LEWIS A. CONNER MEMORIAL LECTURE

The Cardiac Catheter and the American Heart Association

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This year we are met not only for the 46th Annual Scientific Sessions of the American Heart Association but also to celebrate its 25th year as a national voluntary health agency. The Association came into being in 1922, and Lewis A. Conner of New York was elected the first President. Also, he was the first editor of the American Heart Journal which the Association began in 1926. I do not have the privilege of knowing Dr. Conner, but I share your admiration of the wisdom and dedication of our predecessors, which set the stage for the great accomplishments of this organization. Twenty-five years ago, the change was made from a medical society to a national voluntary association committed to raising funds from the American public and to using these funds for the cure of heart disease. In that year, 1948, the principle was established that the primary emphasis of the American Heart Association was the support of acquisition of new knowledge through research; in the year 1972-1973, over fifteen million dollars was expended in research support.

By 1948, it was evident that the cardiac catheter provided unique opportunities for the study of the human circulation, and the funds provided by the American Heart Association for training and supporting investigators did much to let us realize its full potential. As experience was gained, all chambers of the heart became accessible for study, and the concomitant developments of manometers, oximeters, and indicator-dilution technology permitted an exponential growth of knowledge of the normal and the abnormal circulation. As we reflect on the many who contributed to this knowledge, it is fitting that this year the Cardiopulmonary Council has established the Dickinson W. Richards Lectureship and has invited Dr. André Cournand to give the first lecture. In 1956, Dr. Cournand was awarded the Nobel Prize in Physiology and Medicine, jointly with Dr. Richards and Dr. Forssmann, "for their discoveries concerning heart catheterization and pathological changes in the circulatory system."

Today, enriched by the information that the cardiac catheter has made it possible to obtain, it is appropriate to ask how far we have progressed in achieving the knowledge required for the cure of the cardiovascular diseases. Certainly much has been accomplished, but mainly in the description of cardiovascular events. Little still is known of the mechanisms that underlie these events. If 100% represents a full understanding of the behavior of the cardiovascular system, my guess is that we are about 10% of the way.

Time will permit only a brief look at one of the many complex problems we face in reaching the full understanding — namely, the reflex control of systemic arterial blood pressure. This is a topic that concerns all of us because more than 23 million people in this country currently have derangement of this control, manifested as hypertension. To illustrate the complexity of this control, I have taken work carried out in the past five years by young physicians undergoing training in research with Dr. David Donald

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and myself prior to taking up academic positions in medical schools.

I do this deliberately because early in 1973 the decision was made by the Federal government to discontinue financial support for such research training. Fortunately, as a consequence of logical arguments and wise counsel from national organizations and esteemed individuals, the decision has been reversed and there has been partial restoration of funds. Because of its long-standing commitment to the support of research and its belief that research training is essential to the national effort in the conquest of cardiovascular diseases, the American Heart Association played a prominent role in the efforts to achieve the reversal of that unfortunate decision.

The factor of prime importance in the regulation of arterial blood pressure is the reflex control of the systemic resistance vessels by the sympathetic adrenergic nerves. Patients with idiopathic orthostatic hypotension have lost this control. They cannot maintain their blood pressure in the standing position (fig. 1) or during exercise in the supine position.

The major reflexes concerned in blood pressure regulation are those that originate in the sino-aortic region (the carotid and aortic baroreflexes and chemoreflexes), those that originate in the mechanoreceptors in the heart and lungs, and those from receptors in the skeletal muscles (fig. 2). A brief review of some recent studies will serve to illustrate how much still is to be learned about the nature of the receptors concerned in these reflexes, the location of the reflex centers within the central nervous system, the integration of information within and between these centers, and the translation of the resulting changes in sympathetic adrenergic outflow into contraction and relaxation of the peripheral blood vessels by alterations in the contractile proteins of the vessel walls.

Sino-aortic Reflexes

The importance of these reflexes in circulatory control has been recognized since the work of DeCastro, Hering, Koch, and Heymans in the years between 1924 and 1931. It has been assumed, mainly for want of direct evidence to the contrary, that the carotid sinus and aortic arch baroreflexes are equivalent in the reflex regulation of arterial blood pressure. That they are not equivalent can be demonstrated by examining the ability of the carotid and aortic reflexes to compensate independently for a hemorrhage of 8% of the blood volume. In vagotomized dogs with only the carotid reflex operative, the hemorrhage caused a decrease of 14% in mean aortic blood pressure; with only the aortic reflex operative, the blood pressure decreased by 38%. With no baroreflexes, the decrease was 48%. Thus, the aortic reflex in the dog is ineffective in combatting hypotensive situations (fig. 3).

That the aortic baroreceptors are involved mainly in the control of high blood pressure is evident from a comparison of the pressure-dependent changes in afferent nerve activity from multifiber preparations of the aortic and carotid sinus nerves (fig. 4 left). The mean systemic arterial pressure to which the baroreceptors were exposed varied from 50 to 220 mm Hg. The two stimulus-response curves are S shaped, with that for the aortic nerve displaced to the right of that for the carotid sinus nerve. The aortic nerve curve is approximately linear over the pressure range from 200 to 120 mm Hg; the carotid sinus nerve curve is linear from 180 to 80 mm Hg. The threshold pressure

![Figure 1](http://circ.ahajournals.org/)

**Figure 1**

"Marked decrease in systemic arterial blood pressure on standing in a patient with idiopathic orthostatic hypotension due to extensive loss of sympathetic nerve function. (Unpublished observations by Marshall et al.)"
Major reflexes concerned with regulation of systemic arterial blood pressure. Stimulation of baroreceptors causes inhibition of reflex center; stimulation of chemoreceptors and muscle receptors excites it. On efferent side, + and − indicate that changes in sympathetic adrenergic outflow from reflex center may not be uniformly distributed to all parts of cardiovascular system; outflow may increase to some parts and decrease to others.

Figure 2

for the aortic receptors is higher than that for the carotid sinus receptors, 100 mm Hg for the aortic compared with 70 mm Hg for the sinus.

Figure 4 right depicts the reflex vascular responses to changes in pressure in the vasoconstricted, blood-perfused aortic arch and carotid sinus preparations in the same dogs. The vascular responses were measured in a hind limb perfused at constant flow. For comparison, the change in perfusion pressure is plotted as a percentage of the maximal response. Maximal dilatation of the hind limb vessels occurs when the baroreceptor pressure is high, and the vessels constrict as the baroreceptor pressure is decreased. The carotid sinus curve is symmetric about the range of normal blood pressure for the dog, while the aortic arch curve is displaced to the right. Thus, the carotid sinus predominates in the regulation of arterial blood pressure, the aortic reflex assuming importance only when the pressure is abnormally increased.

Whether the dissimilarity between the aortic and carotid sinus reflexes is due to two different populations of receptors or to the fact that the same receptors are situated in vessels of different sizes and characteristics has not been established. Recent studies in rabbits indicate that with the development of renal hypertension there is an impairment of function or a decrease of baroreceptor units, an increase in the threshold pressure, and a diminution in the sensitivity of the baroreceptors. Thus, an impairment of the baroreceptor reflexes can contribute to the hypertension already produced by a renal cause. Also, the mild hypertension in rabbits with atherosclerosis may be reflexly engendered through an increase in sympathetic nerve activity and, hence, in peripheral vascular resistance resulting from a decrease in baroreceptor population and in baroreceptor sensitivity.7

Chemoreflexes

The carotid body, recognized since the studies by DeCastro and by Heymans in 1926 and 1927,4 is thought by many to function primarily as a respiratory

Figure 3

Aortic blood pressure response to 8% blood loss, showing roles of carotid and aortic baroreflexes. Data are means ± SE for eight dogs with vagi cut. (Redrawn from Eds.4)
chemoreceptor that responds to arterial hypoxemia. However, recent studies emphasize that the chemoreceptors are an important control mechanism in the regulation of the circulation. Activation of the chemoreceptors excites the reflex center, in contrast to activation of the baroreceptors which inhibits the center. The chemoreceptors are characterized by a high oxygen uptake/blood flow ratio and by the presence of an enzyme system with an unusual oxygen affinity. Although it is commonly thought of as an electrode-like structure that monitors the chemical composition of arterial blood, the actual receptor has not been identified and the mechanism of stimulation is still unknown.

In addition to the physical processes of diffusion of gases from capillaries to the sensor in the chemoreceptor, the carotid bodies also may be affected by changes in their metabolism and by changes in the volume and patterns of capillary blood flow; the latter may be altered by parasympathetic and sympathetic nerves acting as negative and positive feedback loops, respectively. Thus, the carotid and aortic bodies, through their efferent nerves, may participate in the vascular responses that they have initiated.

The vascular effects of graded stimulation of the carotid chemoreceptors were studied in anesthetized and artificially ventilated dogs, and stimulus-response curves were defined (fig. 5). The experiments were designed to analyze the responses of these chemoreceptors to independent changes in arterial oxygen or carbon dioxide tension and hydrogen ion concentration. The carotid bodies were isolated and perfused with autologous blood and stimulated by changing the $P_{O_2}$, $P_{CO_2}$, and pH of this blood. The systemic arterial blood gases and pH were kept normal. The vascular responses were measured in a hind limb perfused at constant flow.

With a decrease in the $P_{O_2}$ of the blood perfusing the carotid bodies, with the pH and $P_{CO_2}$ normal, a reflex constriction of the hind limb vessels did not occur until the $P_{O_2}$ decreased to 70 mm Hg. Thereafter, the constriction increased as the $P_{O_2}$ was decreased. When the blood perfusing the carotid bodies was made hypercapnic, with normal $P_{O_2}$, so that the pH decreased as the $P_{CO_2}$ increased, the hind limb vessels constricted strongly as soon as the normal values were exceeded and continued to constrict as the hypercapnia increased in severity.

In the bottom two panels of figure 5 the separate effects of changes in $P_{CO_2}$ and pH on the chemoreceptors are illustrated. An increase in $P_{CO_2}$ alone is a weak stimulus; a decrease in pH alone is a strong stimulus. In combination they provide a potent stimulus to the chemoreceptors and cause important reflex circulatory adjustments as soon as the pH and $P_{CO_2}$ depart from normal values.

In recent years there have been attempts to treat asthma by carotid body removal, a procedure that seems to have little experimental foundation and could be a hazard to the patient who becomes hypoxic as a consequence of his disease. The ventilatory response to hypoxia is lost after carotid body resection.
and hypotension supersedes the normal hypertensive response to hypoxia.

Stimulation of the chemoreceptors also can be used to demonstrate that the changes in sympathetic adrenergic outflow with activation of receptors may be nonuniform. With chemoreceptor stimulation, the muscle resistance vessels and the splanchnic veins constrict, due to an increase in sympathetic outflow, whereas the cutaneous veins dilate, due to a simultaneous decrease in the sympathetic outflow (fig. 6). Other investigators15 have shown that with stimulation of left atrial receptors there is an increase in activity in cardiac effenter sympathetic nerves, a decrease in activity in renal nerves, and no change in activity in efferent nerves to the spleen. This adds to the increasing evidence that the sympathetic outflow does not function uniformly in response to changes in the afferent input to the reflex centers.

Cardiopulmonary Baroreflexes

In recent years, studies mainly using recordings of impulses in sensory fibers have identified numerous receptors in the heart, great vessels, and lungs that are stimulated by certain chemical substances or are depressed by local anesthetics. It is likely that the normal stimulus of these receptors is mechanical deformation. These electrophysiologic studies have generated interest in the histology of these receptors, in the mechanism of impulse initiation at their generator region, and in efforts to determine their physiologic role.14-16 The receptors that are connected to the brain by medullated afferents in the vagi are present in specific regions, have a conduction velocity ranging from 8 to 29 m/s, and have a rhythmic pattern of discharge with the cardiac cycle and with respiration. Those connected to nonmedullated vagal afferents are distributed more widely, have a sparse and irregular discharge under normal conditions, and have a conduction velocity less than 5 m/s;16 they can

Figure 5

Vascular responses to graded stimulation of carotid chemoreceptors in seven dogs with vagi cut (mean ± se). Carotid bifurcations were isolated and perfused at constant pressure. Autologous blood collected in a reservoir was equilibrated at Pca ranging from 104 to 36 mm Hg; Pco, 39 to 81 mm Hg; and pH, 7.46 to 8.87. This was used to stimulate carotid chemoreceptors. Systemic arterial Pca, Pco, and pH were normal. A hind limb was perfused at constant flow with autologous blood; thus, changes in perfusion pressure were caused by constriction or dilatation of the hind limb resistance vessels. Increase in perfusion pressure is plotted as percentage of maximal response obtained when carotid bodies were stimulated with severe hypoxia (Pca = 34 mm Hg). Upper Left: Response to graded hypoxia (Pco, 36 mm Hg; pH = 7.35). Upper Right: Response to hypercapnia (Pco, 109 mm Hg). Lower Left: Response to hypercapnia with normal pH. Lower Right: Response to decreasing pH with normal Pco. (Redrawn from Pelletier14)

Figure 6

Vascular responses to hypoxic stimulation of carotid chemoreceptors in dog. The vagi were cut; carotid sinuses were vascularly isolated and pressure within them was maintained at 40 mm Hg to eliminate inhibitory influence of carotid baroreceptors on vasomotor center. Stimulation was caused by perfusion with autologous blood at Pco, 37 mm Hg. Systemic arterial Pca, Pco, and pH were normal. Muscle resistance vessels and cutaneous vein were perfused at constant flow with autologous blood; thus, changes in perfusion pressure were caused by constriction or dilatation of the respective vessels. Response of the splanchnic veins was estimated from changes in pressure in the spleen, whose circulation was temporarily arrested.11 (Redrawn from Pelletier14 and Pelletier and Shepherd16)
be stimulated mechanically or by chemicals such as phenyl diguanide.

The following studies were undertaken to further our knowledge of the role of these receptors in the regulation of the cardiovascular system. The aortic baroreceptors and chemoreceptors in dogs were denervated and carotid chemoreceptor activity was held constant. With a hemorrhage of 10% of the blood volume and only the carotid baroreceptors operative, the arterial blood pressure decreased by 18%; with only the vagal afferents from the heart and lungs operative, the decrease was 24%. With no baroreflexes, the decrease was 42%. Obviously, the cardiopulmonary receptors can have a substantial role in blood pressure control (fig. 7).

An important question is whether the cardiopulmonary receptors, like those of the carotid sinus, exert a continuous restraint on the vasomotor center. This can be tested by examining the vascular effects of interrupting the traffic from these receptors (conveniently, by cooling both vagi in the neck). The carotid sinus and aortic nerves in dogs were cut to eliminate the influence of the carotid and aortic baroreflexes and chemoreflexes. The vagi were cut below the diaphragm to eliminate any influence of receptors in the abdomen. The aortic blood pressure increased with vagal cooling, and the maximal increase occurred when both heart and lungs were present (fig. 8); for comparison purposes this increase, which averaged 56 mm Hg, is taken as 100%. When a bypass procedure was used and the lungs were removed while normal pressure was maintained within the heart, the vagal block still caused an increase in aortic pressure. Also, after removal of the heart, with the lungs in situ, the pressure still increased. Thus, receptors in both heart and lungs are involved, and the increase in aortic pressure with the vagal cold block indicates the magnitude of the inhibitory influence exerted by the cardiopulmonary receptors on the vasomotor center prior to the block. It is evident from these experiments that vagal afferents from the heart and lungs tonically inhibit the vasomotor center.

In further studies, Donald and Mancia (unpublished observations) have shown that the inhibition exerted by the heart is caused by receptors in both atria and ventricles. This was done by cooling the vagi in dogs in which the lungs and the ventricles had been removed but the beating atria left and in dogs in which the lungs were removed and the atria were denervated but the working innervated ventricles left.

![Figure 7](http://circ.ahajournals.org/)

*Mean aortic blood pressure response to 10% blood loss, showing roles of carotid and vagal baroreflexes. Mean ± SE in eight dogs with aortic depressor nerves cut. (Redrawn from Pelletier et al.)*

![Figure 8](http://circ.ahajournals.org/)

*Increase in mean aortic blood pressure with cold block of the cervical vagi, showing contribution of heart and lung receptors in dogs with carotid sinus and aortic nerves cut. Response with heart and lungs intact (ΔP 56 ± 10 mm Hg) is expressed as 100%. (Unpublished data of Mancia and Donald.)*
How do the inhibitory influences of the carotid pulmonary receptors and the carotid baroreceptors interact? The increase in aortic blood pressure with vagal cold block is a function of the carotid sinus pressure. When the carotid sinus pressure is low and the inhibition of the vasomotor center is minimal, the response to the vagal block is maximal; on the other hand, when the carotid sinus pressure is high and the inhibition of the vasomotor center from the carotid sinus is at its maximum, there is no increase in aortic pressure when the vagi are blocked (fig. 9). At normal carotid sinus pressure, both the cardiopulmonary and the carotid baroreceptors contribute to the inhibition of the vasomotor center.

Examination of the sympathetic outflow shows that the adrenergic nerve activity to the kidney is markedly increased when the influence of the cardiopulmonary receptors is removed by vagal cooling. In the experiment shown in figure 10, the aortic blood pressure increased with the vagal cold block from 115 to 175 mm Hg, and this was accompanied by a marked increase in the sympathetic nerve traffic to the kidney. In addition to their influence on the renal vessels, the cardiopulmonary receptors control the amount of renin released by the kidney. This is shown by the marked increase in the amount of renin released when the vagi are blocked (fig. 11). Thus, the mechanoreceptors in the heart and lungs exert a continuous restraining influence on the sympathetic outflow to the kidney, thereby preventing the renal vessels from constricting and at the same time inhibiting the release of renin.

A reflex from the lungs affecting the systemic blood vessels was first demonstrated by Brodie and Russell in 1900 and has been studied in detail by Daly and Robinson. Figure 12 shows the effect of lung inflation on the renal vascular resistance in the rabbit. The carotid sinus and aortic depressor nerves were cut to eliminate the influence of the carotid and aortic baroreflexes and chemoreflexes. When the artificial ventilation was suspended, so that the lungs were deflated, the gradual accumulation of carbon dioxide excited the vasomotor center by a direct action, with a resultant increase in sympathetic outflow and constriction of the kidney vessels. When the experiment was repeated and the lungs were inflated on two occasions during the period of no ventilation, to activate the bronchopulmonary stretch receptors, this activation inhibited the vasomotor center, counteracting the excitatory action of the carbon dioxide accumulation and causing relaxation of the kidney vessels, as shown...
Effect of renal vein renin kidney by the vagal block. (Unpublished data of Mancia, Romero, and Shepherd.)

by the decrease in perfusion pressure. The threshold for this reflex is low, 1 to 2 mm Hg. This lung inflation reflex permits renal blood flow to be selectively main-
tained during hypercapnia, suggesting a role for these receptors in acid-base balance. Other receptors in the lungs, described by Paintal, include the jux-
tapulmonary capillary receptors; these are activated by pulmonary congestion and cause dyspnea, bradycardia, and hypotension.

Obviously, much remains to be determined about the cardiopulmonary receptors. Another example of their complexity is the fact that, in addition to the afferent cardiac vagal fibers, afferent fibers running in the sympathetic nerves, with atrial and ventricular endings, provide the spinal cord with continuous information on cardiac events. More details are needed about the histology of the cardiopulmonary receptors and the precise roles of the different groups. Perhaps some are more involved in hormonal release and kidney function and others are more involved in general circulatory control. Their functions may be modified by heart disease. For example, some of the circulatory changes observed at the time of coronary artery occlusion in cats and dogs can be ascribed to an alteration in discharge from receptors in the heart.

Skeletal Muscle Receptors

Another group of receptors that play a key role in the regulation of arterial blood pressure are those in the skeletal muscle. Activation of these, like activation of the carotid and aortic chemoreceptors, excites the vasomotor center, in contrast to the carotid and aortic

Figure 11

Effect of bilateral vagal cold block on renin release from the left kidney in six dogs with aortic nerves cut and carotid sinus pressure maintained at level of mean aortic pressure present prior to block. Vagal block was maintained for 3 minutes, and blood samples for renin measurements were drawn simultaneously from aorta and left renal vein before block (control) and during the third minute of block. (Unpublished data of Mancia, Romero, and Shepherd.)

Figure 12

Effect of lung inflation on kidney perfusion pressure in rabbit with carotid sinus and aortic nerves cut. Kidney was perfused at constant flow with autologous blood; thus, changes in perfusion pressure were caused by constriction or dilatation of kidney resistance vessels. Animal was ventilated artificially with oxygen. Stopping the ventilation (upper dotted line) caused a small immediate increase in perfusion pressure (lower dotted line) and a larger rapid increase after about one minute. Return to artificial ventilation reversed the increase in perfusion pressure. Inflation of the lungs twice to 10 cm H₂O during cessation of ventilation (upper solid line) caused a decrease in perfusion pressure (lower solid line). The first inflation (at relatively low PaCO₂) caused a small decrease in kidney perfusion pressure whereas the second inflation (at a higher PaCO₂) caused a marked decrease. (Redrawn from Ott and Shepherd.)

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baroreceptors and the cardiopulmonary baroreceptors which inhibit it (fig. 2).

In 1938, Alam and Smirk described what they called the blood pressure raising reflex — namely, a strong sustained contraction of small muscle groups can cause a marked increase in systemic arterial blood pressure (fig. 13). The increase is due to activation of the sympathetic adrenergic nerves to the heart and blood vessels. Where does the stimulus arise? It could arise in the higher centers of the brain or come from receptors in the contracting muscle.

That such receptors are present in muscle and can cause reflex vascular changes is shown by the following experiment. In the dog with vagi cut and carotid sinus pressure controlled at a low level, electrical stimulation of the muscles of one hind limb sufficient to cause their tetanic contraction provokes an increase in aortic blood pressure, a reflex constriction of the muscle vessels of the opposite hind limb and of the splanchnic veins, and a reflex dilatation of the cutaneous veins. When the same electrical stimulation is applied but the muscles are prevented from contracting by a neuromuscular blocking agent, the blood pressure decreases, the muscle resistance vessels and splanchnic veins dilate, and the cutaneous veins constrict (fig. 14). Hence, muscle contraction was necessary for the pressor response. Because the pressure increase still occurred when the muscles were separated from the joints and tendons, it was caused by the muscle contraction activating receptors in muscle. Whether these are "metabolic" receptors responding to chemical changes in the muscles or mechanoreceptors is not yet known. It is likely that the same receptors are involved in the reflex circulatory changes seen during rhythmic exercise and that are essential for the maintenance of systemic arterial blood pressure and for the distribution of the increase in the left ventricular output to the active muscles.

Other Parts of the Reflex Arc

Although it is often concluded that the integration of information arising from the cardiovascular and pulmonary mechanoreceptors and chemoreceptors is mediated entirely through centers located in the pons and medulla, recent studies indicate that higher autonomic centers participate. Regarding the sympathetic ganglia, new work by others indicates something of the complexity here. The acetylcholine liberated at the preganglionic ending acts not only to cause depolarization of the ganglion cell but, through the intermediary of an adrenergic interneuron, also acts on the ganglion cell to cause hyperpolarization.

Let us conclude by a brief look at the neurovascular junction (fig. 15). Since Von Euler’s demonstration in 1944 that norepinephrine was the sympathetic

![Figure 13](https://example.com/figure13)

**Figure 13**

Response of mean aortic blood pressure before, during, and after sustained 50% maximal voluntary hand-grip contraction that was held to the point of fatigue. (Modified from Lind AR, Taylor SH, Humphreys PW, Kennelley BM, Donald KW: The circulatory effects of sustained voluntary muscle contraction. Clin Sci 27: 229, 1964. By permission of the Medical Research Society and the Biochemical Society.)

![Figure 14](https://example.com/figure14)

**Figure 14**

Vascular responses to stimulation of receptors in skeletal muscle (dog with vagi cut and carotid sinus pressure maintained at 40 mm Hg to eliminate inhibitory influence of carotid baroreceptors on vasomotor center). Muscle resistance vessels and cutaneous vein were perfused with autologous blood at constant flow; thus, changes in perfusion pressure were caused by constriction or dilatation of the respective vessels. Response of splanchnic veins was estimated from changes in pressure in spleen in which circulation was temporarily arrested. (Redrawn from Clement et al. and from unpublished observations of Webb-PEploe and Shepherd.)
neurotransmitter, much has been learned about the release and reuptake mechanisms at the adrenergic nerve terminals. We know that angiotensin can increase the output of norepinephrine and that prostaglandins of the E type can decrease it. The possibility has been raised of a histaminergic neuron, acting either directly on a receptor or through a histamine-releasing cell. Also, the norepinephrine liberated from the adrenergic nerve endings may control the release of histamine.\textsuperscript{32-34}

We have explored the possibility that acetylcholine liberated from a cholinergic fiber may decrease the output of norepinephrine from the adrenergic nerve. A strip from a dog's lateral saphenous vein was incubated with radioactive norepinephrine and placed in an organ bath. Electrical stimulation caused the strip to contract and to release norepinephrine from the nerve endings, as shown by the increase in tension exerted by the strip and the concomitant increase in the amount of radioactive norepinephrine released from the nerve terminals (fig. 16). A small dose of acetylcholine decreased the tension of the strip by decreasing the output of norepinephrine from the nerve endings.\textsuperscript{35} Experiments in vivo suggest that acetylcholine has this same effect on the sympathetic nerve endings.\textsuperscript{36}

\textbf{Comment}

Many other examples could have been selected to illustrate my thesis, which is that our understanding of the mechanisms that control the cardiovascular system is still rudimentary. Until we gain this understanding, hypertension, atherosclerosis, and their sequelae will continue as major causes of death and disability. Studies of the type I have described require the participation of young investigators, anxious to test their abilities in the research laboratory. If we fail to provide financial support for the continued training of investigators, we will slow the acquisition of the new knowledge that is indispensable for the treatment, prevention, and cure of disease. The advent of the cardiac catheter demonstrated how much can be achieved by a close interchange between the practicing cardiologist and the laboratory scientist. If we fail to provide the opportunities for the young M.D. to train in research, we will lose that interchange.

The American Heart Association has much to be proud of in its wise and sustained policies for research support. A good example of this is the Established Investigatorship program. These awards are made for five years to individuals of outstanding research promise who are selected by the system of peer review. The program began in 1949. Of the 306 investigators who completed their tenure by June 1973,
281 or 92% have remained in academic medicine and research. This splendid record attests to the judicious selection and to the effect of the program on the career choices of the persons involved.

These troubled times for the biomedical scientist, who is confused by the lack of a consistent national policy for research. I hope that the American Heart Association will continue, as in the past, to demonstrate how much can be achieved by supporting the man of ideas and especially the young and promising scientist through the critical years of his training. By this example we may help to counter the erroneous concept, so popular today, that the scientist who is coralled by bureaucracy and made "relevant to society" can find the cause and cure of disease more quickly than can the unfettered man of ideas.

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