he could have saved her if he had been able to substitute an extracorporeal pump for the heart long enough to do the embolectomy (14). He spent the next 24 years designing, testing, redesigning, retesting in cats and dogs, the problem of clamping off the pulmonary arterial system long enough to accomplish embolectomy. He didn't get anywhere with his extracorporeal pump until Best reported an effective preparation of heparin (3) to maintain solvency of blood within the machine, another research story based totally on animal experiments. Gibbon's first successful use of the pump in a human patient was in 1953, and that patient is still alive today. Understanding of both oxygen and carbon dioxide ex-

change mechanisms within the pump system had to be achieved, again, procedures totally dependent on living animal models for their development.

The story behind the development of the Swan-Ganz catheter became very real to me when this instrument was floated into my right heart, because I realized that I had sat on the Study Section and had chaired the National Institutes of Health (NIH) Site Visit that evaluated the grant application proposing this gadget as a possible research and clinical tool. But when I recently reread Swan's paper, I discovered that the idea of a flotation catheter was really first introduced in Rahn's physiology laboratory, where he was measuring respiratory gas exchanges in the dog (17). And near the summit of the mountain, I found the pioneering angiographic studies of Mason Sones (1958), who visualized the distribution of opaque dyes within the coronary arteries, first in dogs and then in human patients (20).

The concept of vascularization of the myocardium directly from an artificially created shunt was introduced by Vineberg (in the dog heart) in 1946 (21), but nearly 20 years elapsed before Diethrich successfully grafted autogenous veins between the aorta and tunnels in the anterior left ventricle (again in the dog heart) (10). These experiments eventually permitted Drs. Favaloro (11, 12) in Cleveland (1968), Pifarre (18) in Washington (1968) and surgeons around the world to establish the procedures of saphenous vein grafting (of course, in the dog heart).

Note further, the crucial role of the experimental dog model employed in Dr. Ormond Julian's surgical laboratories just across the street from my own laboratory in Chicago in 1957. Dr. Julian stated

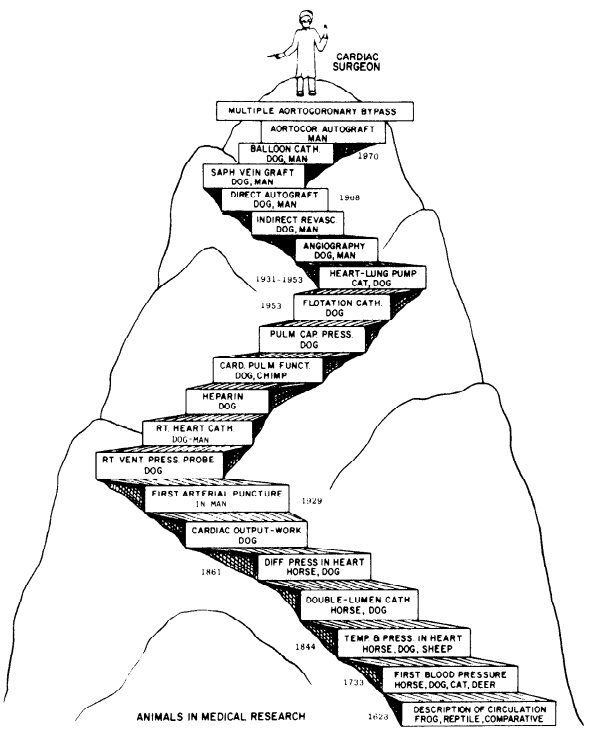

Figure 4
The back of the mountain as it had to be climbed by generations of scientists and surgeons before aortocoronary bypass could be possible. Virtually every step required initial stages of study on living animal models.

". . .the controversy over results of indirect myocardial revascularization led us to explore direct (grafting) techniques. Twenty-seven medium to large sized dogs were provided with extracardiac sources of circumflex coronary artery blood supply. In some, the internal mammary artery was anastomosed to the coronary artery, end-to-end, while in others, a graft (external iliac artery) was implanted between the ascending aorta and the circumflex during asystole and total cardiac bypass" (16). No reliable clinical methods were available in 1957 for precise localization of a coronary artery obstruction. A diagnosis of coronary artery disease was not possible until 1–2 days **after** an acute occlusive episode. With the hope of perfecting a reliable method of localizing obstructive lesions in the coronary tree, Cannon experimented with techniques of coronary angiography in the dog (4). Absolon et al. considered the technical feasibility of direct surgical anastomosis on the coronary arteries of humans, since many of their implant dogs became long-term survivors of their initial vascular grafts (1).

Coronary bypass illustrates only one mountain peak; similar ascents of all cardiovascular peaks would produce entirely comparable stories of whole-animal involvement in biomedical research. But the vital animal components of progress are generally forgotten or ignored in our focus on the ultimate, and sometimes spectacular, achievements in medicine. This role of experimental animals is not elaborated by our scientific papers and not even **recognized** by the editorialists, the celebrities, the emotionalists, or the legislators who now seem to believe that all that remains is to substitute available data into mathematical formulas, a computer program, or cell cultures serving as **alternatives** to animal models. I wonder if you computer enthusiasts have contributed to that serious misunderstanding? Organ-system physiologists **know** this is ludicrous, but we have not stood up and informed our senators, our congressmen, and, as importantly, our personal physicians or even our neighbors about our utter dependence on animal models for progress in medicine. Arthur Guyton has argued for years that we must aggressively assume the offensive on this point, but to date we haven't paid much attention to his warnings.

Yes, there are still many areas of complete ignorance of simple anatomy and function in Physiology which can only be rectified from animal-based laboratory experiments. When your Congressman sustains his myocardial infarction, suggest to him that his treatment will be by a new drug proved only through its actions on the circumflex arterial system of an IBM computer. You **must** convince him of the fallacies inherent in that important point, and you must warn him that if he makes animals unavailable to our laboratories, he will be personally responsible for tragically blunting progress in the conquest of human disease.

Appreciation of Research by Practicing Physicians

Why do medical students generally not recognize the relationship of research to their own future ability, as physicians, to offer their patients the best in medicine? Do we as role models fail to transmit a sense of excitement for new developments in our own field? In medicine as a whole? Do we infect our students with a sense

of excitement for assimilation of new knowledge? Do we stimulate their natural curiosity about the physiological complexities they encounter every day? I am afraid the answers to these questions are resounding "no's!" If the practicing physician (who was formerly our student) were to instruct his patients on the role of research in his ability to treat their illnesses, the public would **be** more aware of the importance of research, and Congressmen would be less likely to look here for an easy place to pinch pennies. I am saying that we, as teachers, have failed to convince our medical students (the future physicians) of the essential implications of research. We **may** even convince them that everything they ever need to know is in their textbooks. Haven't we as a profession abrogated our reliance on the laboratory as the place to learn Physiology; responsibility for teaching the principles of the scientific method? Haven't we succumbed to the temptation to emphasize handouts; reward the student for memorizing our lecture notes? Don't we cite the high cost of animals and instrumentation for our deletion of laboratory teaching, or duck out of personally teaching in the lab because we need more writing and research time to achieve promotion or renewal of our grants? How many animal labs does your course incorporate today? Do you really think your lectures are better than a meaningful physiology lesson personally learned by "hands on" experience in the animal lab? How many medical students get through all the basic sciences today without seeing the warm, vigorously beating heart, surrounded by the successively inflating and deflating lungs? How many actually "feel" the strength and coordinated rhythm of ventricular pumping? How many personally **experience** the dynamic changes in ventricular pumping action at the onset of fibrillation? Compare and contrast in your own mind the impact of just **reading** about fibrillation in the textbook, with that elicited by **holding** the dog heart in your hand at the very instant fibrillation is induced.

Physiology is a Laboratory Science

Many of your answers to these questions are unfavorable to us as teachers of Physiology. We have, in fact, opted for "easier" ways of teaching. Some may argue that the new ways are better. Some will defend the teaching machine, the slide-tapes, the problem-programmed computer, or carefully worked-up case study, but if these **substitute** for the teaching laboratory, I do not accept your argument. But I do acknowledge with conviction that laboratory teaching is hard work, that it is expensive in terms of time, effort, and money. It requires total commitment from the **best** teachers in your department, and it demands time away from the research laboratory. On the other hand, if your definition of a student laboratory experiment is nothing more than a group of naive students "cook booking" through a dog experiment, my argument is lost. I also grant that your Dean would like to save the money required for lab teaching, and many, perhaps most, departments have acquiesced (19). So our medical students get through the basic sciences with virtually no research experience, often no laboratory at all, and are forced to depend entirely on sheer memory for all they know. Could we **design** a more intellectually stupefying, stultifying framework in which to learn Physiology?

Let's Tote up the Score

Without laboratory teaching during the last 10–15 years, what have we harvested? A generation of young physicians who have memorized textual knowledge and who can master our machine-designed examinations to prove it. However, they do **not know how** to do an experiment, and even more damning, they have little or no interest in learning. They feel little or no compulsion to apply principles of the controlled experiment in their consideration of, or diagnostic approach to, their patients. They do not appreciate their heritage from research. They have become physicians who fail to recognize their dependence on research for their own ability to effectively treat their patients. The National Heart, Lung, and Blood Institute (NHLBI) recently published statistics proving that the percentage of physician-investigators among applicants for research grants has declined from 52% in 1971 to 28% in 1982. Dr. Wyngaarden dramatically detailed the progressive decline of physician interest in research in his article on the physician-investigator as an "endangered species" (22). How can your institution's Director of Cardiology expect his brightest young residents and fellows to opt for a year or two in research if they have never been in the laboratory, never actually performed an experiment? How can we expect young cardiologists to elect academic positions and the associated lower stipends if they have never personally perceived the challenge and **exhilaration** of a creative, insightful, and **successful** laboratory experience? Still worse, our negligence in not insisting on laboratory learning has **convinced** these young people that we believe such experiences are unimportant. Thus, of course, it is uncommon to hear a practicing physician extolling the virtues of research. He has had no contact with the laboratory. He doesn't know anything about research, much less his total dependence on it for his livelihood and his ability to maximally help his patients.

Research and Research Training

While NIH is probably our primary source of research funding, we are all aware of the critical shortage of money available to NIH. Four billion dollars is a lot of money, but so much of it is allocated to ongoing costs of operation and to committed funding that there is relatively little money available to fund new applications; less than 5,000 research applications will be funded this year. If Reagan and Stockman had their way, only 3,600 would be funded. Only a few research fellowships will be funded. So all of our medically oriented research training and pursuit of bench experiments must come out of a relatively small fraction of the 4 billion dollar pool. And Congress repeatedly dissects out bits and pieces from these allocations for nonmedically oriented set-asides. What did **you do** about the proposed set-aside for Small Business Innovative Research? Whatever, it wasn't enough, and you recently received announcement that such funds must be **subtracted** from NIH's overall biomedical research budget. Fortunately, the final allocation was relatively small in amount (although one-fourth the total funds available were originally requested), but it still deletes funds that should otherwise have gone to support biomedical research—perhaps your application that

won a priority of 1.68 but could not be funded due to lack of NIH research dollars. This incident bespeaks the lack of appreciation among legislators for what biomedical research funding accomplishes and stands starkly as a spector of what can happen down the road.

Thus Congress feels constrained to curtail health research expenditures where "savings" of only a very small fraction of 1% of the total Federal budget can be implemented while continually augmenting another pool of more than 240 billion for annual military expenditures. I guess I wouldn't be as upset if I thought the Pentagon exerted comparable concern for elimination of waste, with justification of every dollar expended, that you and I are required to demonstrate under NIH or National Science Foundation research funding. Have you stopped to realize that the cost of just one B1 bomber is the budgetary equivalent of two NHLBI's? Do you not agree that the leadership of this country should get back to the drawing board and rethink its priorities?

The Health-Oriented Research Payoff

Virtually all that is known in modern handling of cardiovascular disease has evolved within our lifetime. Our generations have seen the emergence of almost 90% of what is known in medicine, thus accounting for most of the modern physician's ability to diagnose and treat disease. **All as a Result of Research.** Do we convey that story to our students? Do we tell our neighbors about it? Do we write our impressions for our local newspapers? Do we vigorously and realistically recognize and contest the exaggerated claims and the outright falsehoods perpetrated by the antivivisectionists? Do we instruct our legislators in Washington and in our state capitols appropriately? Again, I am afraid the answer to most of these questions is unequivocally, **No.** Could this negligence on our part account for the public's ignorance, its gullibility, and its apathy concerning legislative inroads on sources of animals and funding that are absolutely essential to biomedical research and training?

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GUIDING PRINCIPLES IN THE CARE AND USE OF ANIMALS

Approved by the Council of The American Physiological Society

Animal experiments are to be undertaken only with the purpose of advancing knowledge. Consideration should be given to the appropriateness of experimental procedures, species of animals used, and number of animals required.

Only animals that are lawfully acquired shall be used in the laboratory, and their retention and use shall be in every case in compliance with federal, state and local laws and regulations, and in accordance with the NIH Guide.

Animals in the laboratory must receive every consideration for their comfort; they must be properly housed, fed, and their surroundings kept in a sanitary condition.

Appropriate anesthetics must be used to eliminate sensibility to pain during all surgical procedures. Where recovery from anesthesia is necessary during the study, acceptable technique to minimize pain must be followed. Muscle relaxants or paralytics are not anesthetics and they should not be used alone for surgical restraint. They may be used for surgery in conjunction with drugs known to produce adequate analgesia. Where use of anesthetics would negate the results of the experiment such procedures should be carried out in strict accordance with the NIH Guide. If the study requires the death of the animal, the animal must be killed in a humane manner at the conclusion of the observations.

The postoperative care of animals shall be such as to minimize discomfort and pain, and in any case shall be equivalent to accepted practices in schools of veterinary medicine.

When animals are used by students for their education or the advancement of science, such work shall be under the direct supervision of an experienced teacher or investigator. The rules for the care of such animals must be the same as for animals used for research.

Effort Successful in Repeal Proposed Ban on Funds For DOD Animal Uses

A threat of a Congressional denial of funds for the Department of Defense for the purposes of purchasing or using animals in the training of personnel and conducting research in the treatment of combat wounds has been modified by the last minute efforts of several Washington-based scientific groups.

As a result of last summer's airing by an animal rights group of a proposed wound laboratory at the Uniformed Services University of the Health Sciences (USUHS) at Bethesda, MD, language was incorporated in both the House and Senate military spending bills for the next fiscal year that would prohibit the expenditure of any funds for training and research programs in wound treatment that involve the use of animals.

Although the deliberations of the House and Senate subcommittees concerning military appropriations are closed hearings, it was learned by several Washington-based scientific associations that both bills did contain language that said in effect: "No funds appropriated pursuant to this act shall be used to purchase animals or otherwise fund the use of animals for the purpose of training students or other personnel in surgical or other medical treatment of wounds produced by any type of weapon."

It is believed that the language for this restriction was added to the defense appropriations bills by Rep. Tom Lantos (D-CA), who was responsible for having Defense Secretary Caspar Weinberger shelve the proposed USUHS wound laboratory last summer after it was made public by *The Washington Post.*

Because of the late discovery of this prohibition by the scientific community, efforts to have the language modified by the House subcommittee were unsuccessful. However, substitute language prepared by the scientific community limiting the prohibition to only cats and dogs was offered to the Senate subcommittee by Sen. Daniel K. Inuoye (D-HI) and was adopted.

The joint House-Senate conference committee then agreed upon the Senate version despite a House floor resolution instructing the House conferees to insist upon the restriction of all animals.

While 31 Washington-based associations and several veterans organizations responded in support of Sen. Inuoye's initiative, many senators suddenly found themselves swamped with telephone calls and telegrams and others were met at their office doors by animal rights activists seeking commitments to repeal the language change when the bill comes to the Senate floor for vote. Sen. Inuoye's office reported that the day after the Senator offered the language modification he received more than 150 telephone calls from Hawaii condemning his action (and only one telephone call from Hawaii in support) in addition to more than 100 telephone calls from animal rights advocates on the mainland.

In suggesting the proposed language change to restrict the prohibition to only cats and dogs, the scientific community provided several reasons why a legislative ban on all animals in the military's wound treatment programs would be unwise. Among the reasons cited are the following.

- Alternative ways for training military medical personnel in the care of the wounded are severely limited. If physician, nurse, corpsman, and others are not trained by appropriate use of anesthetized animals in supervised laboratories, it would mean training on a learn-as-you-go basis on wounded military personnel. It is not possible to provide such training at local hospital emergency rooms because combat wounds are from high-velocity weapons not found in the civilian world.
- The enactment of legislation prohibiting the use of any animal in wound treatment programs would deny those who serve our country now and in the future the best possible medical care for injuries from an enemy bullet or fragments from exploded weapons.
- Many individuals apply the education and training obtained while in the armed forces as civilians after leaving the military, and restrictions on adequate training to care for wounds would compromise the care provided to the rest of our countrymen.
- Some health sciences centers have affiliation agreements for educational purposes with military hospitals and such relationship could be jeopardized by this intrusion into the education and training programs for health professionals.
- An unstated major concern to the scientific community is that if a total ban on the purchase and use of all animals can be accomplished within one Federal agency by legislative fiat, a precedent would be set for similar bans in other Federal agencies now supporting educational and research programs that involve the use of animals.

18-Month Study Begins on Nonanimal Methods

The Office of Technology Assessment (OTA) started an 18-month study in November to make "a scientific evaluation of alternative methods to animals in research, experimentation, and testing." The request for the study was initiated by Sen. Orrin G. Hatch (R-UT) who is the chairman of the Senate's Committee on Labor and Human Resources.

In addition to examining the use of nonanimal research methodology, Sen. Hatch also requested OTA to advise on the effects increased utilization of nonanimal methods might have on the total biomedical research effort, the effects of previous legislation on animal testing, and the types of nonanimal research that seems to be the most promising.

The study has been designed to accomplish the following.

- Examination of current patterns of animal acquisition and use and assessment of the accuracy, predictability, and costs of existing animal models in toxicity testing and in biomedical and behavioral research.
- Analysis of the state-of-the-art of new technologies that could serve as possible alternative methods and the forecast for their application.
- Evaluation of the specific requirements for toxicity testing of the various regulatory agencies.
- Survey of the ethical positions on the use and care of laboratory animals.
- Preparation of policy recommendations for operations.

An advisory panel of 14 to 18 members will assist in the study. The panel will represent the scientific disciplines, legal expertise, data-based management, economics, and bioethics.

The study is divided into two separate areas, one concerned with toxicity testing and the other concerned with basic and applied biomedical and behavioral research.

William M. Samuels, CAE

From *The Washington Post* September 12, 1983

Dear Ann Landers:

Last night I read an article that made me cry. It described the mutilation of animals in laboratories for the purpose of medical research. It told about how animals were poisoned, blinded by acids, subjected to repeated electrical shock, disemboweled and had their spinal cords cut.

You would do a tremendous service if you exposed the horrible torture of helpless creatures and put a stop to it. I beg you to act on this.—

Tami In Mpls.

Dear Tami:

A great deal of propaganda, accompanied by heartbreaking photographs, has ignited a campaign to halt the alleged cruelty to animals in research laboratories. But before you get out your crying towels (and checkbooks), folks, here are the facts.

Some animal lovers have gone so far as to suggest that prisoners and elderly patients be used instead of animals. Add to that bizarre notion the fact that 13 million dogs and cats were destroyed in shelters last year because no one wanted them. Yet thousands of well-heeled organizations are trying to stop the use of animals in medical research laboratories. I ask you, does this make sense?

Animals housed in universities, medical schools, hospitals and research centers are monitored by the U.S. Department of Agriculture. Periodic surprise inspection visits are conducted under the Animal Welfare Act. The National Institutes of Health have standards governing such experimentation for all scientists who receive NIH funds. Animals' quarters must meet space specifications, be air-conditioned and kept clean. Potentially painful experiments must be done under anesthesia.

Animal experimentation made it possible to immunize millions of children all over the world against polio, diphtheria, mumps, measles, hepatitis and other diseases. Add to that list every person who receives an antibiotic to fight infection, insulin for diabetes, anti-inflammatory agents for arthritis, chemotherapy for cancer, medication to control hypertension and drugs for the treatment of mental illness. Every person who has undergone the replacement of a joint, or the re-attachment of a severed finger or limb, kidney dialysis, heart surgery or organ transplantation owes a debt to animal experimentation.

Pet lovers should be aware that the progress made in veterinary medicine is due largely to experiments on animals.

There has been a decline of approximately 50 percent in the use of animals for laboratory testing since 1968 due to the development of highly sophisticated test-tube techniques, but experiments involving the heart and the brain cannot be perfomed in test tubes. They must be conducted with live tissue.

No person in his right mind wants to see an animal suffer, but until the day comes when all medical problems are solved we must experiment with animals. **So let's hear it for the dogs that went to Harvard. They may well have made a more meaningful contribution to humanity than some people we know.**

To Ann Landers:

Your answer to the question about alleged laboratory animal abuses undoubtedly will bring you a ton of mail from the small minority (estimated to be less than 5 percent) who want to abolish the use of all animals for research and education.

Without the use of animal models, research advances would be minimal at best and the education of tomorrow's scientists and health practitioners would be stifled. Nobel Prizes for scientific achievement most often are for projects involving animals because other testing models are not yet available. Nations where the use of laboratory animals have been restricted, such as the United Kingdom, have not produced scientific breakthroughs as this nation has in recent years.

What is needed is an effort on responsible pet ownership so that the more than 13 million dogs and cats need not be destroyed—sometimes in an inhumane fashion—by animal pounds at the tax payers expense. An irony is that some of these dogs and cats could be used for research and education.

Orr E. Reynolds
APS Executive Vice President

To Orr E. Reynolds:

Thanks very much for your good letter of September 13th.

As you can well imagine, I am being bombarded unmercifully with letters from the anti-vivisectionist groups, so it was a great pleasure to receive a letter like yours.

You can be sure I will be in the forefront with those who are battling for the continued use of animal experimentation. Without animal research, medical science would come to a grinding halt.

Ann Landers
Field Newspaper Syndicate
Chicago, Illinois 60611

Leaving the Island Behind: An Approach to the Animal Experimentation Issue

THEODORE COOPER and JOSEPH E. GALLIGAN
The Upjohn Company
Kalamazoo, Michigan 49001

Of the many profound things written by the English poet, John Donne, the longest-surviving and most widely remembered is this: "No man is an island, entire of itself." Unfortunately, we seldom take to heart the meaning of these words, even if we do remember them. All segments of humanity are intrinsically linked, and overlooking that fact leads to confusion and uncertainty. We know that science is accomplishing a great deal and has the promise to accomplish a great deal more, yet we are nonetheless subject to attack on a number of fronts. We have not responded very well to these attacks because too often we have not **anticipated**, yet alone understood, them. We tend to think of biomedical research as taking place on an island, with supplies (i.e., funding) coming in from the mainland of the National Institutes of Health or the corporate budget or the board of directors of a university hospital.

Some very loud criticism from the animal welfare-rights movement is now starting to be heard again. If we are to understand and deal with this criticism, it is necessary for us to abandon our island mentality, if not the island itself.

Such criticism tends to confound us, because we know that animals are used much differently than they were 20 to 30 years ago. One reason for this is that our culture has a different attitude toward animals—wild, domestic, or laboratory—than it did in 1950 or 1960. We are members of the culture before we are scientists or physicians, and we are therefore influenced by cultural forces, if only subliminally. We are also influenced by political forces, and here the effects are much less subliminal.

Anyone who works with animals in research knows the myriad procedures that must be followed before an experiment can even **begin**. There is a consensus, therefore, that sufficient oversight and regulation already exists to ensure the welfare of laboratory animals. To argue that and nothing else is a mistake, however. Rallying around the status quo is ineffective in political circles, and it was in those circles that the Research Modernization Act, the Animal Welfare Act, and others arose to so greatly complicate our working lives. There is always room for negotiation, for giving this to get that, but not if you remove yourself from the atmosphere in which public policy is made.

Biomedical science has often reacted to new legislation with collective handwringing and going around telling ourselves how right we are. Unfortunately, such self-congratulatory messages are never heard by the legislators, regulators, journalists, and influential citizens who have taken up the cause of animal welfare and animal rights. We can no longer afford such a posture.

The animal welfare-rights movement is now attracting people who are essentially professional activists. They know how to make the best use of information channels that flow toward public policy makers. Also flowing in these channels are stories of medical breakthroughs, but rarely do these stories tell about the importance of animal experimentation to the breakthrough in question. Thus biomedical research needs to get itself plugged into those information channels so that our story becomes a routine part of the public policy process, not a reaction to it.

To that end, we need three things. First, we must have reliable and believable information. Second, we need to convince ourselves that involvement in the political process is not demeaning to our overall efforts. Third, and closely related to the second, we need to overcome what appears to be an irrational fear of politicians. How else do we explain the colleagues who are cogent, forthright, and aggressive in the company of scientists and physicians but meek, conciliatory, and deferential in the presence of politicians?

Once shed of this fear, we need to make five basic points and ask one important question. Our message should rest on the following.

- First, animal experimentation is and will be for a long time to come absolutely critical to the safety of persons taking new drugs or undergoing new surgical techniques.
- Second, animal experimentation is a crucial part of determining the efficacy of new drugs. New drugs are desperately needed—anyone who thinks that most diseases can be treated with an armamentarium of five basic drugs is grossly misguided.
- Third, one more bureaucratic layer or one more level of regulation will not necessarily do anything to ensure that laboratory animals are treated any more humanely than they are now. "Humane" is a difficult concept to define, let alone mandate.
- Fourth, animals that provide disease models are crucial not only to ongoing research but also to the effort to better understand the etiology and progression of disease. If we are ever to have workable computer models of disease, it's obvious that we are going to need a better understanding of disease processes. Thus any effort to constrict use of laboratory animals now is actually a hindrance to finding alternatives to laboratory animals in the future.
- Fifth, as mentioned earlier, scientific standards inevitably change as cultural standards change. Scientists reflect the ethical concerns of society as much as any other group does. Simply put, scientists are human too, although some groups seem to believe that scientists are sadistic ogres by definition.
- Sixth, there is this important question: "What value does society truly place on biomedical research?"

The answer to that question is difficult to obtain, but it becomes **impossible** if you don't closely watch public opinion polls, Congressional committees and their staffs, regulatory bureaus, state government agencies, zoning and planning boards in local government, and

This essay is in response to the "call for papers" on the use and continuing need for laboratory animals, *Physiologist* 26: 72, 1983.

various persons in the mass media. All of these contribute to how much value is placed on which social institution.

It is the nature of social institutions to be in flux. Thus concerns about biomedical science will always be with us; science as an institution will always be in flux, and so will the institutions with which science interacts. What this means politically is that even if none of the current legislation aimed at experimental use of animals is ever passed, something else will rise up to take its place. Someone will always be challenging the products of research and the methods employed to create those products.

Those challenges can be met only if we realize just how intertwined we are with the rest of society and make it clear just how intertwined the rest of society is with us. Put another way, don't send to know for whom the bell tolls in Washington or on the network news—it tolls for us.

Announcements

NRC Research Associateship Program

The National Research Council announces the 1984 Postdoctoral, Resident, and Cooperative Research Associateship Programs for research in the sciences and engineering to be conducted in behalf of 19 federal agencies or research institutions, whose laboratories are located throughout the U.S. Approximately 250 new full-time associateships will be awarded on a competitive basis in 1984 for research in chemistry, engineering, and mathematics, and in the earth, environmental, physical, space, and life sciences. *Application deadline:* January 15, 1984. *Information* and *application materials:* Associateship Programs, Office of Scientific and Engineering Personnel, JH 608-D2, National Research Council, 2101 Constitution Ave., NW, Washington, DC 20418 (202-334-2760).

Postdoctoral Fellowships for Minorities

The National Research Council plans to award approximately 35 Postdoctoral Fellowships for Minorities in a program designed to provide opportunities for continued education and experience in research to American Indians and Alaskan Natives (Eskimo or Aleut), Black Americans, Mexican Americans/Chicanos, and Puerto Ricans. Awards will be made in the areas of behavioral and social sciences, humanities, EMP fields (engineering sciences, mathematics, physical sciences), life sciences, and for interdisciplinary programs of study. *Application deadline:* January 16, 1984. *Information and application materials:* Fellowship Office, National Research Council, 2101 Constitution Ave., NW, Washington, DC 20418.

Computer Applications In Veterinary Medicine

The Second Symposium on Computer Applications in Veterinary Medicine will be held at the College of Veterinary Medicine, Mississippi State University, Starkville, MS, May 23-25, 1984. *Information:* Dr. Philip A. Bushby, American Veterinary Computer Society, College of Veterinary Medicine, Drawer V, Mississippi State, MS 39762.

1984 Regional Meeting of IUPS

The 1984 Regional Meeting of the International Union of Physiological Sciences will be held in Jerusalem, Israel, August 26-31, 1984. Topics include respiratory physiology, cardiovascular and general physiology, kidney and epithelial physiology, gastrointestinal tract physiology, endocrinology, neuroendocrinology, cellular neurobiology, developmental neurobiology and brain repair, central nervous system, sensory mechanisms of the nervous system, environmental physiology, and the teaching of physiology. *Deadline for abstracts:* May 31, 1984. *Information:* Congress Secretariat, IUPS Regional Meeting, P.O. Box 50006, Tel-Aviv 61500, Israel.

International Society for Heart Research

The Sixth Annual Meeting of the American Section of the International Society for Heart Research will be held in Oklahoma City, OK, September 13-15, 1984. *Information and abstracts:* Dr. H. L. Stone, Chairman, Dept. of Physiology and Biophysics, College of Medicine, The University of Oklahoma, Oklahoma City, OK 73190.

AAMSI Congress 1984

The American Association for Medical Systems and Informatics Congress on Computer Application in Medicine will be held in San Francisco, May 21-23, 1984. *AAMSI Congress General Chairman:* Morris F. Collen, M.D., 3451 Piedmont Ave., Oakland, CA 93611 (415/428-6688). *Information and registration:* AAMSI, Suite 402, 4405 East-West Highway, Bethesda, MD 20814 (301/657-4142).

Burroughs Wellcome Scholar Award in Pharmacoepidemiology

The Burroughs Wellcome Fund and the American College of Preventive Medicine (ACPM) announce a new program to aid the development of Pharmacoepidemiology. Administered by ACPM, the Burroughs Wellcome Scholar Award in Pharmacoepidemiology is intended to support in a US Medical School or School of Public Health a faculty member who is a full-time pharmacoepidemiologist with joint faculty appointments in the appropriate clinical department of the medical school and in epidemiology or statistical sciences. Applications are invited from Deans of Medical Schools or Schools of Public Health. *Deadline: March 1, 1984. Inquiries and applications:* Dr. William Kane; The American College of Preventive Medicine; 1015 15th Street, N.W., Suite 403, Washington, DC 20005.

Sports Medicine and Conditioning Seminar

The 17th Annual Emerald City Sports Medicine and Conditioning Seminar will be held in Seattle, WA, March 16 and 17, 1984. *Theme:* Sports Medicine and the 1984 Olympics. *Registration information:* Beverly Richdale, Program Coordinator, Northwest Sports Medicine Foundation, 1551 Northwest 54th, Suite 200, Seattle, WA 09107 (206/782-3383).

More on Burt Green Wilder at Cornell

LOUISE H. MARSHALL
Neuroscience History Resource Project
Brain Research Institute
University of California
Los Angeles, California 90024

The interesting account in *The Physiologist* for December 1982 (2), of the progress of physiology in the College of Veterinary Medicine at Cornell, contains some fascinating details of Burt Green Wilder's tenure "far above Cayuga's waters." Among those details, Wilder's brain collection is mentioned. Because of the importance then of that collection and the uses it served, it is worthwhile adding a few particulars to the Wilder legend.

Incidental to obtaining his medical degree at Harvard in 1866, Wilder's interest in the nervous system began with his collection of brains for Louis Agassiz. A short two years after his degree, Wilder (Figure 1) was appointed professor of vertebrate zoology and neurology at the newly established Cornell University, and his view of the position of the nervous system was already formed. His protégé, Simon H. Gage, on the occasion of Wilder's retirement 42 years later, wrote, "In the almost universal interest in the nervous system . . . few know that with a kind of prophetic insight Professor Wilder saw that in the progress of anatomy and physiology the nervous system was to play the most important part. In 1870–71 he gave lectures in comparative neurology, and in 1875 vertebrate neurology became an established course in the university" (1, p. 360).

Wilder's passion for collection, stemming from his association with Agassiz, gained full expression at Cornell. His later successor, James W. Papez (Figure 2), noted that Wilder's emphasis "was always to the actual specimen, or the dissection which showed the structures as they are in nature. So necessary a part of instruction did these studies . . . become that he opened a laboratory [and began] the collection of specimens [which] soon formed the nucleus of a zoological museum. He became an assiduous and widely known collector of brains of every available vertebrate. [O]n his retirement from Cornell, the neurological division of the museum comprised some 1600 specimens preserved in alcohol, as follows:

Brains of apes and monkeys	292
Brains of human adults and children	430
Brains of human embryos and fetuses	218
Brains of other mammals	420
Brains of other vertebrates	240

"He early recognized the need of properly prepared and preserved specimens of human brains. He laid much stress on the study of the fissural patterns and of their development. In those days the study of cerebral morphology was receiving much attention. Then as now it was relatively easy to procure the brains of paupers, criminals and insane with no cultural history. He felt that such brains could not be regarded as a reliable source . . . for the study of the human brain" (5, p. 287–288).

Papez was referring to the fact that phrenology was all the rage at the time, and Wilder "believed most profoundly that if there were ever to be a true correlation found between the brain and character of the individual, the brains of people whose life and character were well known must be studied. So convincing were his arguments that many intelligent people made provision that such use was to be made of their brains after their death" (1, p. 360). To this end, Wilder made out the following form for the bequest of brains to him, at Cornell.

> Recognizing the need of studying the brains of educated persons . . . in order to determine their weight, form and fissural pattern, the correlations with bodily and mental powers of various kinds and degrees, and the influences of sex, age, and inheritance, I hereby declare my wish that, at my death, my brain should be intrusted to the Cornell Brain Association . . . or . . . to the Curator of the collection of human brains in the museum of Cornell University, for scientific uses, and for preservation, as a whole or in part as may be thought best. It is my hope that my family and friends may not oppose the fulfillment of this my earnest wish (5, p. 288–289).

Wilder was thus able to acquire the brains of a considerable number of distinguished individuals, such as the Cornell psychologist Edward B. Titchener, economist Jeremiah W. Jenks, pathologist Theobald Smith, feminists Rosica Schwimmer and Alice Chenoweth, and others. "It was characteristic of Doctor Wilder that he would not ask others to do that which he was not willing to do himself. [Accordingly], he had made arrangements that at his death his brain should be removed and sent to the collection at Cornell" (5, p. 289).

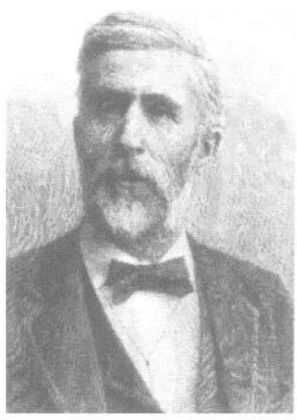


Figure 1 (*left*)
Burt Green Wilder (1841–1925). [From Ref. 5, with permission.]

Figure 2 (*right*)
James W. Papez (1883–1958). [From the National Library of Medicine, with permission.]

Four years after Wilder's death, a description of the man and his brain was published by Papez. "[He] is recognized as one of the great men connected with the early days of Cornell University, to which he rendered more than forty years of active service. He became distinguished as a zoologist, educator, and writer. His pupils remember him as a wonderful and inspiring teacher. As to his traits, [h]e was . . . active and energetic in all that he did. He was a man of strong convictions and for whatever claimed his interest his enthusiasm knew no bounds. [Nonetheless, in his lectures on physiology and hygiene he advocated the exercise of all functions . . . with moderation. He was a lover of music, [and] played the piano well. In his speech [and] composition, he strove for clearness, consistency, correctness, conciseness and completeness. These he called his five C's. He placed clearness first" (5, p. 285, 289), though why he did so is unclear.

Wilder's brain weighed 1,150 grams. "The temporal regions were unusually well developed. The fact that he was very musical and had a fine appreciation for the niceties of spoken language may be considered in this connection. The brain as a whole was relatively well developed, especially in the frontal and occipital regions. That this is usually the case in the scholarly group . . . has already been stated in connection with . . . the brain of Helen H. Gardener. This appears to be equally true in the brains of William Osler, G. Stanley Hall, and E.S. Morse. . ." (5, p. 318).

In his recollections of the early meetings of the American Neurological Association (ANA), founded in 1875, Charles K. Mills wrote "[T]he work of Wilder [was] of special interest. At almost every meeting . . . some valuable morphological and anatomical studies of the brain were presented by him. It was during the first quarter of [ANA's] history that Wilder began his propaganda for the revision of encephalic nomenclature. He was earnest and enthusiastic on this subject. . ." (3, p. 25). In 1884, at Wilder's suggestion, the ANA's President appointed a Committee on Neuronymy (Wilder's neologism for neural terms), made up of H.D. Donaldson, C.K. Mills, E.C. Seguin, and E.C. Spitzka, with Wilder as Chairman. Twelve years later, the ANA unanimously adopted the committee's report, advocating some forty single-word terms that have since become enshrined in our textbooks and medical dictionaries.

Other things being equal, the report recommended, mononyms (Wilder's term for single-word terms) were preferred to polynyms. Among those immortal forty nyms were (alphabetically: callosum, chiasma, cuneus, dura, fornix, hippocampus, hypophysis, infundibulum, insula, lemniscus, pia, pons, precuneus, striatum, tegmentum, thalamus, and vermis, all of which are still in use.

His penchant for mononyms again came to the fore in Wilder's Cartwright lectures of 1884, when he proposed "alinjected" as a single-word equivalent of "alcohol injection." In recollections of the early days of the ANA, Charles K. Mills related, "We used to have a joke about this. Members of the Association were sometimes accompanied [at meetings] by their wives, who naturally had a great admiration for high-sounding neurological phrases, and on these occasions the former would camouflage their invitations to take a drink by remarking, 'What about Wilder's alinjected ventrad?' " (3, p. 26).

Fun aside, Wilder was highly regarded by the neurologists, and in 1885 became one of the two nonprofessional, academic figures elected to the presidency of the ANA; the other was Henry H. Donaldson, in 1937. As might have been anticipated, the title of Wilder's Presidential Address—dealing with neurological nomenclature—was "Paronymy versus heteronymy as neuronymic principles" (3, p. 310).

Two years before Papez provided his 1929 account of the brain of Burt G. Wilder, (Figure 3) he published the results of what is probably still the most comprehensive study of the brain of a normal achieving woman, Helen H. Gardener (Figures 4 and 5) (4). An early feminist, after school teaching and administrative positions, she lived in New York City, writing magazine articles, stories, and books. About 1888, she became involved in the struggle for woman's suffrage. At the turn of the century, she moved to Washington and as Vice-President of the National Woman Suffrage Association contributed importantly to securing the amendment to the constitution that gave women the franchise. In 1920, she was appointed by President Wilson as the first woman member of the US Civil Service Commission.

One of Gardener's best-known writings was *Sex in Brain*, reported to have been translated into eight languages (4). "The statement made by a prominent physician, that the brain of a woman was inferior in nineteen different ways, challenged her interest. She spent many months studying brain anatomy and proved that the brain mass of a woman was not provably different from that of a man" (4, p. 30).

Gardener willed her brain to Professor Wilder and the Cornell Brain Association, for subsequent study at Cornell. She died in 1925 at the Walter Reed General Hospital, Washington, where her brain was removed, preserved in Formalin, and sent to Ithaca, where Papez gave it careful scrutiny. In addition to describing "an unusual wealth of development" in three regions of Mrs. Gardener's brain, common to individuals of unusual achievement, he called attention to an unexpected finding. From his measurements of the precuneal area of the parietal lobe, on the medial side of the hemisphere and above the cingulate gyrus, Papez became intrigued with the possibility that it might constitute the cortical receiving area for sexual sensation.

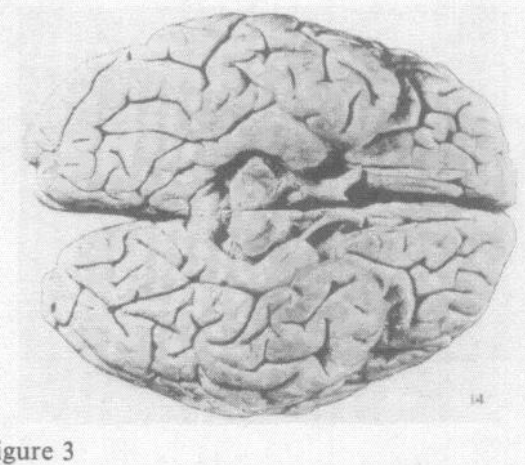
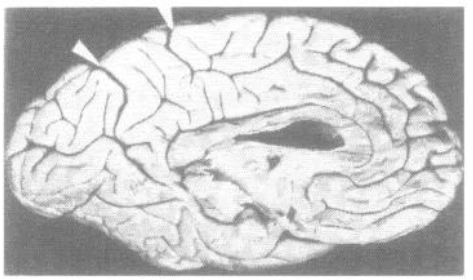


Figure 3
Ventral view of the brain of Burt Green Wilder, showing an atrophied left olfactory lobe due to a sclerotic kink in the left ophthalamic artery. [From Ref. 5, with permission.]

Figure 4
Portrait of Mrs. Helen Hamilton Gardener (Alice Chenoweth Day) (1853–1925). [From Ref. 4, with permission.]



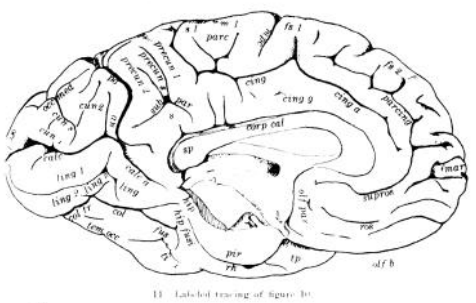


Figure 5
Medial view of left hemicerebrum of Mrs. Helen Hamilton Gardener, showing a smaller than average precuneate area (*arrows*). [From Ref. 4, with permission.]

"In making a comparison of this region of the male and female brains, it soon became evident that the precuneal area is of greater size and complexity in most of the males. This is also borne out generally in . . . published figures of male and female brains. [I]n the Gardener brain the precuneal index (17) is lower than in the average female (19.8) and that, in turn, lower than in the average male (22.2). In other words, the females have a small precuneus, and this appears to be true irrespective of intellectual achievement" (4, p. 47, 48).

Pointing out that Rudinger in 1882 had been the first to call attention to sex differences in this cortical region, Papez continued, "My observations [show] the male precuneaus is 18 per cent larger than the female. Only a little more than 6 per cent or at most 9 per cent of this can be accounted for by the difference in size of the brains of the two sexes. The difference here is probably greater than is shown by the figures, because in the male this region is more complexly fissured.

"All this raises the question whether or not a somatic sex area exists in this region of the brain. Other circumstantial evidence suggestive of this may be mentioned. That the sex organs have a definite representation in consciousness is recognized by psychologists [and many others]. Its primitive nature is often referred to. Cerebral connections of the sex organs can be safely postulated. Brodmann ('09) has shown that the postcingular area with a special cell structure is recognized as one of the eleven regions common to the brains of all primates and other mammals. Since this area first appears as a fundamental part of the mammalian cortex in the smooth brains of the small mammals of the lower orders at an evolutionary level where no true association areas are in evidence, it is fair to assume that it is a sensory area having some special somatic connections. Its direct connection with the hippocampal gyrus . . . puts it in close relation to the hippocampal formation, generally thought to be an olfactory center. By means of the second annectant gyrus, it is connected with the visual area. The continuity of the precuneal area with the superior parietal lobule brings its cortex into direct relation with these supposed cutaneous centers of the lower limbs. The foregoing points may be taken as circumstantial evidence favoring the idea that some special sense center associated possibly with sex sensibility may exist in this region" (4, p. 72–74).

In 1930, Papez published a study of the brain of Sutherland Simpson (1863-1926) who, as a young associate of Sharpey-Schafer at the University of Edinburgh, had been invited to Cornell as Professor of Physiology in 1908. "The main features of this brain," Papez wrote, "are its generally large size [wgt. 1323 grams], a wealth of convolutional development in the parietal, occipital, and temporal regions. The outstanding feature was the exceptionally large size of the precuneus. These lobules are larger in the brain of Dr. Simpson than in any other brain examined by the author" (6, p. 186, 195).

Planimeter readings in Papez's three papers yield the following average square centimeters of the precuneus: Sutherland Simpson, 22.9; Burt G. Wilder, 16.5; twenty males, 15.6; Helen H. Gardener, 13.2; and twenty females, 12.9. In his "A proposed mechanism of emotion" (7) Papez referred briefly to those data. "So far as functions of the gyrus cinguli are concerned, experimental evidence is scant, owing to the inaccessibility of this region. I have noted . . . that in the two sexes the precuneus shows a greater difference in size than any other portion of the cortex, being more highly developed in the male, and it was suggested that representation of the sex organs may be localized there. Sensations related to sex matters possess a high degree of emotional coloring" (7, p. 735).

We may conclude from the studies made of specimens in the collection started by Cornell's Burt Wilder that the "biggest aspidistra in the world" belonged to a male physiologist.

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Pitts and Urine Acidification

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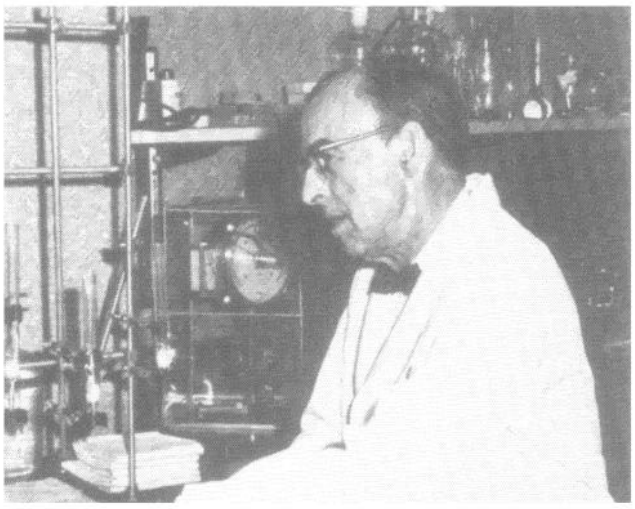
Dramatic accounts of scientific discovery are usually fictional, as anyone knows who has devoted his endeavors to the persistent plodding of the research laboratory. On occasion, however, it can happen. One such breakthrough was the demonstration of acid secretion by the renal tubules (5). Although part of this story has already been told by Pitts (6), I have been urged to complete the record from my vantage point, if for no other reason than the fact that the Pitts account gives no credit to the co-author of the original publication (which, as will be seen, was quite appropriate).

My first encounter with Dr. **Robert F. Pitts** was in absentia on the occasion of my first job interview at New York University in May of 1942. Homer Smith devoted an entire morning of his time to showing me around his department, expounding his unique philosophy of science, and at frequent intervals assuring me that I would not like to work in his department. It was as though he were giving a courtesy interview to someone whom he had already decided he did not wish to employ, although I have never understood toward whom the courtesy was directed. Near the end of our tour he took me into a deserted laboratory which he identified as that of Dr. Pitts, whose departure to accept a position at another institution had created the vacancy on his staff that he wished to fill.

A short time later another job interview was being concluded at Cornell in the office of Dr. Eugene DuBois, who asked me to go to lunch with someone else whom he had just hired. To my surprise, my luncheon companion was Dr. Pitts. Aside from a chance to become acquainted, Dr. Pitts had requested this meeting because of his recognition that, due to wartime exigencies, the two of us would be the only ones doing research in the department. He could not conceive of effective research being accomplished unless I would agree to provide him technical help with some renal studies he wished to undertake, in exchange for which he would train me in some special skills that he had mastered that were of relevance to my research interests in cardiovascular control. Never had a neophyte been offered such a favorable arrangement; I was quick to accept.



Robert F. Pitts had a crisply logical mind and intense ambition. He received his undergraduate education at Butler University in his home town of Indianapolis, where the excellence of his academic record won him a fellowship for graduate studies at Johns Hopkins. He received his Ph.D. in 1932 with a thesis dealing with locomotion in amoebae. In the Hopkins environment, however, Pitts came to feel that academic biologists were second-class citizens and so he opted for an academic appointment where he could also pursue studies toward an M.D. It was under these circumstances that he joined Homer Smith's department, and with an intensity of effort that few could emulate, he managed to complete his M.D. in the next six years on top of full responsibilities as an instructor in Smith's department and a participant in the departmental research program in renal physiology. Pitts then recognized that an additional lever for professional advancement would be completion of a prestigious postdoctoral fellowship, a commodity which at that time was relatively rare. He won the support of the Rockefeller Foundation for two years of intensive research, the first of which was spent in Ranson's Neurological Institute at Northwestern followed by a year with Bronk at the Johnson Foundation. During those two years he mastered the latest state of the art for both a structural and an electrophysiological attack on neural problems and put together a theory of respiratory control which for the next few decades remained a widely accepted concept for respiratory regulation (7). Returning to Dr. Smith's department with a budding international reputation, he was disgruntled to discover that Smith offered him nothing more than a "Welcome back!"; promotions or significant salary revisions were not to be forthcoming at N.Y.U. It was from this background that Pitts was happy to accept the appointment in Dr. DuBois's department at Cornell Medical College.

The working arrangement upon which Pitts and I had agreed yielded a very productive period for both of us. Pitts's first priority was to refute criticisms of his earlier studies of renal phosphate excretion which Smith had made (9, p. 187–188), while I initiated studies on bulbar cardiovascular centers. It was during the second year at Cornell that a most extraordinary outburst took place at the DuBois luncheon table. DuBois had hired a delightful English housekeeper for the department, one of whose functions was to prepare luncheon for a very select group of guests who included the Dean and Associate Dean, the Chairmen of the major departments, and (incidentally) the two young members of the Physiology Department. It was during one of these luncheons that Pitts challenged Vincent duVigneaud,

Chairman of Biochemistry, who at that time was deeply engrossed in peptide research that was to lead to his Nobel prize. Pitts accused him of teaching the students "nonsense" concerning acid excretion by the kidney. duVigneaud was not accustomed to such a frontal attack on his competence and shortly backed himself into an impossible position trying to defend himself. He finally stomped out in a rage, shouting "Damn it; if you think you are so smart, prove it!" For the next ten days, Pitts cloistered himself behind the closed door of his office or quietly slipped down the corridor to the library, working from early in the morning to well into the evening, and without coming near the luncheon table. There followed several days during which Pitts was pounding away at his typewriter. The first contact I had with Pitts since the day of the argument was when he came striding into my office one afternoon, placed a freshly typed manuscript on my desk and made the startling comment: "Bob, I ask you to read this manuscript very carefully. You will note that it is all ready to submit for publication except that the data are not there. When you have finished, drop down to my lab so we can get busy and obtain the data." The paper, which I proceeded to read, was published in due course with the data added (5).

The nonsense to which Pitts referred evolved from studies of L.J. Henderson (4), who demonstrated that in normal acid-base regulation the acid excreted in the urine is chiefly represented by the acid phosphate ion ($H_2PO_4^-$). This led many textbook authors to suggest in one way or another that the renal tubules could selectively reabsorb the basic form of the ion (HPO_4^{2-}). A popular example was Bodansky's text, which many professors of that era, including duVigneaud, were assigning their students; it stated, "Na_2HPO_4, as it proceeds through the tubule, gives up part of its Na, which is reabsorbed by the tubular epithelium" (1). Such statements encouraged students, and even professors, to forget that the phosphates in the glomerular filtrate constituted an ionized equilibrium mixture. Equilibrium kinetics would totally preclude manipulating the cations related to one anionic species without altering the state of the other species. The explosive argument which Pitts had with duVigneaud in regard to this "nonsense" was actually the culmination of several weeks of a running battle with one of duVigneaud's staff on this point. He was particularly sensitive to the importance of this relationship in view of the studies of renal phosphate excretion that we had just completed; should it be possible for the renal tubules to treat the two species of phosphate ions independently, his working hypothesis of a single tubular transport mechanism for phosphate would be invalidated.

Pitts cannot be given the credit for first conceiving of a mechanism of H^+ ion secretion in exchange for Na^+ ion, nor for the idea that urinary acidification was related to bicarbonate reabsorption. His former mentor, Homer Smith, had speculated in his classical monograph of 1937 (9), "It may be supposed that the urine is acidified by the tubular excretion of H^+ in exchange for B^+"; Sendroy, Seelig, and VanSlyke (8) had conjectured that the acidification of urinary phosphate was somehow associated with HCO_3^- reabsorption. A similar exchange mechanism was also part of the theory of gastric acid secretion being propounded by Davenport (2) from whose work Pitts gleaned the idea that the carbonic anhydrase mechanism would be a likely source of the H^+ ion. Indeed, it is an interesting historical coincidence that the publication of the theory of urinary acidification by the carbonic anhydrase mechanism was in press at the moment when Davenport was in the process of retracting his analogous gastric acid theory (3). The contribution for which Pitts should clearly and uniquely be given credit, however, was the design of a brilliant series of experiments which replaced speculation with definitive evidence. He unequivocally fulfilled duVigneaud's mandate, "Prove it!"

In specific reference to the extraordinary circumstance of the manuscript being written before the first experiment had been started, the most remarkable aspect of this was the precise description of the experimental methods and the accurate description of experimental results, a tribute to the meticulous attention to experimental design which was characteristic of Pitts's work. His preliminary analysis of the experimental protocol was so thorough, both qualitatively and quantitatively, that it was typical of his endeavors to find the discrete data points falling almost exactly where he had projected them. One idiosyncracy that contributed to this success was his insistence that he alone would wash all the glassware, a task usually relegated to subordinates and often overlooked as a crucial determinant of scientific precision. As a consequence of this rigorous attention to details of experimental design, he rarely performed an experiment that did not yield publishable data, data which demonstrated relations so vividly that statistical verification was often not required. In this particular instance, Pitts was so convinced that there was only one conceivable mechanism to account for the known urinary findings, and so anxious to be certain that he did not stumble and find himself forced to eat crow before his biochemical colleagues, that he carried his reasoning all the way through to the final polished state of the manuscript before he ventured into the laboratory. Looking back close to his retirement, he remarked, "I would judge this to be one of the best papers I have ever written" (6).

My respect for Pitts's genius for experimental design should prompt me to end the story here. The dictates of honesty, however, demand that I add a postscript to reveal a blemish that spoils the ultimate perfection of his achievement but restores his quality of human fallibility. To the best of my knowledge, every word in the preliminary manuscript appeared in the published ver-

sion, but the converse is not true. The crucial first argument of the paper can be simply stated: that more acid should appear in the urine than was filtered at the glomeruli because the filtered HPO_4^{2-} was being titrated to $H_2PO_4^-$ by the tubular secretion of H^+ ion. As the columns of data began to fill up our workbooks, Pitts lost his usual jovial manner and became hypercritical of everything taking place in the laboratory. Eventually he resorted to something he had rarely done before: he asked me to check his arithmetic. Not only was the urinary acid substantially in excess of the filtered acid, but it was also significantly in excess of what could be accounted for by titration of the copious amounts of phosphate with which we were infusing the dogs. By my arithmetic as well as by his arithmetic, our results were too good to be believed! It was only after several days of anguish that we finally awoke to the explanation. As Pitts had overlooked and I had never realized, the generous amounts of creatinine that we were administering to achieve a very accurate measure of glomerular filtration constituted an effective urinary buffer. Once the source of the discrepancy had been diagnosed, frustration was converted to elation when Pitts added further experiments in which creatinine rather than phosphate was the intended urinary buffer, thereby strengthening the evidence that the tubules were exchanging H^+ ion for Na^+ ion by a mechanism which had no unique dependence on phosphate.

If the curious reader wishes to check the original publication (5), he will note that the introduction and the METHODS make no mention of these additional creatinine experiments. The four pages of DISCUSSION also ignore these experiments except for a single sentence appended to the last paragraph. The significant additions to the manuscript are confined to the RESULTS where the creatinine experiments were inserted and the calculations of the phosphate experiments were modified to include the creatinine buffering. In the process of discovering the mechanism of urine acidification, Pitts had inadvertently discovered that even renal physiologists must confront the Heisenberg Principle: that one's method of measurement may distort the very parameter that one is attempting to measure. It was fortunate that in this instance the distortion exaggerated rather than obscured the truth and a new scientific theory was born.

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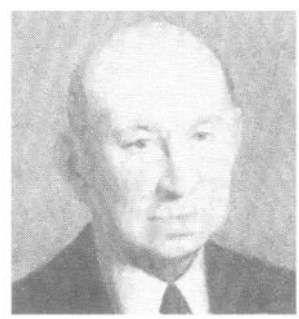
Departmental History

Department of Physiology University of Cincinnati College of Medicine

In 1983 the University of Cincinnati College of Medicine will complete its 164th year of providing medical education. This makes it the oldest continuous medical school west of the Allegheny mountains and the seventh oldest medical school in the United States. The Medical College of Ohio (now the University of Cincinnati College of Medicine) was chartered by the State of Ohio in 1819, largely through the efforts of Dr. Daniel Drake, a Cincinnati pioneer in the practice and teaching of medicine. Drake lectured on Physiology to the first classes in rented rooms above his father's store. In 1821 he offered a silver medal for the best research thesis by a student. After several years in temporary quarters, the Medical College of Ohio obtained State funds and moved into its own building on Sixth Street between Vine and Race Streets. A description of the College in 1827 includes mention of a professor of Anatomy and Physiology. From that time to the present the school changed from a private, to a municipal, to a state-supported College of Medicine, and, finally, to a State medical school. Since 1973 the faculty has increased from 300 to 738, the number of students from 120 to 192, and the annual budget from 12 million dollars to 70 million. In 1974 the College moved into a new Medical Sciences Building which is one of the largest single structures for medical education in the United States.

During the 1900s Physiology was taught by practicing physicians who devoted only a fraction of their time to teaching. Shortly after the turn of the century, the Cincinnati Academy of Medicine raised $28,000 to endow a chair in Physiology in the name of Dr. Joseph Eichberg, a greatly admired Cincinnati physician. This was the first endowed professorship in the College of Medicine and marked the emergence in 1908 of the modern era of Physiology in the Medical School. It is interesting to note that under the terms of the gift, the interest from the donation (about $750 per year) was to be added to the salary offered by the College so that the position would be attractive to the most outstanding Physiologists in the country.

Dr. **Martin H. Fischer** came to the College in 1910 to devote full time to the Department as the first Joseph Eichberg Professor of Physiology. His principal scientific interest was in the exciting new field of colloid chemistry, which he had learned about in Germany in the laboratory of Wolfgang Ostwald. He published 14 books and 256 articles, many of which were in nonscientific areas, since he was an eclectic man interested in art and philosophy as well as science. In 1926 Dr. Fischer donated to the University the replica of



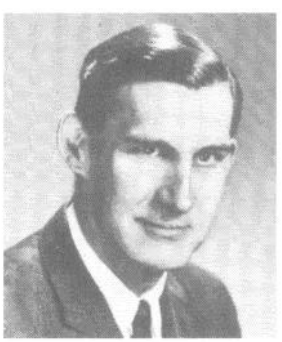
a 15th Century Italian apothecary containing dozens of ceramic jars inscribed with the Latin names of drugs. These had been manufactured in the 19th Century during an attempt to revive the production of majolica ware. Sixty-three classes of students have become familiar with this Cantagalli Pottery, which was first displayed in the lecture room and is now exhibited in the Historical Library of the Medical School.

Martin Fischer was an artist as well and hung his paintings on the walls of the lecture room. One of his contemporaries told me that Fischer invited a colleague who was leaving the city to select one of the pictures as a gift. Unfortunately, the friend picked the only one in the room that wasn't a Fischer!

Martin Fischer was a dynamic individual who charmed his contemporaries with his personality, wide interests, and witty observations and also infuriated many with his idiosyncrasies and dictatorial manner. It is said that no student learned Physiology from him, but all of his lectures were SRO affairs. He once interrupted a lecture to throw a question at the audience and offered a prize for the correct answer. The prize turned out to be a brown paper bag that contained a small tin of smoked oysters. The winner was a medical student named William Lotspeich who was destined to be Fischer's successor! Fischer is best described as "the head of the table no matter where he sat." At Dr. Fischer's death, his admirers increased the endowment of the Eichberg Chair nearly 10-fold.

Among Dr. Fischer's many associates during his tenure as Professor of Physiology and Chairman of the Department from 1910 to 1950 were Drs. Robert Kehoe and Gustav Eckstein. Dr. Kehoe, after several years in Physiology, became director of the Kettering Laboratory in 1924 and planned its first building which was completed in 1926. He developed the Laboratory into a world-renowned center for the training of Public Health personnel from many countries around the globe and for the study and measurement of environmentally important substances. Dr. Kehoe retired in 1965 and was succeeded by Dr. Theodore Radford, and the Kettering Laboratory became the Department of Environmental Health. A number of Physiologists, including Dr. Radford, participated actively in the Physiology medical and graduate student teaching and research programs. This association has been long lasting, and Drs. Ernest Foulkes, a renal physiologist and more recently Dr. Dale Johnson, also a renal scientist, are at present valuable joint appointees from Environmental Health to Physiology.

After the retirement of Dr. Fischer, the Department was maintained by Dr. Eckstein for a year, until Dr.



William Lotspeich was appointed to the chair in 1951. Dr. Lotspeich combined the rare qualities of being a dedicated scientist and a warm humanist. The medical student course became a true course in Physiology, a graduate training program was instituted, and Lotspeich made valuable contributions to renal physiology. One of his former students, Dr. Jean Weister, remembers that his notebooks were "pieces of art" and that his instruments were treated as "jewels." Dr. Weister also stated that his humility made it somewhat overwhelming to be with him. He left Cincinnati in 1958 to join the faculty at the University of Rochester. It is said that he felt frustrated in Cincinnati at the lack of opportunity to build a stronger Department. It is possible that his discontent was aggravated by the policy of the medical school at that time to refuse to apply for Federal funding, fearing that the independence of the school would be impinged upon. After a few years at Rochester, Dr. Lotspeich resigned to give his full attention to the humanistic side of his character within the Quaker Movement.

From 1958 to 1960 the Department was again kept going by Dr. Eckstein who served as Acting Chairman. Dr. Eckstein, however, had many other consuming interests (see below), and the program initiated by Dr. Lotspeich was not maintained during this interim period. In 1960 Dr. **Irving Schwartz** became head of the Department. He had gained a considerable scientific reputation at the Rockefeller Institute and at the Brookhaven National Laboratories. He maintained an active program at Brookhaven in vasopressin research but had difficulty giving attention to the Department in Cincinnati. One of his colleagues said that "he had his head in the clouds, his heart at Brookhaven and his body in New York City." After 4 years as chairman, he resigned in 1964 to take the first Chairmanship in Physiology at the new Mt. Sinai Medical School in New York City. Dr. Harold Burlington, a Lotspeich appointee, served as Acting Chairman from 1964 to 1966. He later rejoined Dr. Schwartz shortly after the author of this history was named chairman.

When I was being interviewed for the Directorship in the Spring of 1966 by Dean Clifford Grulee, Jr., he told me that Dr. Gustav Eckstein, an emeritus professor who had retired in 1960 at the age of 70 was a living legend in Cincinnati. At his retirement he had been asked what he wanted as a retirement gift, and he asked for a room and a secretary. Remarkably, this request was honored by the combined efforts of the Departments of Physiology, Neurology and Psychiatry until his death. Dean Grulee said that he appreciated my need to build a strong department, and he would help me in every way he could, but he hoped there would always be room for "Gus," who would only be active for a few more years. Fifteen years later; (Gus remained active until he died in 1981), I had come to appreciate him as one of the most vital, stimulating, and warm persons I have ever known. Gus was not an experimenter but was a keen observer of animal behavior—a forerunner of today's ethologists. His laboratory held a large group of canaries, each of whom was an individual in his eyes. While Gus observed the canaries closely, his writing was never sentimental or anthropomorphic. His stories, published in many magazines, had attracted the attention of Alexander Woolcott, who read them to a large radio audience. Through Woolcott, Gus established lifelong friendships with theatrical figures such as Lunt and Fontanne, Laurence Olivier, Ruth Gordon, Garson Kanin, and many others.

Gustav ("Gus") Eckstein (*left*) and Daniel L. Kline, Chairman from 1966 to 1983.

He wrote seven books, the best known being *The Body Has A Head*, which became a Book-of-the-Month Club selection. His biography of Pavlov, the Russian scientist, will be published posthumously through the efforts of Miss Martha Keegan, a friend and quasi-secretary of Gus's.

In 1980, a year before his death at 91, the graduating medical class chose him to be the principal speaker at their Commencement. He said to the class, "I guess you expect me to tell you about your responsibilities as doctors. Well, I think you'd rather hear about my first trip to Greece." And he proceeded to regale the class and their assembled families by leading them with amusing anecdotes from Cincinnati to New York, to London, Paris, Rome, and finally to Athens. He told them how much he had admired the architecture that he had seen in each city, but when he got to Greece, he realized that all of the buildings until then had been derivative. Now he was seeing the originals. He then faced the audience and said, "If there's any point to my talk, it's to remind you that you are all originals. There may be people who are better or worse than you, but you are an original. Live your lives to preserve and express those unique qualities that only you have." And he sat down. I still get chills recalling that moment.

Today (1983) as I prepare to turn the Department over to Dr. Nicholas Sperelakis, I can count more than 50 Ph.D.'s who graduated during my 17 years as Chairman. Income from grants increased from zero to nearly $1,000,000 per year, and the faculty has grown from 4 to 14. Last year the medical course in Physiology received the highest rating by students of any first year course. The Department is strongly represented in the areas of smooth and coronary muscle by Drs. DiSalvo, Grupp, Paul, and Solaro, who bring biochemical, biophysical, molecular, and whole-organ approaches to their work. Endocrinology is represented by Drs. Baldwin and Wilfinger, hemostasis by Drs. Highsmith, Lowenhaupt, and myself, gastrointestinal physiology by Drs. Fondacaro, Jacobson, and Nathan, neurophysiology by Drs. Behbehani and Suszkiw, and renal physiology by Dr. Banks. Drs. Foulkes and Johnson of the Department of Environmental Health and Dr. Kleinman of the Department of Pediatrics are also renal physiologists who work closely with the Department. We have established working relationships with laboratories in Germany, Belgium, Poland, England, and Sweden as well as with laboratories in the US. We anticipate that under the leadership of Dr. Sperelakis, who combines neurophysiological and cardiovascular physiological interests, the Department will continue to grow and achieve an ever more important place for itself in the field of Physiology.

Some of the material in this article was obtained from articles that appeared in the *Cincinnati Journal of Medicine* (G.X. Schwemlein, The origin of the University of Cincinnati Medical Center, 49: 69, 1968; and C. Striker, Physiology, 57: 159, 1976).

Daniel L. Kline

Dedication of the Nello Pace Laboratory

One of the happiest experiences of my life was the privilege on August 7, 1983, of participating in the dedication of the reconstructed laboratory at White Mountain's Barcroft Facility to its creator, Nello Pace. Several weeks earlier I had received from the Department of Geology, UCLA, an invitation to the dedication. Along with the invitation came a T-shirt decorated with a logo depicting White Mountain and a bristlecone pine encircled with "University of California White Mountain Research Station."

My greatest source of happiness was to observe this honor come to my friend Nello Pace, whose concept, vigor, and determination were responsible first for the Crooked Creek facility at 3,080 m in 1950, the Barcroft facility at 3,800 m in 1953, then bull-dozing a road to the summit, and with the help of students building a stone laboratory and living quarters there at 4,300 m.

The affair brought back happy memories of the men and women who have collaborated with me in research on White Mountain, first in 1962 and finally in 1978. One of those with me in 1978 was Stanley Hillyard, now chairman of the Department of Biological Sciences, University of Nevada, Las Vegas. With a University "International" vehicle we reached Bishop on the afternoon of August 6. While registering at the Sportsman's Inn, I met Clarence Hall, whom I learned was Professor of Geology at UCLA and the present director of White Mountain Research Station.

We reported to the Base Station, 3000 East Line St. about 6 p.m. The first friend I met was Duane Blume, formerly resident biologist at the Station, now with Bakersfield State University. He was a member of the celebrated 1982 Everest Expedition led by John West. Another friend, Don Buser, was and is a key member of the staff of the Bishop Base Station. I was happy to find friends John Severinghaus and his wife, Eleanor. John helped us in 1962 as I have recounted (1) and again in 1978 when he had three collaborators, Mary Stafford, Peter Hohn, and Malin Ingvar (from Sweden).

Soon we lined up to fill our plates with an excellent dinner prepared and served by the staff. I chose barbecued ribs. Over the years at White Mountain one of the memorable features of mealtime has been conversations with resident and visiting scientists. This mealtime was no exception. Sitting next to me was Laurie L. Holbrook, who is in her fifth year of geology at UCLA and currently was attending a course in mapping that was due to meet at Crooked Creek Sunday morning.

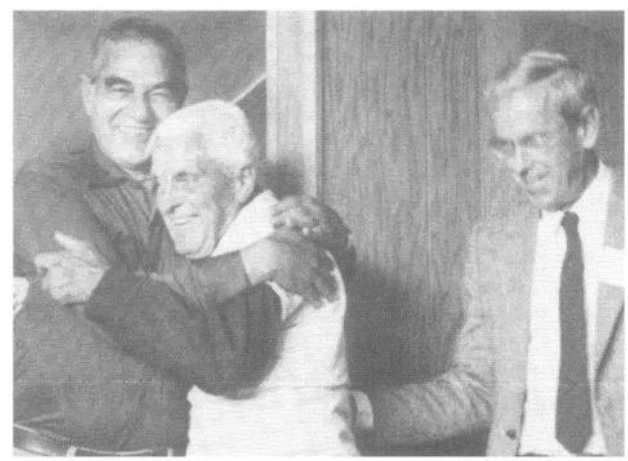
I was curious about how Laurie became interested in geology. She gave me a vivid account of when the flame was kindled. A fifth grade teacher once asked her to cup her hands and then poured into them black sand that came from a black beach in the Hawaiian Islands. Years later Laurie's brother financed her trip to Hawaii. One of her prime goals was to visit that beach of black sand.

As her education broadened, she became enthusiastic about biology, but a course in geology in her freshman year at UCLA rekindled the old flame and it has been burning brightly ever since.

I told her of my experience with high school student assistants and my conclusion that the life pattern of high school students has changed in the past 30 years and that today the elite who run student affairs are honor students who may also be athletes; none smoke cigarettes nor use drugs. Laurie told me that in her high school class of 600 students she had been one of about thirty-five such students of the qualities described above.

Stan Hillyard and I had a good night at the Sportsman's Inn and were up early enough to report to the Station for a breakfast of blueberry pancakes and sausage. During breakfast, Nello Pace arrived with David Dill Cudaback, professor of astronomy at UC, Berkeley, and formerly director of the White Mountain Research Station. They had just arrived by air from Berkeley. Both were in high spirits. We had been intrigued to discover in correspondence a few years ago that we shared the name Dill. This was the first time we had met. His mother was a Dill whose family had lived in Canada; we found no tie between our families.

After breakfast, the caravan of eight vehicles left for high altitude by way of Big Pine, across the Owens River, up to Westgard Pass, about 2,000 m, and up the mountain on a blacktop road as far as Shulman's Grove, where the oldest bristlecone pine has stood since its birth 4,600 years ago. After several miles over a graveled road the caravan stopped for a while at Crooked Creek Station (3,080 m). This station has been



Nello Pace and Bruce Dill (*left*) with Clarence Hall (*right*). [Photo by Stan Hillyard.]

reconstructed for joint use with the US Forest Service. All was in good order. A geology "mapping" class was in session.

The caravan negotiated the steep graveled road around Sheep Mountain past many snow banks and a few marmots before reaching at noon the completely reconstructed laboratory soon to be dedicated to Nello Pace.

Walking through a chilly rain we entered the laboratory and observed with amazement the transformation. After a brief tour I was escorted down the hall on the ground floor to observe that my picture, in a new frame, hung on the wall in distinguished company. We were advised that the cold buffet lunch was ready. Eleanor Severinghaus took responsibility for selecting viands for my lunch, and then we sat together for the second time this year, the first was at the Banff hypoxia symposium in January.

There were many conversations with interesting people before we were called to order by Director Clarence Hall. He gave a gracious and well-organized tribute to Nello Pace's vision and skill in planning and building the laboratories on White Mountain. I'll not attempt to report his talk, since I am confident it and Nello's response will be published. Nello responded to the dedication in grand style and then called on me, remarking that reading as a young physiologist my *"Life, Heat and Altitude"* had settled his mind on a career in high-altitude physiology. I reminisced about a site visit to the Barcroft facility February 22, 1957, along with Carl F. Schmidt, Maurice B. Visscher, Louis Levine, Arthur Otis, and Freeman Quimby. We were there to review a proposal to the National Science Foundation for a grant of $125,000 for a power line. Our site committee approved the proposal and also expressed the view that the White Mountain Research Station was destined to be a continuing national asset not only for physiology and other life sciences but also for other fields of science. As I finished, pictures were taken of Nello and me in a friendly hug.

I have a few final words about Nello Pace. His creation of the White Mountain Research Station has been accompanied by notable scientific achievements. He is known both nationally and internationally for his research on body composition. At the 1982 Fall Meeting of the Physiology Society he presented a paper on estimating muscle mass in laboratory animals from their creatine content. Last year I arranged for the loan of his two man-size manikins, containing precisely known amounts of potassium. They were used in standardizing the K-40 instruments at the EPA laboratory in Las Vegas and in the laboratory of Brooks AFB at San Antonio. At these ceremonies I learned from his secretary that he had just returned from a trip around the world, first to Tokyo and then to Moscow to attend the fifth annual commission on Gravitational Physiology where he presented two papers. Congratulations, Nello!

The closing ceremony was a round of toasts including one with my young friend Laurie Holbrook. Stan Hillyard and I were ready to depart for Boulder City with memories of a great day.

Reference

1. Dill, D. B. Reunion at high altitude. *Physiologist* 6: 40–43, 1963.

D. Bruce Dill

130th APS Business Meeting

Time: 4:30 P.M., Monday, August 22, 1983
Place: Sheraton Waikiki Hotel, Honolulu, HI

I. Call To Order

President Alfred P. Fishman called the meeting to order and welcomed the members to the 130th Business Meeting of the Society. The agenda and ballot for Election of New Members were distributed to the members in attendance.

The Society has again broken with tradition by having the Past President's Address precede the Business Meeting. Dr. Fishman introduced Dr. Walter C. Randall, who presented the Past President's Address, "Crises in Physiological Research" (p. 351).

II. Report on Membership

The President-Elect, Dr. John B. West, reported on the current membership and deaths since the Spring Meeting.

A. Summary of Membership Status. The Society's membership has continued to increase at a relatively slow rate. As of July 27, 1983, the membership reached 6,144 distributed as Regular 4,494, Honorary 10, Corresponding 101, Emeritus 556, Associate 718, and Student 265.

B. Deaths Reported Since the Spring Meeting. The names of those members whose deaths have been reported since the Spring Meeting were read, and the membership observed a moment of silence in tribute to them (p. 380).

III. Election of Members

The primary activity of the meeting of Council was review of membership applications, and the recommendations of the Membership Committee were approved with one minor change. Dr. Fishman expressed Council's appreciation to the Committee for an excellent job.

With the endorsement of the Honorary Membership Committee, a candidate for Honorary membership has been included on the ballot. Dr. Feng De-Pei, a distinguished physiologist, is Director of the Shanghai Physiology Institute, President of the Chinese Physiological Society, and Vice President of the Chinese Academy of Sciences. If elected to membership, Dr. Fishman said he will be honored to present Dr. Feng with a certificate when a delegation meets with representatives of the Chinese Physiological Society in September.

Another category of membership on which the Society wishes to place emphasis is Corresponding membership. The APS plays a major role in international science and is involved in the International Union of Physiological Science. An opportunity to relate more firmly to international science is through Corresponding membership, and the Society will benefit enormously from closer association with its foreign colleagues. The qualifications for Corresponding membership are similar to Regular membership, and Dr. Fishman urged APS members to propose their colleagues for Corresponding membership.

A. Appointment of Tellers. Tellers Lee Langley and Arthur Otis were appointed by the President and asked to collect the ballots for the Election of New Members.

B. Election of Members. It was announced by the Executive Secretary-Treasurer, O. E. Reynolds, that all candidates on the ballot were elected to membership. (p. 373).

IV. Actions of Council

In addition to reviewing applications for membership, Council received information on other activities.

A. The Accreditation Council for Continuing Medical Education has approved the reaccreditation of the Society for a six-year period.

B. The Animal Care and Experimentation Committee Chairman, Helene Cecil, presented a status report relating to the possible modification to the Guide for the Care and Use of Laboratory Animals and the relation of these guidelines to the current activities of the Institute of Laboratory Animals Resources (ILAR) to propose modification to the NIH Guide. Three APS members presented testimony at public hearings in Washington, DC, Chicago, IL, and San Francisco, CA. Helene Cecil's written statement is published in *The Physiologist* 26(3): 113–114, 1983. The testimony of Walter Randall and David Ramsay appears in *The Physiologist* 26(5): 273–274, 1983.

C. The Society continues to actively pursue the animal care issues and pending legislation in Congress, which is regularly reported in *The Physiologist*. The use of live animals in research must be preserved, and Dr. Fishman emphasized the need of physiologists to protect the right of animal experimentation under proper controls and conditions.

D. As a result of action taken at the Spring Business Meeting, a proposed resolution against nuclear war and the proliferation of nuclear weapons was distributed to the membership for a mail vote. The response was overwhelmingly in favor of the resolution (1,509 approved and 384 disapproved). The majority of the opponents were of the opinion that the subject was inappropriate for Society action.

E. Dr. Fishman's President-Elect's tour, which took him to England to meet with European physiologists, was twofold. Because of his interest in publications, the desirability of establishing an European office for the *Journal of Applied Physiology* was discussed with the conclusion that such an office was not required. However, a desire to have greater European participation was expressed. Also, discussions were held with representatives of the International Union of Physiological Sciences, which has had a continuing interest in having a publication of its own, and would like to draw upon the Society's expertise. Council is, of course, interested in making a contribution to this endeavor without undoing its own publications.

Of the many other items under consideration, one of significance is long-range plans of the Society. Therefore, a special meeting of Council will be held in November primarily to review the recommendations of the Long-Range Planning Task Force. A complete report of the deliberations of this meeting will be published in the February issue of *The Physiologist*.

With regret, Dr. Fishman announced that Dr. Reynolds informed council of his intention to retire from the position of Executive Secretary-Treasurer in July 1985 after a busy fifteen years. He will not completely retire but will remain to work on the Society's Centennial. A Search Committee is actively seeking a replacement and announcements of the position will be published in the various Society journals early in 1984.

Future Meetings

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

*Campus meeting

V. New Business

A member asked if Council has considered the problem of "no shows" at the APS meetings. This problem is becoming more serious, and he strongly urged the society take a firm stand. Dr. Fishman said he will refer this item to the Program Committee.

With no other business, the meeting was adjourned at 6:30 p.m., August 22, 1983.

John B. West, President-Elect

APS Sections

Cardiovascular

New Fellows

R. H. Freeman, University of Missouri-Columbia
R. K. Hermsmeyer, University of Iowa
M. L. Hess., Medical College of Virginia
A. K. Johnson, University of Iowa
G. S. Malindzak, Jr., Northeastern Ohio Universities
J. C. Parker, University of South Alabama
R. L. Prewitt, Louisiana State University Medical Center, Shreveport
W. J. Stekiel, The Medical College of Wisconsin
F. Urthaler, The University of Alabama in Birmingham

Renal

This is a midyear report of the activities of the Renal Section of the American Physiological Society.

The last meeting of this group was held in the Waldorf Room of the Conrad Hilton Hotel in Chicago, April 14, 1983. Seventy-eight persons attended. The generous contributions of several pharmaceutical companies (American Hoechst, E. R. Squibb, Merck, Sharp & Dohme, and Smith, Kline & French) kept the cost of the annual dinner within reach of all.

Following the business meeting, Bodil Schmidt-Nielsen delivered an entertaining and educational talk entitled "History of Renal Physiology at Mount Desert Island Biological Laboratory," which has been submitted for publication in *The Physiologist* [26(5): 261–266, 1983).

A short business meeting followed the dinner. Donald Marsh (Chairman of the Renal Section) chaired the meeting. Thomas Northrup (Treasurer) gave an informal report of our finances. David Warnock (Program Representative) gave a brief description of plans for the 1985 FASEB symposia and talked about the important role played by Program Representatives of the Renal Section. Since this was the second year of David Warnock's two-year term, an election was held, and Gabriel Navar is our new Program Representative. He will be working with Peter Aronson (Program Representative, elected to a two-year term in 1982).

The next item on the agenda was the presentation of the Award for Excellence in Renal Research. This award, consisting of a certificate prepared by the American Physiological Society and a check for $100, went to Stephen C. Sansom, of the University of Texas School of Medicine, Houston.

Ballots for electing the new officers of the Renal Section were mailed on May 17, with a response deadline of June 15, 1983. The results were as follows: Chairman, Paul Churchill; Secretary, Edward Schneider; Treasurer, Lawrence Sullivan.

Please note: During the 1982 Annual Meeting, it was decided that in order to be eligible for the Annual Award for Excellence in Renal Research, a student's advisor (or a postdoctoral fellow's sponsor) must nominate each person in writing. Regrettably, there were no nominees among those presenting at the Fall Meetings of the American Physiological Society in Honolulu. Please send your nominations to the Chairman (submitting name, place, date and time of the presentation) well in advance of the 1984 FASEB Spring Meetings.

E. G. Schneider, Secretary

APS Journals in the Eighties

In December the terms end for the last two editors who began the reorganization of the research journals of the American Physiological Society in 1976–1977. The Publications Committee thanks these two individuals, **Thomas E. Andreoli** and **F. Eugene Yates**, for their service to the society, their fields, and physiology in general. The Committee also thanks all who have been involved in making this experiment a success: the editors, associate editors, editorial board members, reviewers, authors, and subscribers. Each issue is a record of the renewed vigor of the journals. The increase in the amount published in the journals of the society is phenomenal—from about 8,000 pages in 1976 to 18,000 in 1983. In the past eight years the publishing program has evolved in a strong, orderly manner. At this time, however, the Publications Committee believes that a special review of the program is appropriate. We shall begin such an examination in 1984 and welcome your comments and suggestions.

H. E. Morgan, Chairman
L. E. Farhi
E. E. Windhager

APS Plenary Session

FASEB Spring Meeting
April 4, 1984

Second Annual APS Physiology in Perspective Lecture
Wednesday, April 4, 1984
Clarion Hotel (formerly Stouffers Riverfront)
St. Louis, MO

9:00 A.M. Prostacyclin—From Discovery to the Clinic
J. R. Vane, Director
Group Research and Development
The Wellcome Research Laboratories
Beckenham, Kent, UK

9:45 A.M. APS Business Meeting
A. P. Fishman, President
American Physiological Society

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

Immediately after the lecture, the American Physiological Society will hold its Business Meeting. No scientific sessions other than Dr. Vane's lecture will be scheduled by APS for Wednesday morning. Following the Business Meeting, the remainder of the morning will be left free for visiting the exhibits at the Convention Center.

Membership Status

Regular	4,494
Emeritus	556
Honorary	10
Corresponding	101
Associate	718
Student	265
Total	6,144

NEWLY ELECTED MEMBERS

The following, nominated by Council, were elected to membership in the Society at the Fall Meeting, 1983.

Regular Members

ABERCROMBIE, RONALD F.
DEPT. OF PHYSIOLOGY
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ATLANTA, GA 30322

AVIV, ABRAHAM
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CHILDREN'S HOSPITAL MED. CTR.
300 LONGWOOD AVE.
BOSTON, MA 02115

CHEN, YII-DER IDA
DEPT. MED.-DIV. ENDOCRINOLOGY
RM. S-005 MEDICAL CENTER
STANFORD UNIV.
STANFORD, CA 94305

CHEUNG, JOSEPH Y.
26 HICKORY RD
SUDBURY, MA 01776

CHIN, WILLIAM W.
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MASSACHUSETTS GENERAL HOSPITAL
BOSTON, MA 02114

DHARMSATHAPHORN, KIERTISIN
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UCSD MEDICAL CENTER
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SAN DIEGO, CA 92103

DRUMMOND, WILLA H.
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DEPT. OF PEDIATRICS, JHMHC
GAINESVILLE, FL 32610

DURHAM, JOHN H.
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MT. SINAI SCHOOL OF MEDICINE
100ND ST. AND 5TH AVE.
NEW YORK, NY 10029

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UNIV. S. CALIF. HEAL. SCI. CAM
LOS ANGELES, CA 90033

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MACNICHOL, EDWARD F
MALONEY, PETER C
MALVIN, RICHARD L
MAROTTA, SABATH F
MARSH, JULIAN B
MARSHALL, LESLIE B
MARSHALL, LOUISE H
MARTIN, DUNCAN W
MARTIN, JOSEPH B
MARTIN, RICHARD R
MATHEWS, DONALD K
MAUCK, HENRY P
* MAYERSON, HYMAN S
MCCAA, CONNIE S
MCCAA, ROBERT E
MCCAFFREY, THOMAS V
MCCALEB, MICHAEL L
MCCONN, RITA
MCCROREY, H LAWRENCE
MCDONOUGH, KATHLEEN H
MCFARLAND, WILLARD L
MCMANUS, THOMAS J
MCMURTRY, IVAN F
MCNAMARA, M C
MEAD, JERE
MEIKLE, THOMAS H
MEISS, RICHARD A
MENGEBIER, WILLIAM L
MEYER, DALLAS K
MICHAEL, ERNEST D
MICHAEL, ULRICH F
MIDGETT, RONALD J
MISTRETTA, CHARLOTTE M
MOHRMAN, DAVID E
MOLE, PAUL A
MOORE, JAMES C
MORALES, PEDRO G
MORGAN, DONALD P
MORTIMORE, GLENN E
MOSCHOS, CHRISTOS B
MOSER, KENNETH M
MULLINS, RICHARD J
MULLINS, RICHARD J
MURPHY, RICHARD A
MURRAY, RAYMOND H
NAFTCHI, NOSRAT E
NEUFELD, GORDON R
NEVILLE, J RYAN
NEWTON, JOSEPH E O
NGAI, SHIH H
NICOLL, CHARLES S
NIEMETZ, JULIAN
NIGHTINGALE, THOMAS E
NIRDLINGER, EDWIN L
NORRIS, JEANNE
NYE, ROBERT E
ODELL-SMITH, ROBERTA M
OKEEFE, DENNIS D
OLSSON, RAY A
ONEILL, JOHN T
ORDWAY, GEORGE A.
OTIS, ARTHUR B

*Emeritus Member; #Student Member.

OZA, NARENDRA B
PANG, LEILA MEI
PAPPENHEIMER, JOHN R
PARADISE, NORMAN F
PARKER, HAROLD R
PATTERSON, JOHN W
PENHOS, JUAN C
PENNOCK, BERNARD E
PERKS, ANTHONY M
PETERSON, BARRY T
PEYTON, MARVIN D
PICK, RUTH
PIERSON, RICHARD N
PINCUS, IRWIN J
PINSHOW, BERRY
PITKOW, HOWARD S
PIWONKA, ROBERT W
PLISHKER, GORDON A
POLGAR, GEORGE
POTTER, DAVID D
POWELL, FRANK L
PREISIG, PATRICIA A
PRIVITERA, C A
PURI, PRITPAL S
QUAY, WILBUR B
RALL, JACK A
RALL, WILFRID
RALPH, CHARLES L
RALSTON, HENRY J
RANCK, JAMES B
REDWOOD, WILLIAM R
REEVES, JOHN T
REGEN, DAVID M
RENKIN, EUGENE M
* RENNICK, BARBARA R
REYNOLDS, ORR E
RHOADS, JONATHAN E
RHODES, JAMES B
RICHARDSON, DANIEL R
RICHARDSON, DAVID W
RITCHIE, J MURDOCH
RITMAN, ERIK L
ROBERTSHAW, DAVID
ROBERTSON, JAMES S
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ROHEIM, PAUL S
ROLF, LESTER L
ROMANO, FRED D
ROMANOFF, ELIJAH B
ROSOMOFF, HUBERT L
ROSS, JAMES N
ROYCE, PAUL C
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RUIZ-CERETTI, ELENA
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RUTLEDGE, LESTER T
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SATO, TOSHIRO
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SCHAUB, ROBERT G
SCHEEL, KONRAD W
SCHIFFRIN, MILTON J
SCHMID-SCHOENBEIN, GEERT W
SCHRAER, HARALD
SCHRAMM, LAWRENCE P
SCHULTZ, HAROLD D
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SEARLE, GORDON W
SECHZER, JERI A
SELKURT, EWALD E
SETLER, PAULETTE E
SEXTON, ALAN W
SHADE, ROBERT E
SHAFFER, AARON B
SHAIN, WILLIAM G
SHARP, JOHN T
SHEARIN, NANCY L
SHELLABARGER, CLAIRE J
SHEPHERD, A P
SHORE, VIRGIE G
SIEGMAN, MARION J
SILVA, PATRICIO
SIMON, ECKHART H
SIMPSON, DAVID P
SIMPSON, JOHN W
SINTETOS, ANTHONY L
SLEATOR, WILLIAM W
SMALDONE, GERALD C
SMITH, LAWTON H
SMITH, O L K
SMITH, ORVILLE A
SMITH, THOMAS G
SMUD, ROBERTO
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SOBIN, SIDNEY S
SOLARO, R JOHN
SONDEEN, JILL L
SONNENSCHEIN, RALPH R
SPARKS, HARVEY V
SPERELAKIS, NICK
SPRING, KENNETH R
ST JOHN, WALTER M
STAHLMAN, MILDRED T
STAINSBY, WENDELL N
STARR, ISAAC
STAUB, NORMAN C
STEWART, JENNIFER K
STINNETT, HENRY O
STOKES, JOHN B
STOLZENBERG, SIDNEY J
STONE, DANA
STONE, DANIEL J
STOTHERT, JOSEPH C
STRAND, FLEUR L
STROMBECK, DONALD R
STRUMWASSER, FELIX
SUGA, HIROYUKI
SULLIVAN, STUART F
SULLIVAN, W JAMES
SUNDBERG, DAVID K
SYLVESTER, J T
SZWED, JAMES J
TAKADA, AKIKAZU
TAKADA, YUMIKO
TAKISHIMA, TAMOTSU
TANNER, GEORGE A
TAPPER, DANIEL N
TAPPER, EDWARD
TAUB, EDWARD
TAYLOR, JOHN M
TAYLOR, REGINALD M
TENNEY, STEPHEN M
TEPPERMAN, HELEN M
TEPPERMAN, JAY
TESCHAN, PAUL E
THOMAS, LYELL J
THOMPSON, LARRY L
THOMSON, ASHLEY E
THRASHER, TERRY N
THURBER, ROBERT E
TIETZ, WILLIAM J
TORRES, JOSEPH C
TRAPANI, IGNATIUS L
TRAVIS, DAVID M
TRIANTAPHYLLOPOULOS, D C
TRIPPENBACH, TERESA A
TROUTH, C OVID C
TUCKER, H ALLEN
TYLER, WALTER S
TZANKOFF, STEPHEN P
ULRICH, FRANK
VALTIN, HEINZ
VAN HUSS, WAYNE D
VAN LIEW, HUGH D
VAN MIDDLESWORTH, LESTER
VANATTA, JOHN C
VEICSTEINAS, ARSENIO
VELARDO, JOSEPH T
VICK, ROBERT L
VILLARREAL, HERMAN
VOELKEL, NORBERT F
VOROSMARTI, JAMES
WALTER, DONALD O
WANG, BIN CHING
WANGENSTEEN, O DOUGLAS
WATKINS, CLYDE A
WEBBER, CHARLES L
WEBSTER, PAUL D
WEINSTEIN, ALAN M
WEIR, EDWARD K
WELCH, BILLY E
WELCH, HUGH G
WENGER, CHRISTIAN B
WEST, JOHN B
WHEDON, G DONALD
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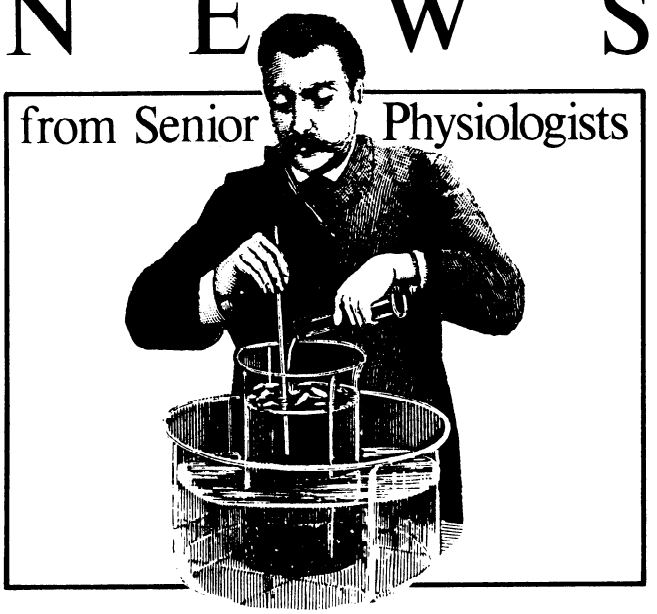
NEWS from Senior Physiologists



Bill Kubicek to E. B. Brown:

I retired from the University of Minnesota Medical School, effective January 1, 1982. I reached the age of 70 on January 26, 1983. Retirement has been as interesting as I wish to make it and occasionally is mixed with some boredom. I have been a long-time activist in the Democratic Farmer-Labor Party in Minnesota. This type of activity naturally leads to an interest in local, national, and international political events. For many years I have been interested in the problems of world peace and the frightening escalation in nuclear armaments. About the time of your letter, I received the request from Orr Reynolds to cast a vote, yes or no, regarding a proposal for a *verifiable* nuclear arms freeze. I voted yes on this proposal. However, as is obvious, the word verifiable is the real problem in this proposal. We tend to blame all of the difficulty on the Soviet Union regarding the word verifiable. However, if one wished to verify anything that our President, or anyone else, has said about our own nuclear armaments, it would probably be dismissed as being classified information. The Soviet Union is much more difficult to deal with.

In my increased amount of spare time, I have been reading about the years and events preceding World War II. It does seem that the Allied powers were in a weak position compared with the German buildup of armaments. This probably did encourage the conquests by Hitler's Nazi Germany. Therefore, the argument that we must be strong to stand up to the Soviet Union does seem valid. It is interesting that practically all of the protests in this country and elsewhere in the Free World, along with demonstrations, are based on "hindsight." Even before the nuclear bombs were dropped on Hiroshima and Nagasaki, many of the scientists involved in the development and production of these horrible weapons had serious reservations about their use. Almost immediately following the use of these bombs, many of the scientists and others were expressing grave reservations about the future of the world. However, it has taken nearly 40 years since the dropping of these bombs for there to be widespread public protests. When both the United States and the Soviet Union possess nuclear destructive power in mind-boggling dimensions with most of the missles already in place, it seems an exercise in futility to be voting on yes or no for a verifiable nuclear freeze. This is a one-sided discussion, since people in the Soviet Union are obviously not given the same options for a vote.

This brings me to a suggestion for you and your colleagues. At the next International Physiological Congress, let's have a special one-day symposium for the purpose of discussing world peace with the speakers equally divided between the Free World and the Soviet Union. The obvious criticism is that the Free World personnel would be selected by their colleagues and not by the US government, whereas the Soviet delegates would probably be selected by some division of the Soviet government and would be restrained in their remarks. If one looks at the problem of world peace, there will have to be some means to communicate with the Soviet Union directly. If this idea would catch on with other scientists and professional groups having access across the Soviet boundaries, it could possibly yield some useful progress toward world peace. There are, of course, many arguments pro and con about this type of activity. One thing seems certain—in the event of an all-out worldwide nuclear holocaust, there will be no opportunity for "hindsight" protestations. In view of these enormous problems, it is incredible that the President of the United States and the President of the Soviet Union have never met, much less to meet and discuss the situation.

I have become interested in the term "arms race." I looked in the dictionary for a more learned definition of the word race. Much to my surprise, there are quite a number of definitions. The one that may be most appropriate is as follows: "a contest involving progress toward a goal." I see no goal in the procedure that we call an "arms race." A mathematician would probably describe it as a continuous escalation on both sides into infinity or certainly into eternity.

4180 Edmund Blvd.
Minneapolis, MN 55406

Jui S. Lee to E. B.:

I was very happy to receive your recent letter. You are right—I am 70 this year and qualified for Social Security even if I make millions of dollars. I will retire in the summer of 1984, but if a National Institutes of Health grant is available, I would like to do some more work in the area of intestinal absorption of water, especially the role of the lymphatic system. My wife Chung has retired and will visit mainland China this year. I enjoy reading the news in *The Physiologist* very much indeed. Right now I am continuing to work as usual. I may have some definite plans by the end of next year and I will write to you then. Thank you and your colleagues for caring about fellow seniors.

Department of Physiology
University of Minnesota Medical School
Minneapolis, MN

Sid Harris to E. B.:

I want to thank you for the beautiful Beaumont House card in remembrance of my 80th birthday. It is nice to be remembered. Your card also reminded me

that I have not responded to invitations that I received from you and Hy Mayerson to write some autobiographic material for the archives of the Society. Now that I am 80, it seems that the time has come to do it, although it is more pleasant to participate in foreign scientific congresses, give slide shows in Carmel afterward, and study the French language and literature. But I shall also give attention to my own history. My wife and I are planning a visit to Paris and a barge cruise in Burgundy this year.

P. O. Box 4145
Carmel, CA 93921

Al Behnke to E. B.:

Thank you very much for the 80th remembrance birthday card and your discerning comments. During the course of various military stresses, the "Strong Back" syndrome has kept me going, but now I am close to or in the "One Hoss Shay" dilemma. Over the years I have kept close to Bruce Dill in stamina, but I doubt that it will carry me to his + 11 year longevity.

2241 Sacramento St.
San Francisco, CA 94115

André Cournand to Arthur B. Otis:

In the past years I have informed some members of the council of senior physiologists of my activities, which have been multiple since my retirement. I have published on various subjects such as: scientific responsibility, "What is a Scientist," "The Code of the Scientist," "The Role of Science in Society," obituaries, particularly after the death of Dickinson Richards, and the history of circulation and cardiac catheterization. At the present time I am completing an autobiography—purely intellectual and cultural—emphasizing my activities after retirement and the factors which allow me to maintain an active life. I still travel between the US, my adopted country, and France and Europe where I lived for 30 years before transplanting myself to the US. I spend my time while in the US between New York and the Berkshires. I have no words of wisdom to pass to the younger generation, only the desire to dissipate in their minds the notion that old age is a dead end.

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

Paul D. Sturkie to Arthur:

I retired from Rutgers University in 1977 but still maintain an office in the Dept. of Animal Science, where I work from July to January. The remaining 6 months are spent at Hilton Head Island, SC, where I enjoy fishing and taking part in various community affairs. I have written a book *"Basic Physiology,"* Springer-Verlag (1981), and am now working on the fourth edition of *"Avian Physiology,"* first published in 1954. My wife and I have also found time for travel, to Africa, China and Europe, and I attend Federation Meetings about every two years.

Rutgers University
East Brunswick, NJ 08816

Frank H. Johnson to Arthur:

It should be of some interest to mention that I have just completed the main portion of the manuscript of a new book intended to be a popular version of the nature and ramifications of bioluminescence in the living world. This is a project I've had in mind to do for some years, and I have immensely enjoyed doing it without the well-known pressure of simultaneously meeting teaching and other professional responsibilities. The tentative title is *"Naturally Lit-up,"* and it is abundantly illustrated with color photos of, I believe, exceptional interest, which show a few generally familiar, as well as a number of unfamiliar, species of luminescent organisms as revealed by ordinary light and also by their own light.

Department of Biology
Princeton University
Princeton, NJ 08544

Thomas K. Cureton to Arthur:

I am semiretired but maintain an office at the University of Illinois, where I consult, do some research work, write. I also keep up a hard exercise program here. I lead some Physical Fitness Clinics, and give occasional lectures about the University and its environs. I write a good deal for the Bulletins of the President's Council on Physical Fitness and Sports and the Governor of Illinois' Bulletin, Council on Health and Fitness, and am Series Editor of the *Encyclopedia of Physical Education, Fitness and Sports,* sponsored by the American Alliance for Health, Physical Education, Recreation and Dance. We have published three volumes and now are finishing up the fourth. I organized the first Physical Fitness Research Laboratory, 1944, at the University of Illinois, directed it for 25 years, and graduated 88 Ph.D.'s who concentrated in this area. Many of them are now leading figures in Sports Medicine, Cardiac Rehabilitation, and Physical Fitness work in the USA and Canada.

501 E. Washington St.
Urbana, IL 61801

Hurley L. Motley to Arthur:

I retired after some 25 years as Professor of Medicine and Director of the Cardio-Respiratory Laboratory at the University of Southern California School of Medicine. Environmental pollution is an important problem in Southern California. I was chairman of the Los Angeles County Environmental Pollution District and chairman of the Los Angeles County Medical Society Environmental Committee for 7 years. Between 1961 and 1965 I made three trips to the far East as a consultant for the Surgeon General of the Army in regards to the so-called "Tokyo-Yokohoma Asthma." Although retired I do occasionally consult on pulmonary disability cases. In retirement my wife (Cornealia Grace Ellis) and I have season tickets and root for the Dodgers. We can enjoy baseball now that we have time that we did not have before. A cruise trip on the inside waterway from Vancouver to Alaska in 1981 was very enjoyable.

2003 N. Serrano Ave.
Los Angeles, CA 90027

Anna Goldfeder to Arthur:

I am pleased to inform you that I am continuing my research activities on a full scale, and sincerely hope to be able to obtain interesting and useful results. As you might know, a conference on Cell Kinetics, Cell Structure, and Radiotherapy was organized by the New York Academy of Sciences in my honor.

Anna Goldfeder Laboratory of
Cancer and Radiobiological Research
New York University
New York, NY 10003

Mason Guest to Bob Alexander:

I have a half-time appointment at the University of Texas Medical Branch in Galveston. I continue to teach physiology to medical and graduate students. Also I am "Chief" of Hematology at the Shriners Burns Institute. My laboratory at the Institute handles the coagulation and fibrinolytic enzyme assays for the Shriners Burns Hospital. In addition, I am engaged in research. I am using cinematographic techniques, including high-speed photography, to record and evaluate the changes in microvessel flow following burn trauma. These studies are interdigitated with experimental exploration of the role of clotting and fibrinolytic enzymes in the sequellae following trauma, especially heat trauma to the integument. I plan to attend a meeting in Denmark to present observations and data relating to the fibrinolytic enzyme system in burned patients.

Days are not long enough to participate in all activities in which I am interested. I have been much involved with environmental problems. A number of years ago I organized a Sierra Club Regional Group in Galveston County. Our group is active in opposing poorly planned, environmentally destructive developments in Galveston and adjacent counties. We also promote various types of nature-related outings. I spend considerable time and effort in gardening. This is an activity I greatly enjoy. The major drawback to gardening in Galveston is high night temperature during the summer months. Most plants prefer a cooling-off period at night.

Since retiring from the chairmanship of physiology at UTMB in the middle seventies I have found sufficient time to participte in activities involving the arts and crafts. I have taken courses at the local college in various forms of art, but mostly in ceramics. Recently I have dabbled in ceramic sculpture.

Shriners Burns Institute
Galveston, TX 77550

Hy Mayerson to Bob:

Several years ago I lost the small toe on my left foot because of poor circulation in the leg. The surgeons, former students, had a field day, but they did succeed in getting enough circulation in the leg to save it. It talks to me, of course, but we have established a reasonably good relationship. I hobble around the garden, have lunch with the "the boys," and get around reasonably well. We've done a fair amount of traveling to see friends here and there. I resigned from the Tulane School of Medicine in 1965 and spent the next 10 years helping run a 570-bed hospital, Touro Infirmary. I helped rejuvenate the School of Nursing, one of the oldest in the south, beefed up the teaching and research, and in general had a good time. It took me out of the laboratory, and while I tried to keep with the new developments. I wasn't too successful—too much new vocabulary. I enjoy *The Physiologist*, which continues to be excellent, but spend much of my time reading novels and so forth, which I didn't have time to do earlier. I hope you are enjoying being on the Senior Physiologists Committee as much as I did. I do miss hearing from the small member of survivors of my generation.

1140 Seventh St.
New Orleans, LA 70115

Horace Davenport to Edward Adolph:

Thanks for your greetings. We had a small reunion here recently when Hal Davis was given an honorary degree by the University of Michigan ten days before his 87th birthday. I am retired in the sense that the University doesn't pay me anymore, but I am in my office before 8 A.M. I work on a major historical project until I am completely exhausted. I am encouraged by the fact that a reviewer in the *Journal of the History of Medicine* said that my *Physiology 1850–1923: The View from Michigan* was a "major contribution to the history of American medicine and medical education."

1050 Wall St., 7D
Ann Arbor, MI 48105

William M. Hart to Louise Marshall:

I have just returned to the office after a rather extended trip to find your kind letter which takes note of my birthday and raises the question of my current activities. I am pleased to report that I am still working full time in the teaching of Ophthalmology. We have twelve residents in training who keep me challenged and continually busy. My research foundation is still going strong, although I have no direct administrative role in it since I turned everything over to my successor four years ago. It does occur to me from time to time that it would be normal to retire. However, I have no immediate plans to do so as long as I enjoy the current approval of my peers and students. No doubt they will have subtle ways of letting me know when the time has come. It is a pleasure to hear from you and to receive greetings from APS. You may be sure that I will be pleased to hear from you at any time.

Div. of Ophthalmology
The University of Mississippi
Medical Center
Jackson, MS 39216

Thomas C. Sherwood's wife to Louise:

This birthday greeting was a source of great pleasure to my husband. He has recently been very ill, and this remembrance from a group which he holds in high esteem was most meaningful, so please remember him on his next birthday, his 80th.

231 Harrison Street
Lake Charles, IA 70601

Leslie A. Chambers to Louise:

It is pleasant to receive evidence of interest in passing birth dates. Thus far health and other circumstances have favored my remaining active in the School of Public Health, University of Texas Health Science Center at Houston, although at half the pace and half the pay which would accrue to a younger person. So long as senility avoids me I plan to continue much as before. The letters from senior members in *The Physiologist* continue to be of great interest, since, in many cases, they provide the only continuing information as to old associates and acquaintances.

The University of Texas
Health Science Center at Houston
P.O. Box 20186
Houston, TX 77025

Hsiang-Tung Chan to Louise:

Thank you very much for your sending me the letter representing the Committee of Senior Physiologists of APS and particularly for your handwritten addendum at the end of the letter.

Shanghai Brain Research Institute
Academia Sinica
319 Yo-Yang Rd.
Shanghai, China

Evelyn Anderson (Haymaker) to Louise:

It was lovely to have your note. Unfortunately I can neither read nor write, but our daughter, Evie, is doing this for me. For the last year I have been losing my sight and cannot keep adequately in touch. Please remember me to any of my old friends whom you have contact with.

16181 Greenwood La.
Los Gatos, CA 95030

Deaths Reported Since the 1983 Spring Meeting

Ahlquist, R. P., Augusta, GA (4/20/83
Armstrong, H. G., San Antonio, TX (3/24/83)
Bartter, F. C., San Antonio, TX (5/5/83)
Bender, M. B., New York, NY (1/23/83)
Cattell, McK., New York, NY (2/83)
DeGraff, A. C., Newtown, CT (5/25/83)
Dotti, L. B., Brick Town, NJ (11/19/82)
Dragstedt, C. A., Shaumberg, IL (3/8/83)
Fam, W. M., Washington, DC (3/31/83)
Field, J., Pacific Palisades, CA (5/17/83)
Gorman, A. L. F., Boston, MA (6/82)
Jefferson, N. C., Chicago, IL (3/21/83)
Maher, J. T., Natick, MA (8/15/83)
Merskey, C., Mamaroneck, NY (11/10/82)
Redfield, A. C., Woods Hole, MA (3/17/83)
Richards, R. K., Los Altos, CA (1/30/83)
Saul, L. J., Media, PA (3/10/83)
Selye, H., Montreal, Canada (10/16/82)
Visscher, M. B., Minneapolis, MN (5/1/83)

THE PHYSIOLOGY TEACHER

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Neurotoxins as Tools for Physiological Investigation

L. FREIRE-MAIA
Departamento de Fisiologia e Biofísica
Instituto de Ciencias Biológicas
Universidade Federal de Minas Gerais
Belo Horizonte, Brasil

In the past, the study of venoms was primarily motivated by medical considerations. An exception was the French physiologist Claude Bernard, who studied the physiological aspects of curare intoxication.

A great scientific interest in venoms has arisen during the last two decades because of the demonstration that very small doses of purified toxins could modify organs and structures in a reliable and predictable way. Thus the toxins purified from animal, plant, and microbial venoms have been used successfully as tools in the investigation of complex physiological processes. Two important discoveries were made by Narahashi *et al.* (50), who showed that tetrodotoxin extracted from puffer fish venom blocked the sodium permeability in lobster giant axons, and by Lee and associates (see review in Ref. 45), who showed that α-bungarotoxin extracted from the venom of the snake *Bungarus multicinctus* has a postsynaptic action, binding specifically and irreversibly to the acetylcholine receptors in mammalian muscle.

In 1971 I submitted an abstract to the Congress of the International Union of Physiological Sciences, held in Munich. In the abstract I called the attention of physiologists to one of these toxins, the tityustoxin, purified from the venom of the scorpion *Tityus serrulatus*. The title of the abstract published in the Proceedings of the Congress was "Scorpion toxin, an important tool for physiological research" (30).

Tutorial Lecture, Fall Meeting of the American Physiological Society, 1982.

A large number of papers have appeared on scorpion toxins and other neurotoxins as tools for physiological investigation in the last decade. Toxins are substances that occur in nature, produced by animals, plants, or bacteria, exogenous to the victims and presenting adverse or deleterious effects when innoculated (64).

The action of a venom or a purified toxin on an organism depends on a number of variables, such as the route of administration, asborption, distribution, passage across a succession of membranes, accumulation at receptor site(s), release of chemical mediators, body weight and sex of the test animal, metabolism, and excretion (60).

Toxins may be classified in a simple way as animal (e.g., scorpion toxin), plant (e.g., veratridine), and microbial toxins (e.g., botulinum toxin). On the other hand, **neurotoxins** could be classified as toxins with action on the nerve fiber (tetrodotoxin and saxitoxin), toxins with presynaptic action (β-bungarotoxin, black widow spider venom, scorpion toxin), toxins with postsynaptic action: (α-bungarotoxin, cobra toxins, crotoxin, histrionicotoxin) and toxins with central excitatory action (apamin, physalaemin) (65).

Since, it is impossible to cover in this tutorial lecture all kinds of toxins presenting such different mechanisms of action, I will only discuss the effects of some neurotoxins that activate or delay inactivation of sodium channels (such as the scorpion toxin veratridine, batrachotoxin, and aconitine) or that inhibit sodium channels (such as tetrodotoxin and saxitoxin) with emphasis on research done in our laboratory using a toxin purified from the venom of the Brazilian scorpion *Tityus serrulatus*.

Chemical Nature of Some Toxins That Act on Sodium Channels

Polypeptide Toxins

For example, scorpion toxins are composed of a single polypeptide chain cross-linked by four disulfide bridges and have a molecular weight of about 7,000 (57).

Lipid-Soluble Toxins

Veratrum is a mixture of alkaloids of plant origin, from which the pure alkaloid veratridine was isolated. Batrachotoxin was isolated from the skin venom of the South American frog *Phyllobates aurataenia*. Aconitine is of plant origin (*Aconitum napellus*).

Heterocyclic Guanidines

Tetrodotoxin (TTX) is a toxin of low molecular weight (319) found in puffer fishes and in certain amphibian species of the family Salamandridae (e.g., *Taricha torosa*) and saxitoxin (STX) is produced by unicellular protistan of the genus *Gonyaulax*. Figure 1 shows the chemical structure of scorpion toxin, veratridine and tetrodotoxin.

Release of Acetylcholine from Auerbach Plexus and Brain Evoked by Neurotoxins

A substance not pharmacologically distinguishable from acetylcholine was released when guinea pig strips were incubated, in vitro, with scorpion venom (19). On the other hand, incubation of rat brain slices with scorpion toxin was also followed by the release of acetylcholine. This release was dependent on the presence of Na^+ and Ca_7^+ in the incubation fluid, independent of K^+ concentration, and totally blocked by TTX (35). Therefore, the release of acetylcholine from brain evoked by scorpion toxin depends on the stimulation of sodium channels (Figure 2).

To study further the relations between the effects of scorpion toxin and tetrodotoxin, experiments were carried out on isolated rat ileum. Scorpion toxin was without effect when added to the organ bath with a piece of rat ileum immersed in Tyrode solution containing TTX. However, after the Tyrode solution (plus TTX) was washed out and replaced by a solution without TTX, a strong contraction of the preparation was recorded. Addition of TTX to the bath brought the muscle back close to its original tone. The contraction recorded after the second washing was abolished, in part, by atropine. The postsynaptic action of acetylcholine (ACh) was not abolished by TTX. These experiments indicate that the effect of the scorpion toxin was presynaptic (Figure 3).

Experiments were then conducted to study the effect of TTX on the release of ACh from slices of rat and guinea pig ilea incubated with purified scorpion toxin. The experiments showed that TTX prevented the release of ACh produced by scorpion toxin; however, after washing the slices with the incubation fluid and reincubation (without further addition of scorpion toxin or TTX), a large increase in the amount of released ACh was measured. Addition of TTX to a medium containing slices of rat or guinea pig ilea did not change the amount of ACh spontaneously released after 30 min of incubation (Figure 4).

The results of our experiments seem to indicate that TTX prevents the effects of scorpion toxin but does not prevent its binding to the nerve membrane. We postulate, then, that scorpion toxin acts at least on two different sites of the nerve membrane, one of which is presumably the TTX-sensitive sodium channel. Our data were presented at a meeting held in Tokyo in September 1974; the abstract was published in 1975; and the full paper appeared in 1976 (32, 33).

Figure 5 is taken from a paper by Hill (38) and shows the blockade of sodium channels by TTX and STX. Our results seem to indicate, therefore, that scorpion toxin binds to a site different from the TTX-binding site, but its physiological effect (e.g., release of ACh) depends on an action on sodium-conducting pore of the channel.

About the same time, Catterall (12) reached a similar conclusion on the binding sites of scorpion toxin and

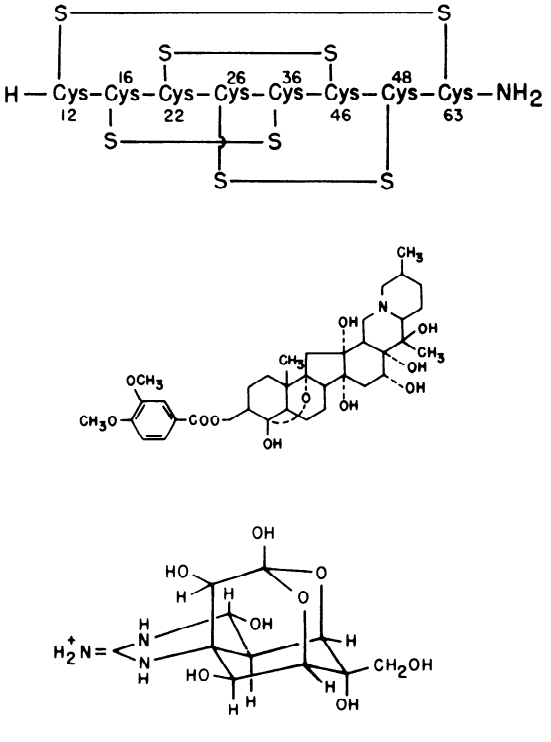

Figure 1
From top to bottom, chemical structures of scorpion toxin (Ref. 57), veratridine, and tetrodotoxin.

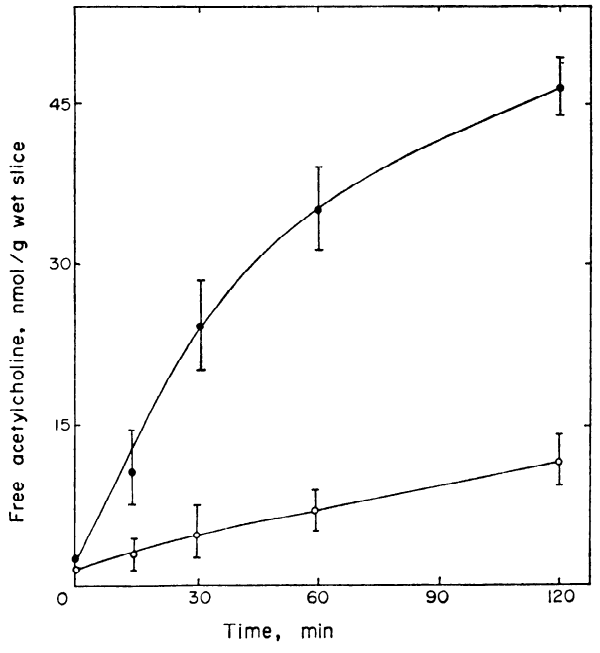

Figure 2
Influence of incubation time on release of acetylcholine from slices of rat cerebral cortex induced by scorpion toxin. Incubation was carried out in Tyrode solution containing physostigmine at 37°C and pH 7.4. o——o, Without toxin; •——•, with toxin (2.0 μM). Points represents means ± SD of 3 experiments. Release of acetylcholine evoked by scorpion toxin was blocked by tetrodotoxin (Ref. 35).

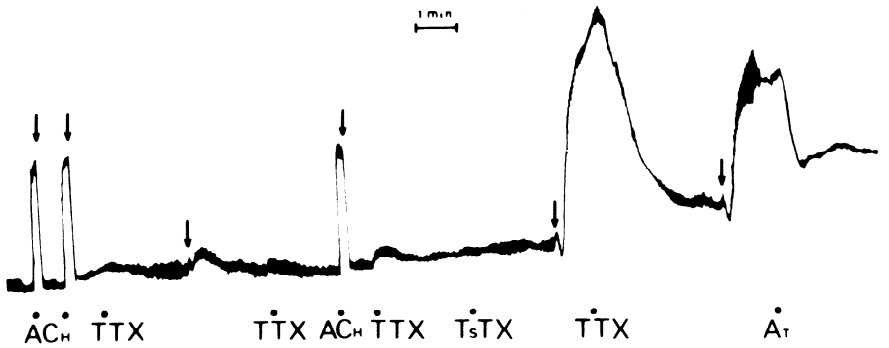

Figure 3
Rat ileum preparation suspended in 10 ml aerated Tyrode solution at 35°C. Acetylcholine (ACh), 1×10^{-7} M; tetrodotoxin (TTX), 2×10^{-7} M; scorpion toxin (TsTX), 5 μg/ml; atropine (At), 1×10^{-7} M. At *arrows*, preparation was rinsed once (Ref. 33).

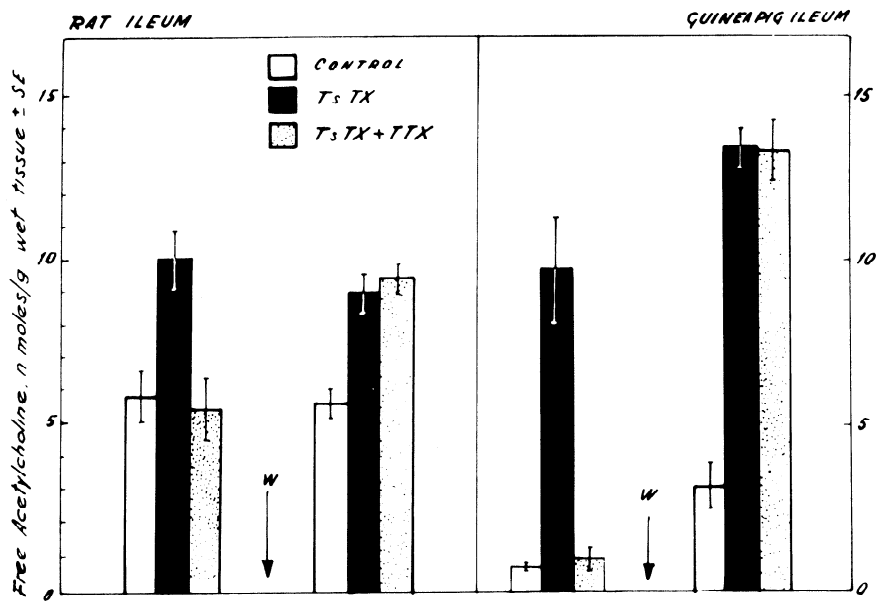

Figure 4
Effect of tetrodotoxin (TTX, 5×10^{-7} M) on release of acetylcholine from rat and guinea pig ilea induced by scorpion toxin (TsTX, 2×10^{-6} M). Mean values ± SE for 6 experiments are presented. Incubation was carried out for 30 min in Tyrode solution containing physostigmine at 37°C and pH 7.4. *Arrows* indicate that slices were washed 3 times with incubation fluid and reincubated for 30 min without further addition of TsTX or TTX (Ref. 33).

TTX. It is interesting to note that Catterall worked with a crude scorpion venom of different species and another preparation consisting of electrically excitable neuroblastoma cells. Moreover, his experiments (13) suggested the existence of three functionally separable components of the action potential Na^+ ionophore; i.e., one binds scorpion toxin, one binds the alkaloids neurotoxins veratridine, aconitine, and batrachotoxin[1], and the last binds TTX. Two of these sites are regulatory, binding activating neurotoxins (e.g., veratridine and scorpion toxin), and interact allosterically, controlling the activity of a third site, which transports sodium ions and is blocked by TTX (Figure 6, Table 1).

These experiments of Catterall's group and ours therefore indicate that scorpion toxin binds to a site other than the TTX-binding site, but the physiological effects of scorpion toxin, such as release of ACh, depend on the activation of a second site in the sodium channel complex. On the other hand, experiments performed with phospholipase C indicate that intact phospholipids of sarcolemmal membranes may be essential for the functioning of the sodium channel (40, 58).

Experiments on Skeletal Muscle

Several authors have studied the effects of crude scorpion venom on skeletal muscle (for bibliography see Ref. 66). Moreover, experiments with pure scorpion toxin have shown depolarization of pre- and postsynaptic membranes by an increase in sodium permeability. It is likely that the postsynaptic site of action is the sarcolemmal membrane, where scorpion toxin prolongs the active phase of muscle contraction. Presynaptically, the toxin has two sites of action; i.e., it depolarizes the nerve terminal, facilitating the release of transmitter, and acts at the membrane of the unmyelinated nerve terminal arborization, where it prolongs the sodium current giving rise to repetitive response to single shocks applied to the nerve (66).

Two Types of Scorpion Toxin Receptor Sites?

Koppenhöfer and Schmidt (42) and Narahashi et al. (51) showed that the effects of *Leiurus* and *Buthus* scorpion venoms were explained by a prolongation of sodium inactivation, whereas Cahalan (10) showed that *Centruroides* scorpion venom induced the appearance of a new sodium current.

According to Cahalan (10) the venoms from scorpions of the New World (e.g., *Centruroides*) induce the appearance of a new sodium current, whereas the venoms from scorpions of the Old World (e.g., *Buthus*) delay the sodium inactivation. In a recent paper, Couraud et al. (17) have shown that there are two types of scorpion toxin receptor sites in the rat brain synaptosomes, one related to the activation and the other to the inactivation of the action potential sodium channel. The toxins, which activate the sodium channels, were ob-

[1]Previous experiments of Albuquerque et al. (2) have shown that batrachotoxin and tetrodotoxin bind to different receptor sites in the sodium channel of the squid giant axon.

tained from scorpions of the New World (*Centruroides*) and were called β-scorpion toxins (β-ScTX), whereas the toxins that slow down inactivation were obtained from scorpions of the Old World (*Androctonus, Buthus* or *Leiurus* genera) and were called α-scorpion toxins (α-ScTX). The binding sites of a α- and β-ScTX are different. These recent experiments seem to give support to the hypothesis of Cahalan (10) that the neurotoxins from New World scorpions present a mechanism of action different from those of the Old World.

Based on the experiments described up to now, it could be concluded that in the sodium channel complex there are at least four different binding sites for α- and β-ScTX, veratridine, and TTX.

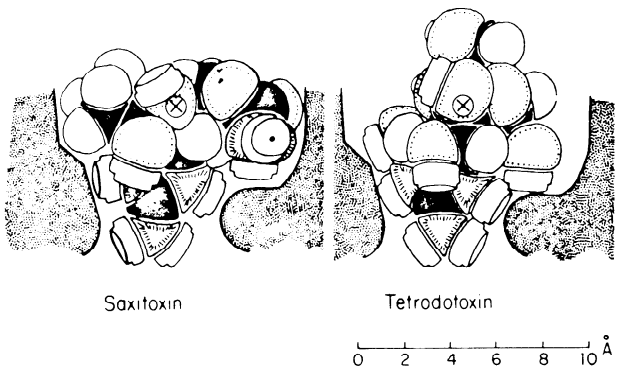

Figure 5
Hypothetical interactions between saxitoxin and tetrodotoxin molecules and sodium channel. Observe that part of channel where neurotoxins stick is the narrow ionic selectivity filter (Ref. 38).

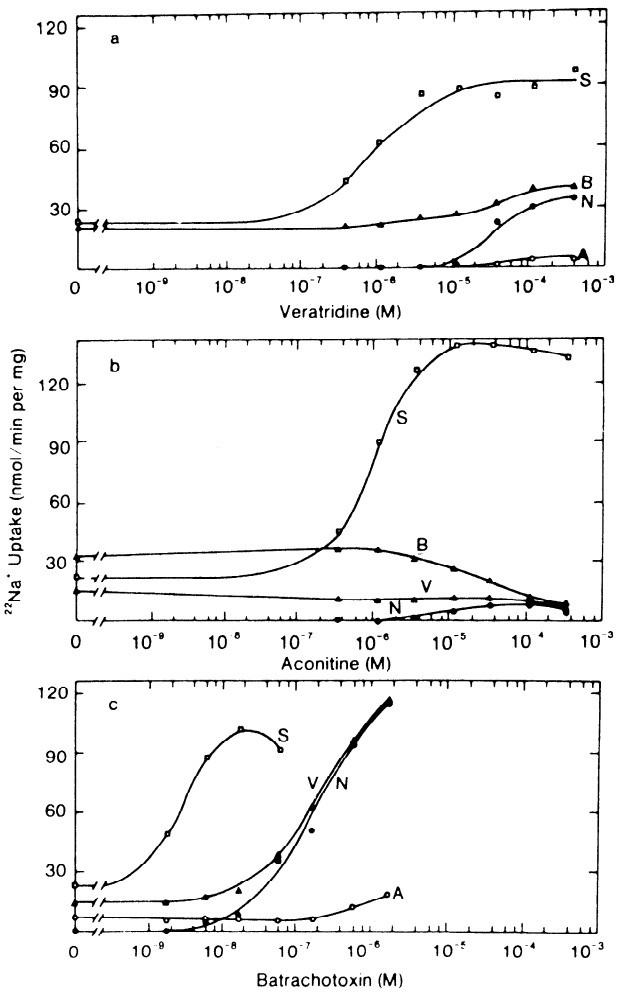

Figure 6
Activation of the action potential sodium channel by alkaloids neurotoxins veratridine (V), aconitine (A), and batrachotoxin (B) and its potentiation by scorpion toxin (S) in monolayer culture of neuroblastoma cells. Each curve N was obtained following incubation of cells with a single alkaloid neurotoxin. Uptake evoked by all neurotoxins was inhibited by tetrodotoxin (Ref. 12).

Release of Catecholamines by Neurotoxins

Adrenals

Injections of scorpion venom in rats led to a depletion of adrenal gland catecholamines, which was prevented by denervation of the adrenal (37).

Rat spleen

It is well known that the spleen has a totally sympathetic innervation (24). For this reason we thought it would be worthwhile to study the effects of scorpion toxin on spleen strips.

The contraction of the isolated rat spleen strip induced by scorpion toxin is a slow type, starting after a latent interval from 30 to 60 s, thereby differing from that produced by catecholamines. The contraction evoked by scorpion toxin was prevented by phenoxybenzamine, reserpine, and TTX. As the contraction induced by norepinephrine was not prevented or abolished by TTX, it is probable that the absence of contraction following scorpion toxin is due to a presynaptic action of TTX. On the other hand, the sustained contraction induced by scorpion toxin seems to be due to a continuous release of catecholamines from postganglionic nerve endings, since the effect is abolished by TTX (31, 33).

Heart

Scorpion toxin releases [^{3}H] norepinephrine from guinea pig atria in a manner similar to that evoked by nerve stimulation, because it is calcium dependent (49). Further experiments with a different scorpion toxin have confirmed the release of [^{3}H] norepinephrine, whereas the main metabolite formed was the [^{3}H] deaminated glycol (44). Another interesting action of the scorpion toxin is to enhance transmitter overflow elicited by nerve stimulation through a prejunctional effect (44).

Table 1
Properties of Neurotoxin Receptor Sites Associated with Sodium Channels

Toxin Receptor Site	Ligands	Physiological Effect
I	Tetrodotoxin Saxitoxin	Inhibit ion transport
II	Veratridine Batrachotoxin Aconitine	Alter activation and inactivation; cause persistent activation
III	Scorpion toxin	Inhibit inactivation; enhance persistent activation by veratridine, batrachotoxin, and aconitine

Modified from Ref. 13

Degranulation of Vesicles

Many venoms degranulate vesicles inside nerve fibers. Some do not act through activation of sodium channels, such as the black widow spider venom (48) and β-bungarotoxin (14), whereas others, like scorpion toxin, produce their effects through an increase in sodium permeability.

Incubation of slices of rat ileum with scorpion toxin led to a decrease in the number of granular (dense) vesicles and a simultaneous increase in the number of agranular (clear) vesicles in the Auerbach plexus, as revealed by electron microscopy (Figure 7). It was suggested that the depletion of the granular vesicles could be related to the release of catecholamines or other active substances, such as substance P, from granular depots (62, 63).

Later, depletion of catecholamines in heart valves of rats after injection of scorpion venom was shown using fluorescent microscopy (59). Partial or total depletion of vesicles in sympathetic nerve endings of the mouse vas deferens was also shown (21).

As far as the effects of scorpion toxin on neuromuscular junction are concerned, electron-microscopic studies have shown swelling of mitochondria and abnormalities in size and distribution of synaptic vesicles (7).

Cardiac Effects of Neurotoxins

Crude scorpion venoms of several species produce contradictory results when applied to isolated heart preparations (3, 16). Because of these differences, our group performed experiments using a purified scorpion toxin (3). The positive inotropic effect evoked by scorpion toxin is dose dependent, whereas the positive chronotropic effect is not. The absence of a direct relation between dose and positive chronotropic effect is due to bradycardia evoked by the larger dose of toxin (30 μg) in some experiments. Therefore, a similar dose of toxin is capable of inducing a positive chronotropic effect in one guinea pig and a negative chronotropic effect in another. Electrocardiogram shows that the increase in rate is due to sinus tachycardia, whereas the decrease is due to sinus bradycardia, sinus arrest, atrioventricular block.

The bradycardia is caused by a stimulation of parasympathetic fibers, whereas the tachycardia is caused by a stimulation of sympathetic fibers.

After the initial events evoked by scorpion toxin, periodic changes in heart rate, inotropism, and coronary flow are observed during a period of 5–15 min. The periodic increase in heart rate is associated with a positive inotropic effect. The coronary flow varies inversely with the rate and the inotropism, but the most important cause of the variation is the inotropism (there is a reduction in coronary flow in presence of negative chronotropic effect and simultaneous positive inotropic effect). These experiments allow us to separate the influence of inotropism and heart rate on coronary flow in isolated heart preparations. Of course, this is impossible using either catecholamines or ACh (Figure 8).

What is the cause of the periodic changes in cardiac function? The electrical activity of the heart shows that changes are due to "wandering pacemakers." As blockade of muscarinic receptors with atropine prevents the wandering pacemakers, it seems that ACh plays an important role in its genesis. It is well known that ACh activates presynaptic muscarinic receptors, decreasing the release of catecholamines evoked by electrical stimulation of nerves (47). Our hypothesis is that ACh, released by toxin from postganglionic vagal fibers, decreases the release of catecholamines from postganglionic sympathetic fibers through a presynaptic effect and by acting simultaneously on postsynaptic muscarinic receptors produces bradycardia.

The sympathetic innervation is richer in the sinoatrial node than in the atrioventricular node (61). Perhaps, for this reason, scorpion toxin acting in small doses on sinoatrial node always induces sinus tachycardia, and an increase in the release of ACh at atrioventricular node would induce atrioventricular block, since it is known that catecholamines do not prevent atrioventricular block evoked by ACh (54).

These experiments show that scorpion toxin is an interesting tool for the study of cardiac arrhythmias. Many other neurotoxins, such as aconitine, also cause cardiac arrhythmias in vitro.

Circulatory and Respiratory Effects of Neurotoxins

The route of neurotoxins administration is a very important factor in the pattern of response recorded. For this reason, I will discuss the circulatory and respiratory effects elicited by neurotoxins injected either into a cerebral ventricle or systemically.

Intracerebroventricular Injections of Neurotoxins

TTX and STX injected into a lateral cerebral ventricle of anesthetized cats and rabbits caused respiratory failure, hypotension, and death. The inspiratory phase was moderately prolonged in rabbits, whereas periods of respiratory arrest in inspiration (apneusis) were recorded in cats (8, 39). TTX injected into cisterna was relatively ineffective, and for this reason it was suggested that its action was probably at a site rostral to the medulla (8). On the other hand, electrical microelectrode stimulation of several regions in the rostral brain stem evoked respiratory changes (23). There is also a sensitive region in the posterior hypothalamus, close to the walls of the third ventricle in rabbits and cats, that induces cardiovascular and respiratory effects as part of the defense reaction when electrically stimulated (1, 6, 23).

It would be interesting to compare the effects of TTX and STX, which block sodium channels, with those induced by a toxin that activates the sodium channels (e.g., scorpion toxin), producing effects similar to those evoked by electrical stimulation.

The experiments by our group have shown that the effects induced by injection of scorpion toxin into a lateral ventricle of an anesthetized rat were completely different from those elicited by TTX and STX and consisted of tachypnea, hyperpnea, gasping, and a small hypotensive effect. These early and transient findings were followed by prolonged arterial hypertension and hyperpnea, which lasted longer than 1 h. The early respiratory arrhythmias were prevented by intracerebro-

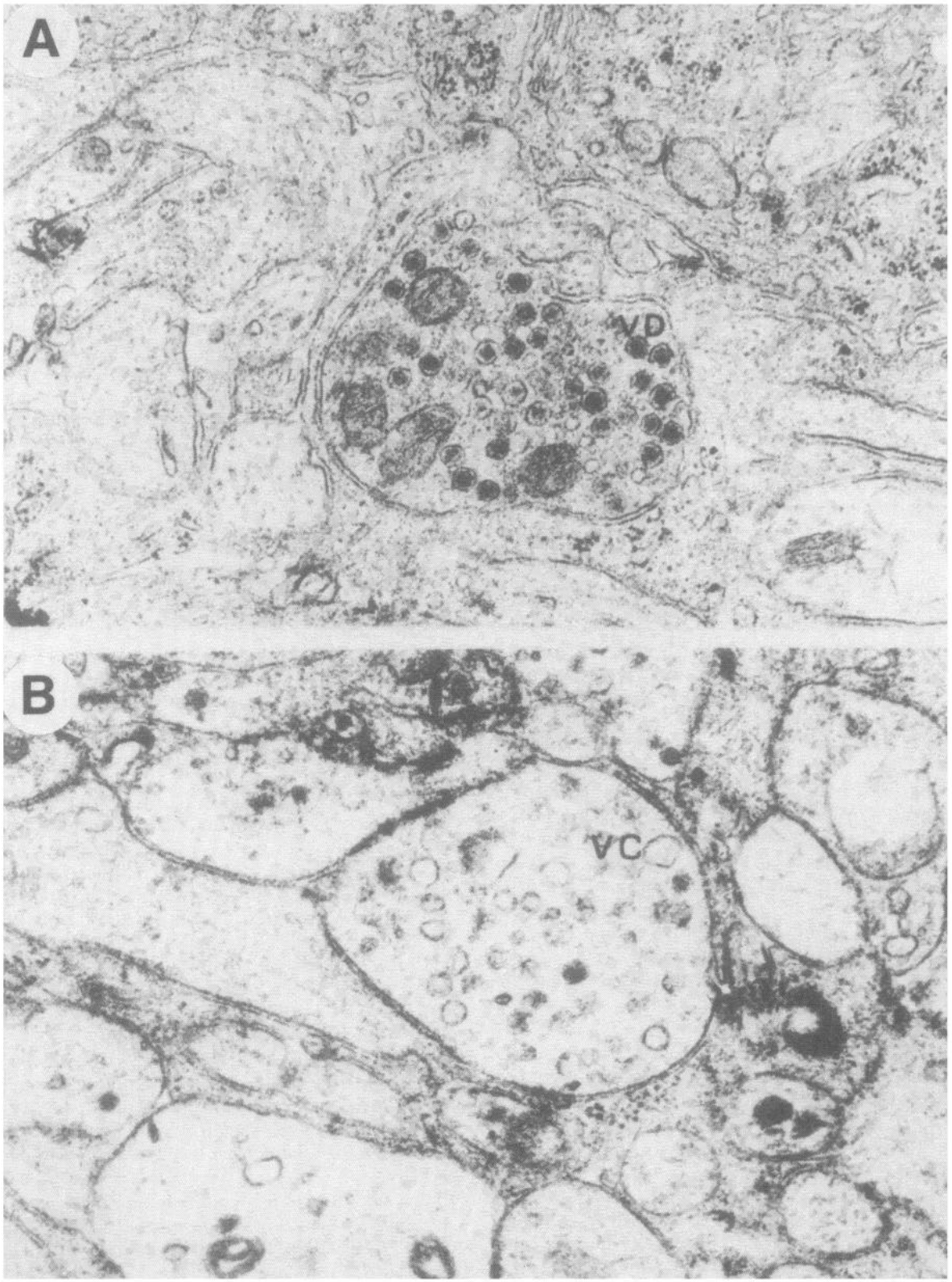

Figure 7
Electron microscopy of Auerbachs plexus in rat ileum. Vesicles were counted in 1,300 transversely cut axons chosen at random, 650 in control group (*A*) and 650 in scorpion treated group (*B*). Observe predominance of granular or dense vesicles (VD) in control group and clear vesicles (VC) in group treated with scorpion toxin. 28.000. (Modified from Ref. 63.)

ventricular (icv) atropine and are assumed to be due to central release of acetylcholine, whereas the arterial hypertension was inhibited by icv phenoxybenzamine and would be due to central release of norepinephrine (46).

These experiments show that it is possible to activate "nerve endings" in the brain in vivo, with the release of chemical mediators and consequent respiratory and cardiovascular effects. On the other hand the toxin-induced sustained arterial hypertension could be used as a

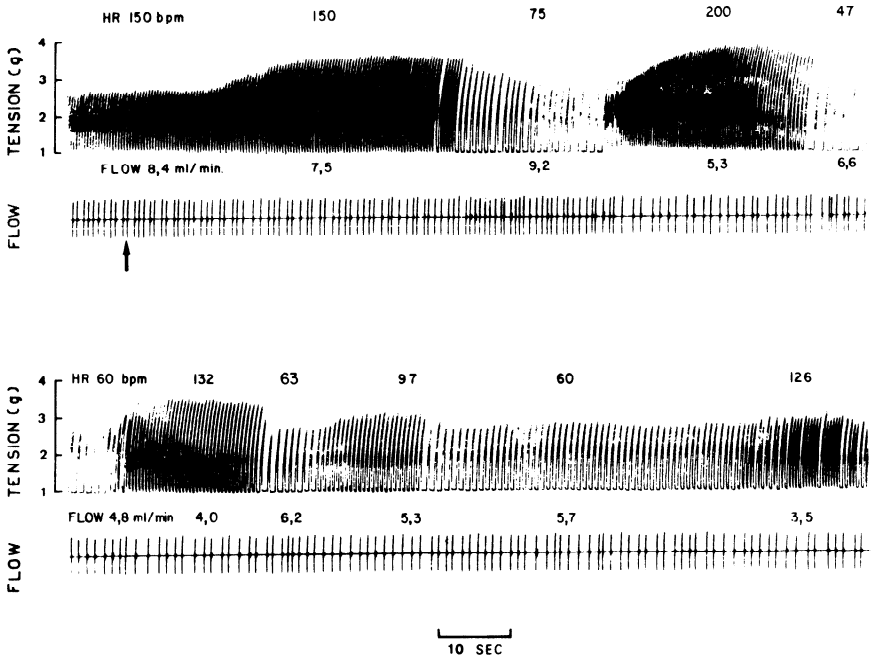

Figure 8
Isolated guinea pig heart perfused by Langendorff's method. Arrow indicates injection of a single dose of scorpion toxin (30 μg). *Lower tracing* is a continuation of *upper tracing*. Observe periodic changes in mean heart rate (HR), inotropism (tension), and coronary flow; bpm, beats per min. (Modified from Ref. 3.)

model in the study of neurogenic hypertension.

In vitro experiments have shown that scorpion toxin incubated with rat brain slices releases ACh or norepinephrine (35, 49). It has also been shown that icv injection of the cholinergic agent carbachol in rats induces arterial hypotension (9), whereas icv norepinephrine heightens the blood pressure (41), thus supporting our experiments with scorpion toxin.

Experiments performed in unanesthetized rats have shown that bilateral lesions of the nucleus tractus solitarii of the medulla oblongata induce arterial hypertension and pulmonary edema as a consequence of an increased sympathetic vasomotor activity (20). Bilateral electrolytic lesions of the anterior hypothalamus also result in arterial hypertension and pulmonary edema, which depend on the release of catecholamines from the adrenal glands (32).

Our group has shown that icv injection of scorpion toxin in unanesthetized rats induced dramatic neurological signs, such as impairment of righting reflexes, tremors, twitching, hyperreactivity, convulsion, and pedaling. An acute hemorrhagic edema of the lungs was also observed in all rats prior to death 4–9 min later. The edema was prevented by injection of guanethidine in adrenalectomized rats. For this reason, it was suggested that this type of neurogenic pulmonary edema could be due to the release of catecholamines from adrenal glands and postganglionic nerve endings as a consequence of excitation of central autonomic structures by scorpion toxin (4).

Anethesia prevents the central neurogenic pulmonary edema induced by several procedures, such as lesions of the nucleus tractus solitarii, lesions of the anterior hypothalamus, or icv injection of scorpion toxin (4, 20, 46, 52). It seems that the arterial hypertension in conscious rats is higher than in anesthetized animals, leading to left-heart failure and pulmonary edema.

Small doses of scorpion toxin injected directly into specific sites of the hypothalamus and other areas of the brain could be used in the study of neurogenic arterial hypertension and pulmonary edema.

Systemic Injections of Neurotoxins

Intravenous injection of TTX or STX induces a general paralysis, including that of the respiratory movements. The evidence indicates that this paralysis is due to peripheral and not central actions of the toxins (22). On the other hand, intravenous injections of scorpion toxin or veratridine evoke effects different from those induced by TTX and STX and are due to stimulation of peripheral receptors.

Concept of Chemoreflexes

Sensory receptors are stimulated by their natural stimuli; e.g., the inflation during inspiration stimulates the pulmonary strech receptors. However, receptors could also be stimulated by intravenously injected chemical substances evoking the well-known chemoreflexes (18). We will describe the reflex effects induced by only two neurotoxins: scorpion toxin and veratridine.

Scorpion Toxin and Its Reflex Effects

In anesthetized rats, scorpion toxin evoked a gasping type of breathing, which showed a fairly regular pattern. Ataxic respiration characterized by irregular respiratory movements either in amplitude or rate was recorded interspersed with "gasps" in many experiments. The gasping and ataxic respiration were prevented by bilateral vagotomy and denervation of carotid bodies (27). These experiments indicate that respiratory arrhythmias are reflex by nature. Moreover, in confirmation of the previous results (28), intravenous injection of lidocaine also abolished the arrhythmias (endoanethesia). But, where does the local anesthetic lidocaine act? As the respiratory arrhythmias are reflex by nature, it appears to act on peripheral receptors.

Figure 9 shows that after scorpion toxin injection gasping breathing, apnea, and hypotension occur, and these are abolished by local anesthesia with lidocaine of the cervical vagus nerves (28). The bradycardia evoked by toxin was not abolished by vagal anesthesia and was due to ACh release from postganglionic nerve fibers in the heart (34).

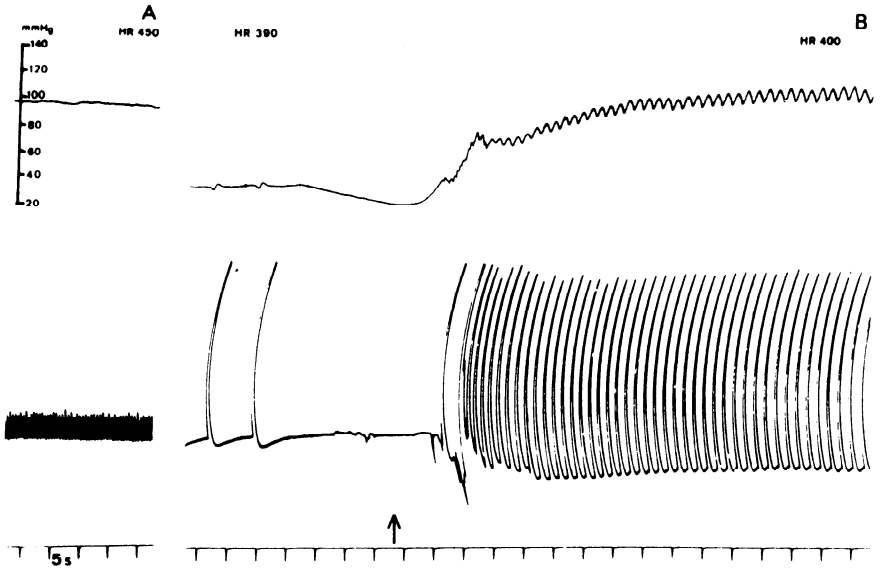

Figure 9
Mean arterial pressure and respiratory movements of an anesthetized rat. Inspirations indicated by upward deflection. Numbers at *top* indicate mean heart rate (HR) before (*A*) and 12 min after (*B*) intravenous injection of 0.8 mg/kg of scorpion toxin. At *arrow*, one drop of 2% lidocaine was applied to each cervical vagus nerve (Ref. 28).

Based on these experiments, I would like to stress the following physiological aspects of the reflexes induced by scorpion toxin (27, 28). *1*) Bilateral cervical vagotomy decreases the respiratory rate in normal rats; however, vagotomy in scorpion toxin-injected rats produces a reverse effect, i.e., an increase in respiratory rate. *2*) All the respiratory arrhythmias induced by scorpion toxin are abolished by intravenous lidocaine (endoanesthesia). *3*) Death is due to respiratory paralysis, which could be prevented by local anesthesia of the cervical vagus nerves; thus the reflex apnea is the cause of the animals' death.

We assume that the receptors responsible for the apnea are located in the lungs. As the pulmonary stretch receptors are supplied by blood through the bronchial circulation (67) and J-receptors[2] are accessible exclusively by the blood in pulmonary capillaries (55), we assume that the apnea could be due to J-receptor stimulation, since the effects evoked by scorpion toxin are greater when injected into the right atrium rather than the left ventricle.

Veratridine and the Bezold-Jarisch Reflex

Injection of veratridine into coronary artery of dogs evokes bradycardia and hypotension of reflex nature. This reflex is called Bezold-Jarisch (43) or coronary chemoreflex (18). Even when used in this limited sense, it seems that this is not a single reflex, since veratridine stimulates a variety of sensory receptors in the heart (55), the vagal C-receptors being the most important (15).

Scorpion toxin releases chemical mediators by stimulation of sodium channels, but the action is blocked noncompetitively by TTX, indicating that these toxins act at separate sites (12, 13, 32, 33). Veratridine acts at a third site of the sodium channel, and its action is potentiated by scorpion toxin (12). Based on these in vitro experiments, we decided to study the possible potentiation induced by scorpion toxin on the effects evoked by veratridine in anesthetized rats.

Preliminary experiments showed that intravenous injection of veratridine (2.5 μg/100 g) in anesthetized rats induces slight bradycardia, arterial hypotension, and apnea, which lasted about 15 s. Twenty minutes after a small dose of scorpion toxin (10 μg/100 g), an identical dose of veratridine produced greater effects on heart rate, arterial pressure, and respiration (the apnea lasted about 1 min). To avoid the possible effects of veratridine on pulmonary receptors (55), experiments were carried out in which a polyethylene catheter was introduced into the left ventricle through the aorta. Veratridine (2.5 μg/100 g) and scorpion toxin (10 μg/100 g) were then injected into the left ventricle. The Bezold-Jarisch reflex induced by veratridine, characterized by sinus bradycardia, hypotension, and respiratory stimulation, was also potentiated by scorpion toxin (29).

[2]The J-receptors described by Paintal (55) are called "pulmonary C-fiber endings" by Coleridge and Coleridge (15).

Other Effects of Neurotoxins

A purified scorpion toxin (tityustoxin) increases the salivary, gastric, and pancreatic secretions in rats, and its mechanism of action has been investigated. Tityustoxin seems to be an important tool in the study of the mechanisms involved in these secretions (5, 11, 36, 53).

Several toxins, isolated from crude scorpion venoms, present a selective affinity for insect neuronal tissue. For this reason, they could be used as tools in the study of insect neurobiology (68).

Summary

Several investigators have used neurotoxins to isolate physiological receptors or components of the sodium channels. For instance, α-bungarotoxin, extracted from the venom of the snake *Bungarus multicinctus*, has been used to isolate nicotinic receptors, whereas saxitoxin, tetrodotoxin, and scorpion toxin have been used to isolated polypeptide components of the sodium channels. Other groups are interested in the possible role for scorpion toxin, veratridine, tetrodotoxin, and other neurotoxins as tools in the investigation of complex physiological processes, such as release of chemical mediators, cardiorespiratory reflexes, cardiac arrhythmias, arterial hypertension, pulmonary edema, and the mechanism of gastrointestinal secretions.

This lecture is dedicated to Professor Mauricio Rocha e Silva.

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A Simple Model of the Pulmonary Circulation for Hemodynamic Study and Examination

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Almost the same amount of blood flows through the pulmonary circulation as flows through the systemic circulation, but under resting conditions blood flow in many segments of the lung is almost completely dormant. As more blood is pumped into the lungs due to increased venous return from the systemic circulation, the pulmonary blood vessels are forced to expand so that the pulmonary vascular resistance becomes greatly decreased. As a consequence, the lungs can accommodate increased cardiac output with only a moderate rise in pulmonary blood pressure. This conserves the energy of the heart and protects against high pulmonary capillary pressure, which could lead to the development of pulmonary edema.

Another protective feature of the pulmonary circulation is seen in moderate left-heart failure. When the left heart fails to pump blood adequately, then the blood returning from the systemic circulation tends to "dam up" in the lungs. Because the lungs can accommodate this additional blood without much rise in pressure the right heart does not have to work as hard.

A unique additional feature of the pulmonary circulation is that removal of significant amounts of lung tissue has little effect on pulmonary hemodynamics in the normal range of blood flows. Indeed, following the removal of one entire lung all the cardiac output flows through the remaining lung with ease.

These and other effects on pulmonary function can be studied with the aid of a computer model. With an appropriate model, a student can investigate important circulatory variables such as "cardiac output," "venous return," "mean circulatory filling pressure," "resistance to venous return," and "equilibrium point." All of these are explained in the section on the circulation in Guyton's *Textbook of Medical Physiology* (Saunders, Philadelphia, PA), and I have incorporated them into a hemodynamic model of the pulmonary circulation. The model used for the simulation is shown in Figure 1. Blood pressures are represented by P, blood volumes by Q, resistances by R, and capacitances by C with appropriate subscripts for arterial (a), venous (v), left atrial (la), and heart (h). Other symbols are Ain, arterial inflow (same as cardiac output, CO); Aout, arterial outflow; Vout, venous outflow; Hin, input for heart filling; K2, heart contract-

ility. Blocks numbered 1, 7, 9, and 11 perform summations. Blocks numbered 3, 5, and 13 perform divisions. Blocks numbered 2, 8, and 12 perform integration. Blocks 4, 6, 10, and 14 perform the functions indicated.

Briefly, beginning with block 1, the cardiac output (CO) becomes the input to the arterial segment. After subtracting arterial outflow (Aout), the result is integrated in block 2 to give the arterial blood volume (Qa). By a similar process venous blood is integrated in block 8. These two blood volumes are then added at block 9 to give the total pulmonary blood volume (Qt). Increasing blood volume in the lungs opens up new channels for blood flow and causes the existing channels to widen. This lowers the vascular resistance in a manner similar to the graph shown in block 10. The individual vascular resistances (R in block 10 is generic) are sent back to blocks 4 and 6. Blocks 11 through 14 establish heart function. Block 11 subtracts the cardiac output (CO) from the venous return (Vout). In addition, this is where extra blood can be added to or subtracted from the circulation by Hin, the value of which is regulated by a game controller paddle. The output from block 11 is integrated in block 12 to give the filling volume of the heart (Qh). Block 13 converts this to left atrial pressure (Pla). Block 14 is a graph of a cardiac output curve representing the left heart. Cardiac output is a linear function of atrial filling pressure. However, by adjusting the value of K2 heart contractility can be made to vary.

The pulmonary model program was written in Applesoft BASIC for implementation on an Apple microcomputer (Apple Computer, Cupertino, CA). For heightening interest, the Apple's excellent high-resolution (HIres) color graphics and one of the game controller paddles (1) were incorporated into the program. However, neither of these features is indispensable, and the program can be modified to run on other computers that support the BASIC programming language.

With so much information on the TV screen it really helps to identify each plotted variable with a different color. But in addition to enhancement with color graphics, an important feature of the model is the way in which the information is output to the TV screen. First, there is a continuous plotting of pulmonary arterial and left atrial pressures in a HIres color graph display. Next, simply pressing any key on the computer keyboard will halt the simulation and bring up a menu page on the TV screen in place of the graph. One of the menu selections (selection 3 in Figure 2) returns the HIres graph with a current set of cardiac output and venous return curves printed on it and an × marking the place in time on the top axis that the event occurred. The point where these two curves meet, the so-called "equilibrium point," determines the values of the left atrial pressure and cardiac output. In addition, the point on the *X*-axis where the venous return curve ends determines the value of the "mean pulmonary filling pressure." Along with this information, the current values of six important variables are printed underneath the HIres picture. The variables are *1*) the amount of time lapse from the beginning of the simulation; *2*) the normalized value of blood flow (cardiac output or venous return); *3*) the pulmonary arterial pressure; *4*) the left atrial pressure; *5*) the normalized value of pulmonary "resistance to venous return"; and *6*) the rate at which extra blood is infused into or withdrawn from the circulation (this is normally set at zero).

The model's parameters can be changed at any time during a simulation. Pressing any key on the computer keyboard halts the simulation and causes the numbered menu of selections to appear on the TV screen as shown in Figure 2. In this example the operator has opted for selection 2, "change parameters." After replying with a

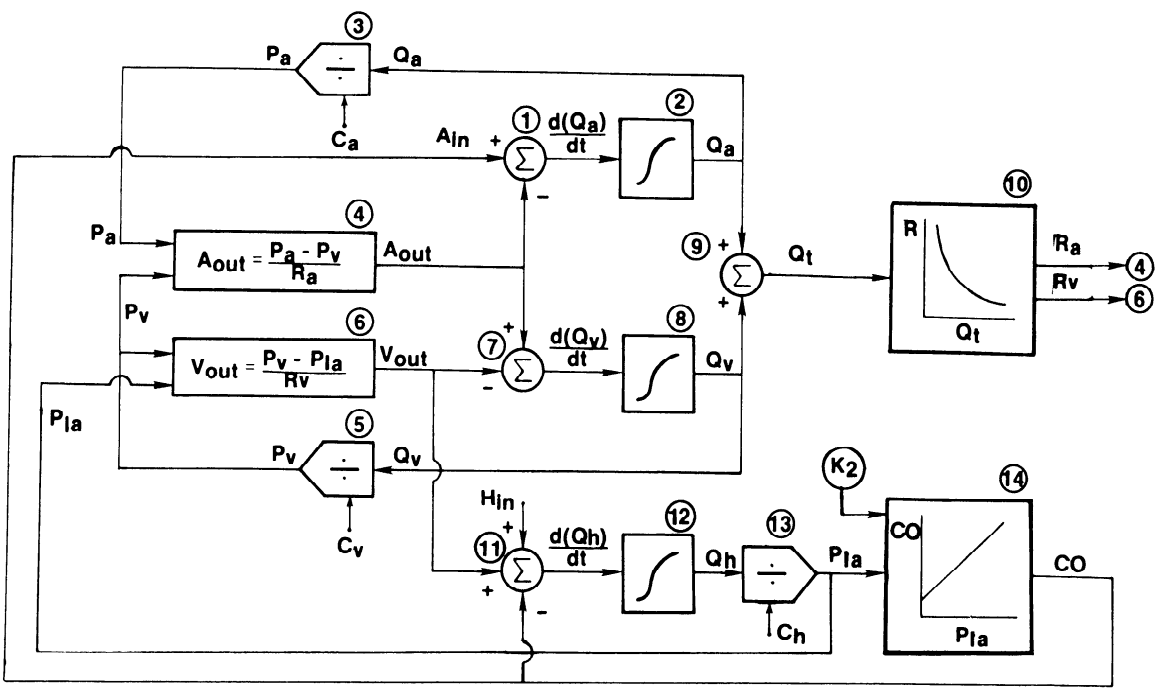


Figure 1
Block diagram for hemodynamic model of pulmonary circulation. A brief description of the model is given in text, including an explanation of symbols used.

```
1-RESUME SIMULATION
 2-CHANGE PARAMETERS
  3-PLOT FUNCTION CURVES
   4-START NEW SIMULATION
    5-QUIT THIS SIMULATION

   SELECTION -> 2

CHANGE RESISTANCE? (Y OR N) :N

CHANGE COMPLIANCE? (Y OR N) :N

CHANGE HEART CONTRACTILITY? (Y OR N) :Y

HEART CONTRACTILITY NOW (1) X NORMAL.
NEW HEART CONTRACTILITY (X NORMAL)? :
```

Figure 2

This shows 5-selection menu that appears on TV screen anytime a keyboard key is pressed while program is running. Also shown is some of the dialogue following selection of option 2. The small black rectangle represents cursor.

Y(es), each parameter is presented in turn and the operator has the option to change or not to change it to some other value. To help the operator, the current value of each parameter to be changed is printed, also.

An example of changing parameters during a simulation is shown in Figure 3. In this example the effect of moderate exercise on pulmonary hemodynamics is demonstrated. Near the 5-s mark the simulation was stopped to print the normal cardiac output and venous return curves on the graph using selection 3 (see Figure 2) and to change parameters using selection 2. In this example only the heart contractility was changed, from 1 to 1.5 times normal. Simply increasing heart strength, however, will not raise cardiac output very much unless sufficient blood is entering the heart to increase the atrial filling pressure. So, beginning at the 5-s mark the paddle (1) knob setting, which regulates the rate of blood infusion into the heart, was elevated causing the cardiac output to begin rising.

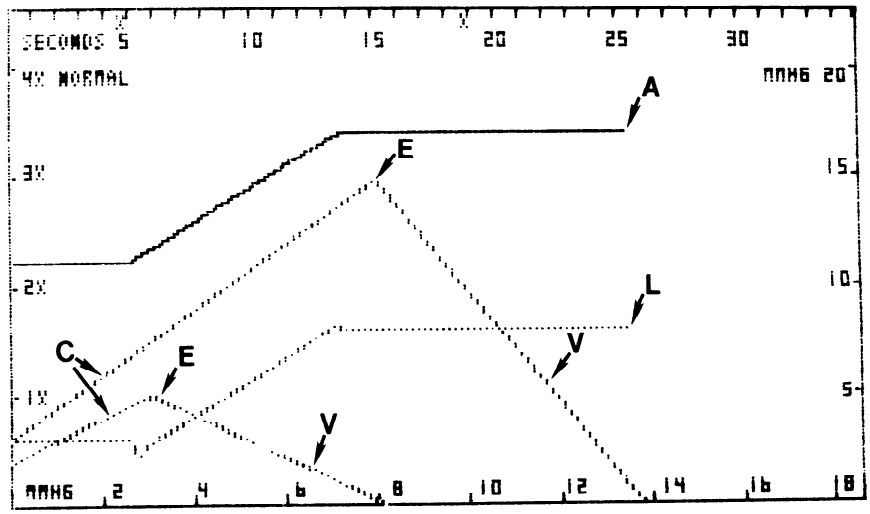
When the cardiac output had risen to 3 times normal the paddle (1) knob was reset to zero. This is indicated on the graph by the blood pressures leveling off. There is now sufficient blood flowing into the left atrium from the lungs to sustain the cardiac output at 3 times normal level. Near the 19-s mark, when conditions have stabilized, a second set of cardiac output-venous return curves is printed on the graph. The intersection of this second venous return curve with the *X*-axis shows that "mean pulmonary filling pressure" has risen to almost 14 mmHg. This is because there is now much more blood in the lungs due to the increased cardiac output. And because there is also much more blood flowing into the left atrium, the left atrial pressure has risen to 8 mmHg. In fact, the so-called "pressure gradient for venous return" (mean pulmonary filling pressure **minus** left atrial pressure) has hardly changed from what it was before. Then **what** is mainly responsible for the greatly increased blood flow through the lungs?

Looking at the values of the variables printed under the graph, we see that the "resistance to venous return" has fallen to almost one-third normal. This is indicated also by the difference in the slopes of the two venous return curves printed on the graph above. Note also that the arterial and venous blood pressure tracings have risen only moderately. In summary, moderate exercise can produce increased blood flow through the lungs without causing excessively elevated pulmonary blood pressures.

Another example is the effect of acute left-heart failure on pulmonary hemodynamics. This is illustrated in Figure 4. The normal cardiac output and venous return curves, shown to the left of the figure, were printed just after the 10-s mark was reached. Following this, the "change parameters" option was selected to reduce heart strength to one-third normal. Almost immediately, arterial pressure fell and left atrial pressure rose slightly. In the meantime cardiac output has fallen to one-half normal, not sufficient to sustain life for very long. To make the weakened heart pump more blood, the heart must be primed with extra blood. Beginning at the 15-s mark the game controller paddle setting, which causes extra blood to be infused into the heart, is increased above zero. When cardiac output has returned to normal, the paddle setting is returned to zero, and the blood pressures attain new plateaus.

To obtain more information, an updated set of cardiac output-venous return curves is printed on the graph at the 29-s mark, just before terminating the simulation. Note that the lowered slope of the cardiac output curve gives a clear indication of the heart's diminished pumping effectiveness. In addition, the excessively high atrial pressure is a common clinical finding in heart failure. Another clinical finding is pulmonary congestion. This is indicated by the "mean pulmonary filling pressure" that has risen from the normal value of about 8 mmHg to almost 15 mmHg. On the other hand, this has caused the pulmonary vascular bed to lower its resistance greatly, which reduces the work load on the weakened heart.

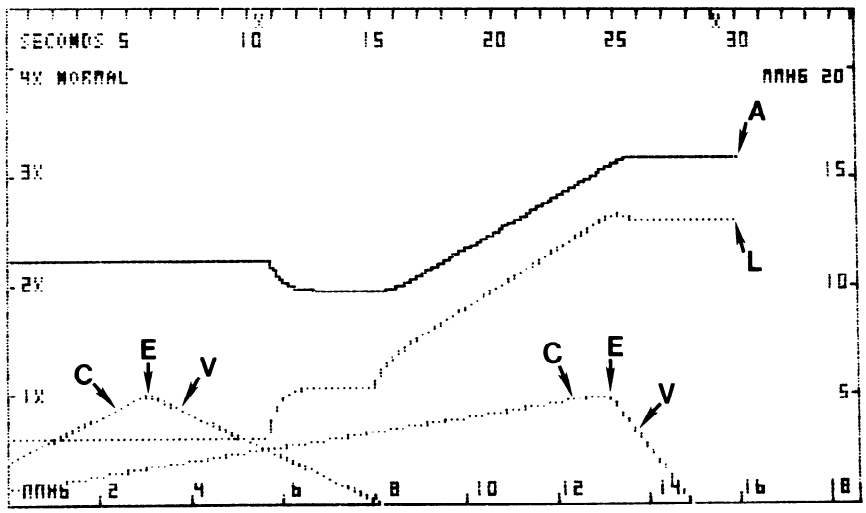
Some additional simulations that are interesting might also be mentioned. One involves the removal of half of the lung tissue, similar to what might occur when one whole lung is removed surgically. Under these conditions, graphs could be prepared showing what happens to pulmonary resistance when blood flow is increased 1, 2, and 3 times normal and comparing these effects when one lung is removed with the effects with both lungs intact. In addition, pulmonary arterial pressure changes could be compared under these same conditions in another graph. Another study might involve preparing several graphs using "families" of 4 or 5 different curves, each depending on a different level of heart strength. For example, an ordinary piece of graph paper could be sectioned into four quadrants. In one quadrant the relationship between cardiac output and left atrial pressure could be plotted; in another quadrant the relationship between pulmonary arterial pressure as a function of cardiac output could be plotted; in a third quadrant the relationship between pulmonary resistance and cardiac output could be plotted; in the fourth quadrant the relationship between venous return and left atrial pressure could be plotted. All of the information needed to compose these graphs can be obtained directly from the TV screen. Several sets of curves can be plotted on each graph; for example, with heart strength set at 0.5, 1.0, and 1.5 times normal. Or another series of two curves could be composed with one curve representing both lungs intact and the other curve representing the effect of removal of one lung.



LAPSED TIME (SEC)	CARDIAC OUTPUT (X N)	ARTERIAL PRESSURE (MM HG)	ATRIAL PRESSURE (MM HG)	RESISTANCE TO VENOUS RETURN (X N)	INFUSION - WITHDRAWAL (ML/MIN)
25.35	3.00	17.21	8.00	0.37	0.00

Figure 3

Moderate exercise (see text for explanation). Picture shown here (and in Figure 4) is a facsimile of HIres picture on TV screen reproduced by a dot-matrix type of printer. Values of variables shown under HIres picture copy are not reproduced by printer, but they represent current values at the time simulation ended. In HIres picture copy blood pressure tracings (A and L) are dynamic; they are referenced to the top (seconds) and right (mmHg) axes. Venous return-cardiac output curves (V and C) are static; they only appear if ordered (by choosing menu selection 3). Usual convention was followed by referencing these to left scale for cardiac output-venous return (X normal) and lower scale for left atrial pressure (mmHg) scale. *Symbols* are as follows: A, mean pulmonary arterial pressure; L, left atrial pressure; C, cardiac output curve; V, venous return curve; E, equilibrium point. X symbols that appear at various locations along the seconds scale were placed there automatically during simulation to indicate when function curves were ordered.



LAPSED TIME (SEC)	CARDIAC OUTPUT (X N)	ARTERIAL PRESSURE (MM HG)	ATRIAL PRESSURE (MM HG)	RESISTANCE TO VENOUS RETURN (X N)	INFUSION - WITHDRAWAL (ML/MIN)
30.02	1.00	16.05	13.10	0.36	0.00

Figure 4

Acute left-heart failure (see text for explanation. *Symbols* and *markings* are same as for Fig. 3.

Having each of these graphs on a single piece of paper would facilitate studying the interrelationships between the different variables.

The above examples and suggested simulations can all be completed within the 35-s time span allowed for each simulation. This is about the optimum for most simulations, considering that longer time spans tend to encourage putting too much information on the HIres picture. Rather, the student is encouraged to attempt only one or two maneuvers during each simulation and to run as many different simulations as needed. This is easy to do, since the average simulation takes only several minutes to complete. If a graphics type printer is available, then each simulation can be permanently recorded.

Some additional suggestions for study are part of the documentation that has been prepared for the model program. This documentation has a complete program listing, a listing and description of all the variables, constants, and other parameters in the program, and all the instructions needed to run the program. A copy of this documentation is available, and Apple users can obtain a copy of the program software on diskette or cassette tape. A microcomputer having a minimum of 48K RAM, capable of running Applesoft programs, is required. For more information, write to K. A. Gaar, Jr., Dept. of Physiology and Biophysics; L.S.U. Medical Center, P.O. Box 33932, Shreveport, LA 71130.

Regulation of Cell Volume and Electrolytes: A Computer-Assisted Instruction Program

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The number of recent articles appearing in the Physiology Teacher section of *The Physiologist* concerning instruction on regulation of cell volume and electrolytes attests to the difficulty of adequately presenting this material to medical and graduate students. Consequently, I have devised a computer-assisted instructional (CAI) program which complements the normal format of lecture presentation of this material.

The CAI program simulates the processes that determine the steady-state distribution of water and electrolytes between the cytoplasmic fluid in a typical cell and its extracellular environment. It solves for, and displays, the changes in this distribution as a function of alterations in such parameters as ionic permeabilities, extracellular ionic concentrations, and the rate of active ion transport. The program is designed to allow a student to manipulate these individual parameters, one at a time, to see how each one affects the chemical composition of the cell. It has been used here for five years as part of the instruction of the Medical Physiology course taken by both medical and graduate students.

Typically, the program is first demonstrated to the students with the aim of showing the interaction of the individual osmotic and ionic phenomena described in detail in a number of preceding lectures. Then the students are allowed to use the program, individually, to reinforce the points made in the demonstration and to study other aspects of this regulation. We have found this exercise to give a degree of insight into the interactions of the multitude of simultaneously ongoing processes involved in cellular fluid and electrolyte balance that cannot be effectively conveyed solely in a lecture format.

There has not been a formal student evaluation of this program. Medical students spent about an hour, on the average, outside of class time working with the program. Their general comments have been that this time is worthwhile for preparing for the examination on this subject matter. Negative comments have been concerned with the difficulty of predicting some of the results before the program is run and then explaining the reasons for these results.

The Computer Program

The program is based on a model of cell volume regulation first proposed by Tosteson and Hoffman (3). A version of their "Pump-Leak" model is pictured in Figure 1. In this model the volume of a cell bathed in an extracellular medium of large volume is regulated by a balance of osmotic and ionic forces perturbed from equilibrium by an ionic exchange pump. Three small ions are considered, Na^+ and K^+, which are actively pumped across the membrane, and Cl^-, which is not pumped and consequently is always at electrochemical equilibrium. In addition a high-molecular-weight anion, X^-, is constrained to remain inside the cell.

To compute the steady-state volume and electrolyte content of such a model cell, three conditions must be met:

1. *Osmotic equilibrium.* The total osmolality inside the cell must equal that outside the cell.

2. *Electrical neutrality.* The sum of the concentrations of cations must be equal to the sum of the concentrations of anions, both inside and outside the cell.

3. *Steady state.* For Na^+ and K^+, the rate at which they are actively pumped across the membrane must equal the rate at which they leak across by electrodiffusion.

The equations describing conditions *1* and *2* are straightforward and require minimal assumptions. In contrast, the equations describing condition *3* are more arbitrary. For condition *3* it was decided to adopt the functional form for the rate of ionic active transport suggested by Tosteson (2). This formula describes a pump whose activity is proportional to intracellular Na^+ concentration and extracellular K^+ concentration and which saturates at extreme values of these quantities. Since this pump formula is specific for red blood cells, it was decided to use this type of cell as a prototype example in the model. Electrolyte diffusion was described by the Nernst-Planck equation, using the constant field assumption (1).

The resulting equations and underlying assumptions are given in Wolf (4) and consequently are not restated here. The equations were combined into a single nonlinear algebraic equation which could be solved to yield the magnitude of the cell membrane electrical potential difference (EPD). However, this solution could only be obtained using numerical techniques and a digital computer (4).

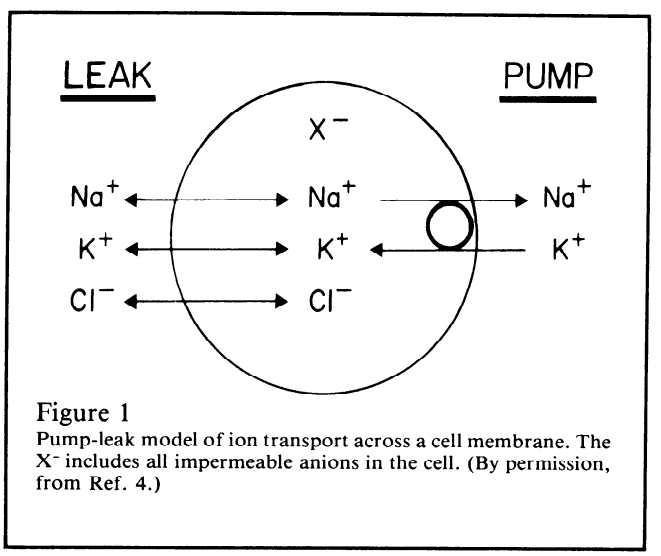

Figure 1
Pump-leak model of ion transport across a cell membrane. The X^- includes all impermeable anions in the cell. (By permission, from Ref. 4.)

A computer program was written to solve these equations (4) using the BASIC language. Then to adapt this program as a teaching tool, additional sections were written to provide an introductory explanation, the ability to change parameter values, and a display of results.

The program begins by displaying a series of options including: an introductory explanation, a display of normal values of the variables in the model, a parameter change selection and an exit from the program. The introductory explanation is a brief description of the object of the program, the variables of the model, and the parameters which can be varied. The parameter selection section again describes the parameters of the model and gives symbols for these and some normal values. Changing parameter values is achieved by the student selecting the number of the parameter and then entering a percentage change from the normal value. Then the computer updates the parameter value, solves the equations, and displays the results.

Table 1 shows such an output display for normal parameter values.

After seeing the normal values, the student will change a parameter value and examine the result. The parameters of the model which may be altered are as follows.

Extracellular Osmolarity

A percentage change in this parameter, as selected by the student, is translated internally in the program to a simultaneous percentage increase or decrease in extracellular Na^+, K^+, and Cl^- concentrations.

Extracellular K^+ Concentration

A selected percentage change is translated internally in the program by incrementing extracellular K^+ concentration by a percentage while maintaining extracellular electroneutrality by adjusting extracellular Na^+ concentration.

Hemoglobin Concentration

The initial amount of hemoglobin in the cell can be changed by the student specifying a percentage change from normal.

Na^+ Pump Activity

A selected change alters the basal rate of ion active transport, but not the 3:2 Na^+:K^+ coupling ratio of the pump.

K^+ Permeability

Altering the value of this parameter does not affect the magnitude of the Na^+ permeability.

Electrical Charge

Electrical charge (valence) of the hemoglobin molecule can be changed by a selected percentage.

Table 1
Cell Volume Simulation:
Results for Normal Parameters

	Na^+	K^+	Cl^-	Osmolarity
	meq/liter			mosmol/liter
Extracellular	155	5	160	300
Intracellular	19	136	111	300

Cell volume: 1 unit
Membrane potential: −9.7 mV

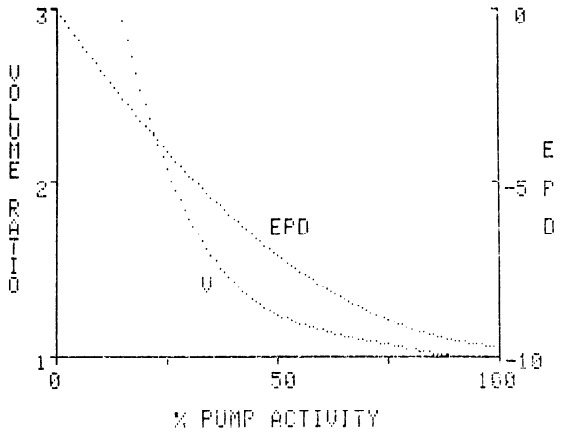

Figure 2
Ratio of new cell volume to normal volume and changes in cell membrane electrical potential difference (EPD, in mV) with decreasing activity of Na^+-K^+ pump.

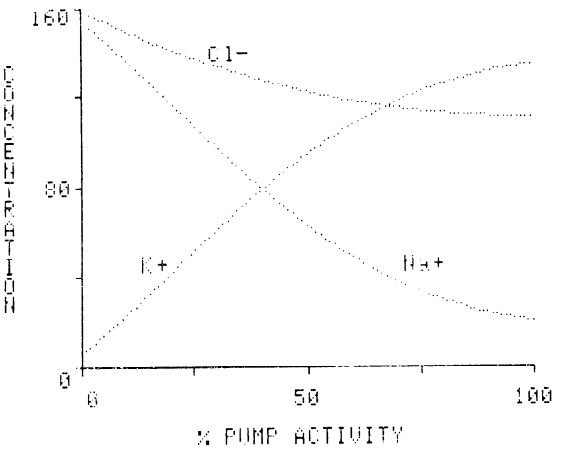

Figure 3
Changes in intracellular ionic concentrations (in meq/l) as pump activity is decreased from normal.

An example of the use of this model as a teaching tool is seen in the results shown in Figures 2 and 3. Figure 2 shows the ratio of new cell volume to normal volume and the resting cell membrane EPD when the activity of the Na^+ pump is decreased from normal. These data were obtained by running the program 10 times at progressively decreasing activities and then fitting a polynomial to these data points, using a curve-fitting program on the Apple computer. Then the graphs shown were generated with a plotting program on the computer and displayed on a video monitor. Each data point required 1-1.5 min of computer time. Alternative methods of display, and the use of less data points, could reduce the time required to generate this information if this were desired.

The results of Figure 2 show the general trend that a decrease in pump activity, as could occur, for example, with a metabolic poison, would lead to an increase in cell volume and a depolarization of the cell membrane. These data illustrate that the pump itself is a major factor in establishing the resting EPD of a cell. Another interesting observation is that the cell appears to be protected from severe volume changes, even to a 50% reduction in pump activity. This result could not have been predicted solely from inspection of the indi-

vidual osmotic and electrodiffusional phenomena by themselves.

The results also show the trend to the limiting case of a dead cell with an infinite volume and an absence of an EPD; however, obviously cells do not reach this point and still remain intact. Consequently, when the cell volume increases beyond a certain point, typically a 70–80% increase, a warning message is displayed to the student that the cell volume increase has caused irreversible damage. Then the program returns to the initial menu of options.

Figure 3 shows similar results for the intracellular electrolytes in the model. Illustrated is the cellular Na^+ entry and K^+ loss as the pump activity is decreased and the Cl^- entry as a consequence of the depolarization. Again, for a dead cell, the intracellular ionic concentrations approach the limiting case of those in the extracellular fluid.

Other suggested student exercises that can be performed with this program include the effects of osmolarity changes on cell volume; the effects of increasing extracellular K^+ concentration on the depolarization of the cell; and the effects of K^+ permeability change on cell membrane EPD. Many other possibilities also exist.

Appendix

For those readers who are interested in the equations of the model as described in Wolf (4), there is a misprint in Eq. 10 of that paper. A pair of brackets were inadvertently left out of this equation. A corrected version is shown below.

$$\left(\frac{\beta\epsilon}{1-e^{-\beta\epsilon}}\right)\left[e^{-\beta\epsilon}-\left(\frac{\bar{\phi}+\bar{Z}}{\bar{\phi}-\bar{Z}}\right)e^{-\beta\epsilon}+\frac{2\bar{Z}}{\bar{\phi}-\bar{Z}}\right]=\frac{1}{[Cl^-]_o}\left(\frac{J_K^P}{\varrho_K}+\frac{J_N^P}{\varrho_N}\right)$$

The CAI program is written in BASIC. It has purposefully been kept free of any special functions unique to an individual computer. Consequently, the program can easily be adapted to the Apple or other microcomputer. A listing of this program is available on request with a self-addressed, stamped envelope; or the program can be obtained for use on the Apple computer by sending a blank diskette and an appropriate self-addressed, stamped mailing envelope.

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1. Plonsey, R. *Biolelectric Phenomena.* New York: McGraw-Hill, 1969.
2. Tosteson, D.C. Regulation of cell volume by sodium and potassium transport. In: *The Cellular Functions of Membrane Transport,* edited by J. F. Hoffman. New York: Prentice-Hall, 1964.
3. Tosteson, D.C., and J. F. Hoffman. Regulation of cell volume by active cation transport in high and low potassium sheep red cells. *J. Gen. Physiol.* 44: 169–194, 1960.
4. Wolf, M.B. A simulation study of the anomalous osmotic behavior of red cells. *J. Theor. Biol.* 83: 687–700, 1980.

Book Review

General and Comparative Physiology (3rd Ed.). William S. Hoar

Englewood Cliffs: Prentice-Hall. 1983, 851 pp., illus., index, $30.95.

Because my teaching has largely been in medical schools, this is not a text that I have used. I have not looked at the earlier editions but have come to this one fresh. There are obviously a different set of problems for the zoologist than for the student of human physiology, and whole sections appear that are not found in texts with a medical bias, as for example Chapter 10 devoted to electric discharge, light production, and color change. Although the overall systems are very similar, there is considerable variation in the particular solutions of each species to an environmental challenge.

The text is well set out, and on the whole the illustrations are good. There is a nice mixture of electron-microscope studies and diagrams. As well as giving general principles, a certain amount of experimental data is included and a number of references cited in the text. The reference list appears at the end of the book. Originally I looked for them at the end of each chapter, but the solution adopted is probably the best one.

The approach of the book is to discuss the adaptive significance of life processes to changes in the environment, and the text opens with a discussion of the environment. Then follows a section on biochemistry. It is difficult to know how much basic biochemistry should be included in a physiology text. I do not feel it is of value to include too much. Limited information is required as to the structures of the various substances and only summaries of the metabolic pathways. This book probably achieves the right balance. Another problem is the order in which the material should be presented. This applies not only to textbooks but to courses on physiology since no system exists independently. An understanding of the nervous system, although a difficult topic, is needed for the understanding of the other systems. The author has therefore chosen to continue with stimulus-response mechanisms and nervous activity. In this section there are, for my taste, too many figures giving action potentials, as, for example, the illustration that when an electrode is placed on either side of the septum of a lateral giant fiber in the crayfish, the electrical response is the same whether the stimulus is delivered to the rostral or caudal part of the nerve. There is a useful chapter on nervous integration.

Included in the material on control mechanisms is a section on the endocrine system. This is a good up-to-date review including material on the endorphins and ensephalins. It is possibly a little basic and certainly a brief outline of the principles of radioimmunoassay should have been included. Most of the hormones are described in detail in the context of the particular tissue involved. Possibly the hormonal contribution to intermediate metabolism could have been included in the chapter on the transformation of energy. There are also helpful chapters on respiratory, cardiovascular, and renal physiology. Although this book is obviously aimed at the zoologist, for any physiologist a general look at the systems of other species helps to focus on certain aspects to see them in a fresh light.

Mary Forsling
Middlesex Hospital Medical School, London

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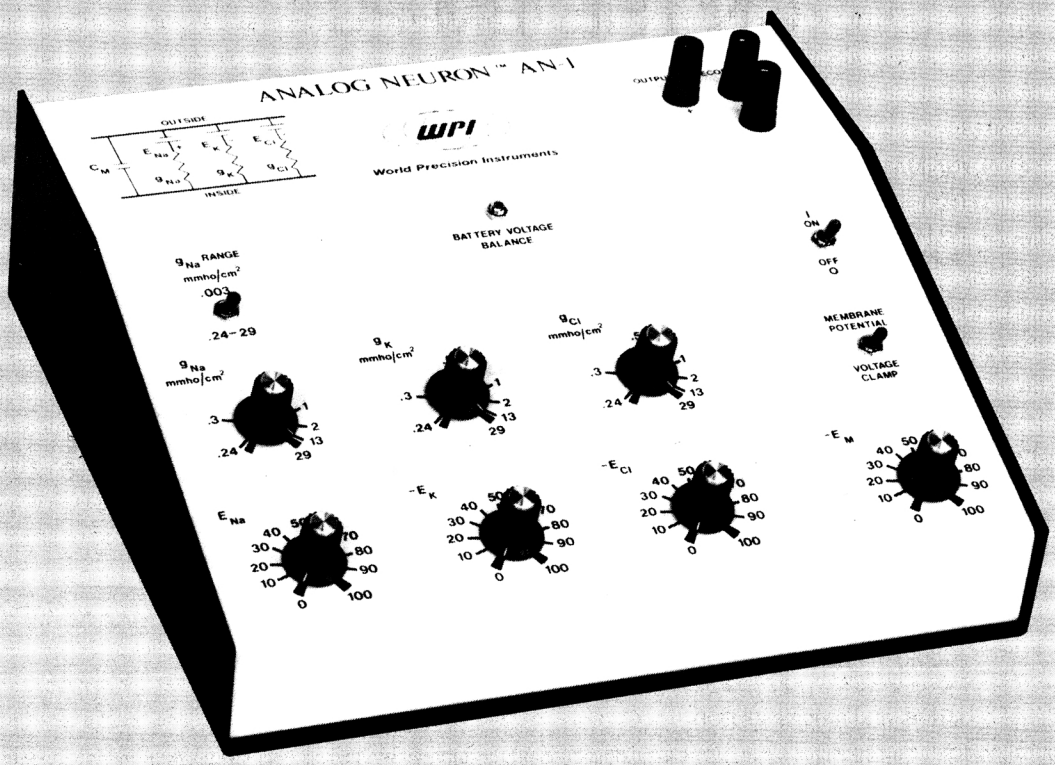

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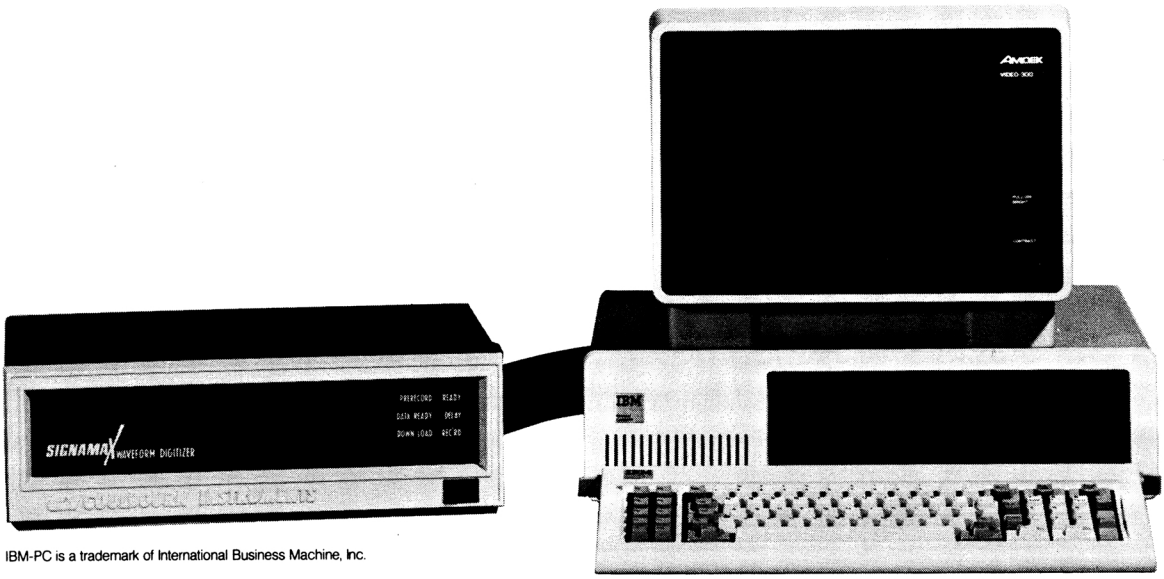

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