

## *Autonomic Regulation of Blood Volume*

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THERE ARE A NUMBER of mechanisms by which the autonomic nervous system can modify the volume or distribution of fluid within the cardiovascular system. Changes in distribution are taken to fall within the scope of this review, because the physiologic consequences of changes in central blood volume are comparable to, and no less important than, changes in total blood volume. Three types of change may be distinguished: *immediate* changes, accomplished by differential constriction or relaxation of capacitance vessels, with immediate redistribution of blood; *early* changes, resulting from gain or loss of fluid across capillaries with changes in postcapillary-to-precapillary resistance ratios; and *delayed* changes, resulting from retention or excretion of sodium and water. The role of the autonomic nervous system in many of the delayed changes has not been established definitely, but much evidence suggests that the autonomic nervous system may influence renal tubular reabsorption of sodium and the secretion of renin (and thus the renin-aldosterone system) and of antidiuretic hormone (ADH), all factors capable of changing the volume of body fluids. Further, high- and low-pressure receptors have been shown to influence the secretion of ADH, renin and aldosterone.

The purpose of this discussion is to review the current evidence relating the autonomic nervous system to the control of all three types of change.

### **Immediate Changes: Redistribution of Blood Volume by Venomotor Reflexes**

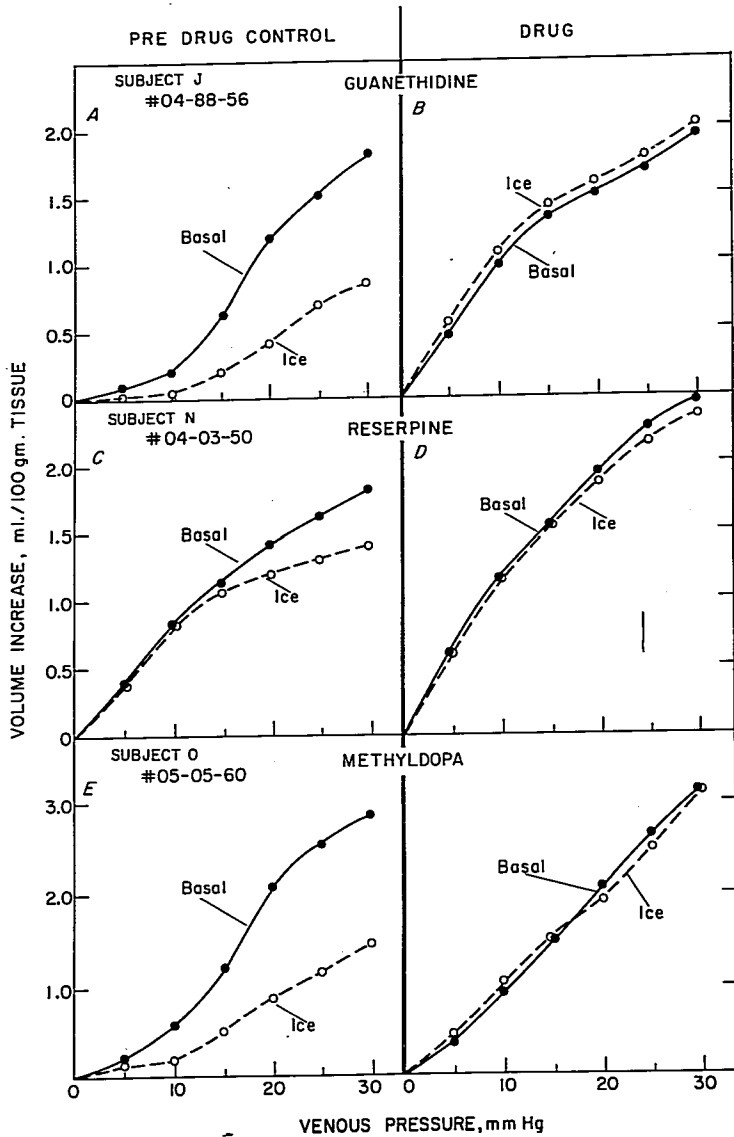
In a consideration of the manner in which the autonomic nervous system can increase

most quickly the volume of blood available for the filling of the cardiac chambers, it is important to recall that the arterial system is relatively noncompliant and preserves its high-pressure characteristics by maintaining high resistance to blood flow in the peripheral arterioles, whereas the low-pressure venous system is easily distensible and contains approximately 85 per cent of the total blood volume of the body. The low-pressure vascular compartments within the chest are considered a part of the low-pressure venous system. When blood is added to the intrathoracic compartment, it may be "stored" in the extrathoracic venous capacitance compartments, which provide a large volume reserve for the atria and ventricles in the control of cardiac output.

It is now clear that the veins participate actively in maintaining circulatory function through reflexes mediated by the sympathetic nervous system, and can constrict in response to a variety of physiologic stimuli, to augment venous return to the heart (fig. 1). Thus, in response to emotion, cold, norepinephrine, hyperventilation, and muscular exercise, venoconstriction occurs,<sup>1-4</sup> accompanied by a shift of blood in extrathoracic venous reservoirs toward the central circulation. This venoconstriction, which is also manifest at rest in congestive heart failure,<sup>5-8</sup> is mediated by increases in sympathetic nervous activity. Since there is more smooth muscle relative to the cross-sectional area in the smaller veins than in the larger veins, a generalized augmentation of venous tone results in mobilization of the peripheral blood into the intrathoracic vascular compartments. In this manner, there is enhancement of effective central blood volume, and this complements the performance of the heart in its delivery of a supply of oxygen adequate to satisfy the requirements of the peripheral tissues for metabolic demands, at rest and during the increased demands of muscular activity. Although it is generally agreed that

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the efferent limb of these vasoconstrictor reflexes for the rapid alteration of the effective blood volume is located in the adrenergic nerves, the position of the receptor cells is not well established. Current evidence suggests that such receptors may exist in the right atrium and perhaps in other low-pressure vascular components within the chest.<sup>2-4, 8</sup>

It is attractive teleologically to speculate that the carotid baroreceptors might initiate venomotor reflexes also. Although there is some evidence from experiments in animals to support the view that marked arterial hypotension leads to venoconstriction,<sup>9</sup> the importance of this reflex during moderate hypotension in man has not been established.<sup>10</sup> Thus, in human volunteers subjected to brief periods of mild or moderate reduction in arterial pressure, produced by the administration of the arteriolar dilating substance, bradykinin, intravenously and the application of lower-body negative pressure, venous constriction does not occur.<sup>11</sup> Studies of the vasodilator action of nitroglycerin taken sublingually give results consistent with this conclusion. Thus, the direct venodilator effect apparently is not opposed by reflex adrenergic discharge to the veins; reduction in venous tone following nitroglycerin is not altered by pretreatment with the antiadrenergic drug, guanethidine<sup>12</sup> (fig. 2).

It has been claimed that the rise in venous tone which may occur in response to the assumption of the upright posture is mediated through the baroreceptors<sup>13, 14</sup> but the weight of present evidence is opposed to this view. The effect is transient, and disappears while other evidence indicates that baroreceptor activity is persisting.<sup>10, 11, 15, 16, 17</sup>

These observations indicate that the systemic venous bed constricts in response to several afferent physiologic stimuli, but not to ordinary stimulation of the high-pressure baroreceptor reflexes. However, it is likely that reflex venoconstriction is produced by significant reduction of arterial pressure. Thus, dur-

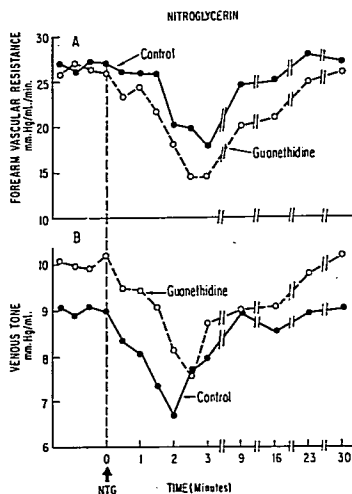


Fig. 2. Average values from studies in eight normal subjects, showing the effects of sublingual nitroglycerin (NTG) on forearm vascular resistance (A) and venous tone (B) during a control period (dots and solid lines) and 20 minutes after injection of guanethidine intravenously (open circles and broken lines). Before the administration of nitroglycerin, guanethidine increased the venous tone, apparently as a result of the release of endogenous norepinephrine at sympathetic nerve endings. Following guanethidine, the decline in arteriolar vascular resistance produced by nitroglycerin was accentuated, suggesting that when nitroglycerin is given in the presence of a normally-functioning sympathetic nervous system, the fall in resistance is partially opposed by sympathetically-induced reflex arteriolar constriction. In contrast, the venodilator action of nitroglycerin was not enhanced by sympathetic blockade.<sup>12</sup>

ing most forms of shock and syncope, reflex rise in venous tone probably occurs. Indeed, recent studies carried out in man have shown venoconstriction, as a compensatory reflex, occurring at the time of vasovagal syncope.<sup>18</sup>

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Fig. 1. Effects of the antiadrenergic drugs guanethidine, reserpine, and methyldopa on the response of venous pressure-volume curves to immersion of the hand in ice water. Venous tone was determined by the progressive, stepwise occlusion of venous outflow from the forearm, and the volume of the venous bed at equilibrium was measured at each level of venous pressure by a plethysmographic technique. The control studies are on the left, and the drug studies are on the right. Prior to adrenergic blockade, ice water provoked a reflex increase in venous tone. At the time of the drug studies, venomotor reactivity was abolished. (Reproduced by permission from ref. 1.)

As the evidence thus indicates that venomotor reflexes do not participate in the adrenergically-mediated hemodynamic adjustments to moderate arterial hypotension, it is of interest that some investigators contend that the control of fluid volume by the kidney ("delayed changes": *vide infra*) is relatively more sensitive to moderate changes in blood volume than is the tone of the capacitance vessels.<sup>19</sup> Thus, the compensatory response to small alterations in blood volume might be mediated chiefly by adjustments in the circulatory volume brought about by the excretory function of the kidney, with little or no reflex-induced change in the distensibility of the venous beds. This contention has been based largely on studies which have suggested: (1) that blood loss of up to 500 ml. in man does not result in vasoconstriction in the forearm<sup>8</sup>; and (2) that blood loss of this magnitude may induce retention of sodium and of water.<sup>20</sup> In opposition to this view, studies in animals have indicated that a generalized vasoconstriction occurs during moderate hemorrhages.<sup>21, 22</sup> This apparent discrepancy can be explained in part if the splanchnic venous system constricts substantially more than the remainder of the systemic capacitance bed at the time of moderate blood loss, as reported for human subjects.<sup>23</sup>

It is clear, however, that acute extensive loss of blood volume results in adrenergically-induced vasoconstriction both in animals<sup>21, 22</sup> and in man.<sup>24</sup> Presumably, the greatly reduced cardiac filling pressure stimulates the atrial volume receptors significantly; further, the striking fall in cardiac output results in severe hypotension and stimulation of the high-pressure baroreceptors as well. From these considerations, venous reflexes appear to assume greatest importance in the immediate, rapid adjustments of the circulation in response to large changes in blood volume and arterial pressure.

#### Early Changes: Sympathetic Alterations in Transcapillary Filtration

It is well documented that an increase in the blood concentration of the sympathetic neurotransmitter, norepinephrine, results in a reduction of the plasma volume within a short period of time. Thus, the administration of

norepinephrine to normal subjects lowers blood volume<sup>25</sup> and the blood volume is diminished in patients with elevated blood concentrations of endogenous catecholamines resulting from pheochromocytoma.<sup>26</sup> The mechanism by which increased blood concentrations of norepinephrine may lead to reduction in plasma volume probably depends upon an increase in filtration pressure between the intravascular and extravascular compartments: of fundamental importance is a rise in the hydrostatic pressure within the capillary beds. The intracapillary pressure is determined by the relation between arterial and central venous pressure and, most importantly, the post-capillary-to-precapillary resistance ratio. Since capillary pressure is particularly sensitive to changes in venous or postcapillary resistance, the increase in venous resistance produced by epinephrine or norepinephrine, as reflected by a rise in venous tone (fig. 3),<sup>27</sup> results in loss of fluid to the extravascular space.<sup>28</sup> Whereas the total blood volume is reduced following the administration of norepinephrine, the effects of prolonged sympathetic stimulation, produced, for example, by a lowering of pressure in the carotid baroreceptor areas, appear to be more complex.<sup>29</sup> Thus, an increase in adrenergic impulse traffic has been shown to reduce capillary pressure in the skeletal muscle circulation in cats, resulting in net transcapillary movement of fluid from this large tissue mass into the vascular system. However, no measurements of total blood volume were carried out in this study.<sup>29</sup>

In agreement with the observations indicating that increases in circulating norepinephrine reduce plasma volume is the documentation that, in normal man, plasma volume expansion results from interference with adrenergic function.<sup>30</sup> Thus, the administration of guanethidine or phenoxybenzamine produces a rise in blood volume, presumably by the action of the drugs to diminish venous tone, post-capillary resistance, and thereby capillary filtration pressure. From the foregoing, it is apparent that the sympathetic nervous system, by virtue of its regulation of venous resistance, provides a second, relatively rapid means for the control of the circulatory volume.

An important clinical consideration relating to the action of norepinephrine on transcapil-

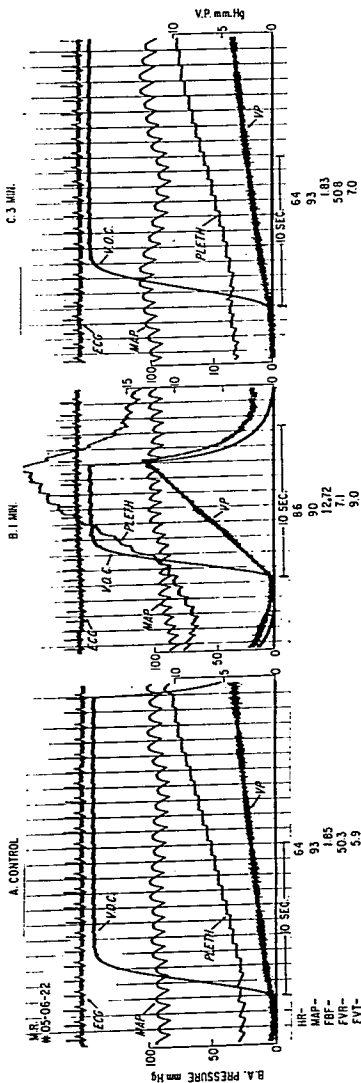


FIG. 3. Three segments of records obtained from a normal subject illustrating the effects of epinephrine on the vascular bed of the forearm. The tracing (left) (A) was obtained during the control period, that in the middle (B), one minute following the intravenous injection of 5  $\mu$ g. of epinephrine, and that on the right (C), three minutes after epinephrine. PLETH: forearm plethysmograph tracing; V.P.C.: forearm venous pressure; MAP: mean arterial pressure; O.C.: venous occluding cuff on the upper arm. The numbers below the tracings indicate the variables which were measured or calculated. HR: heart rate. FBF: forearm blood flow; FVR: forearm vascular resistance; VP: forearm venous tone. Note that in panel B the rise of venous pressure is considerably more rapid relative to the increase in forearm venous volume, as shown by the slope of VP indicating marked venoconstriction produced by epinephrine. The greater rate of rise of PLETH in B shows that that forearm blood flow was increased following epinephrine; since MAP remained essentially unchanged, forearm vascular resistance was reduced.

lary filtration pressure pertains to its use for prolonged periods of time in the treatment of hypotension. Since the blood volume is reduced by this action of norepinephrine, extended therapy ultimately may intensify the shock state. This mechanism should be kept in mind when an attempt is made to "wean" patients from alpha-receptor adrenergic stimulating agents: fluid replacement may be necessary. Finally, in this regard, it is recognized that the greatest loss of plasma volume is observed during therapy with agents such as epinephrine which lower peripheral arteriolar resistance while elevating venous resistance<sup>25</sup> (fig. 3).

#### Delayed Changes: Possible Reflex Mechanisms Acting Through the Kidney on Sodium and Water Balance

There are few definitive experiments relating blood volume to the excretory functions of the kidney via the autonomic nervous system. Indeed, the renal mechanisms operative in the control of body sodium and water are themselves imperfectly understood. Current evidence does support the view, however, that a decrease of sympathetic activity leads to an enhancement of sodium excretion in normal subjects. Before we consider the evidence for this, we must review current concepts regarding the control of urinary excretion of sodium and water.

The expansion of the volume of fluid within the extracellular space in normal subjects, produced, for example, by the administration of saline loads, results in an increase in salt and water excretion. Surprisingly, the precise manner in which this simple intervention is translated into a diuretic response is poorly understood despite intensive investigation. Whereas a detailed consideration of this investigation is beyond the scope of the present work, it is necessary to review the elements known or thought to mediate the diuresis before the role of the autonomic nervous system can be evaluated. These elements are: (1) increase in glomerular filtration rate (GFR); (2) decrease in distal tubular reabsorption of sodium; (3) decrease in the secretion of renin and (4) of aldosterone; (5) decrease in proximal tubular

reabsorption of sodium; and (6) decrease in secretion or release of antidiuretic hormone (ADH).

With infusion of saline, there is frequently an increase in GFR and hence in the filtered "load" of sodium and water. The role of the autonomic nervous system in this response has not been established: sympathetic activity could participate by mediating an increase in the postcapillary-to-precapillary resistance ratio in the glomerulus itself. (We shall see that the increase in GFR with saline loads is frequently greater following adrenergic blockade. This clearly does not rule out an autonomic reflex mediating the smaller increases frequently seen *without* blockade.)

Changes in distal tubular reabsorption of sodium are generally estimated from changes in urinary excretion of potassium or, under rigorously controlled conditions, from changes in excretion of "free" water. (As it is likely that secretion of ADH changes with infusion of saline, *vide infra*, free water changes in the present context cannot be evaluated.) Infusion of saline generally (but not always) increases urinary potassium; accordingly, decrease in the amount of sodium reabsorbed distally probably is not important in the immediate response to saline loads.

The secretion of renin is increased by sodium deprivation and decreased by sodium loading.<sup>21</sup> Corresponding changes in angiotensin secretion might influence tubular reabsorption of sodium both directly<sup>22, 23</sup> and through control of aldosterone secretion.<sup>24, 25</sup> *vide infra*. Furthermore, release of renin may be produced by catecholamines, infused directly, or released by stimulation of sympathetic nerves,<sup>26</sup> or by tyramine.<sup>27</sup> Accordingly, autonomic regulation of blood volume through renal sodium excretion may involve the renin-angiotensin-aldosterone system.

Aldosterone in turn may stimulate (and a decrease in its secretion may lower) reabsorption of sodium both distally and proximally.<sup>28</sup> Furthermore, there is evidence of autonomic control of aldosterone secretion. In the dog, constriction of the common carotid arteries results in an increased secretion of aldosterone,<sup>29, 40</sup> an action which may be mediated by sympathetic afferent fibers, especially those arising at the thyroid-carotid arterial junc-

tion.<sup>39</sup> This effect has been ascribed to ACTH<sup>40</sup> but strong evidence that such constriction increases renin secretion<sup>37, 41</sup> makes it equally plausible that angiotensin stimulates the secretion of aldosterone. This stimulation of renin release, despite increases in systemic blood pressure, may depend on extrarenal receptors, which stimulate the juxtaglomerular apparatus by way of the sympathetic nervous system.<sup>42</sup>

Proximal tubular reabsorption of sodium may be decreased by infusion of saline without any change in sodium-retaining steroids.<sup>43, 44</sup> It is not known to what extent such a change, which may be under hormonal control,<sup>45</sup> can be influenced by the autonomic nervous system.

It has been assumed that a decrease in secretion or release of antidiuretic hormone follows expansion of the intravascular space because such expansion often is followed by a copious diuresis of "free" water. Whereas ADH has never been measured directly in this context, there is considerable circumstantial evidence suggesting that changes in ADH secretion, under autonomic control, may initiate the diuresis. Until direct proof is available, however, it is important to note that changes in proximal reabsorption of sodium and water, without changes in ADH, could account for most of the observations. These observations are reviewed briefly.

Control of blood volume by change of ADH and body fluid volume has been proposed and defended by Gauer.<sup>19</sup> Thus, in dogs with intact vagi, negative-pressure breathing (which distends the atria), inflation of an atrial balloon, or infusion of blood induces diuresis and produces an increase in afferent impulse traffic in the vagus nerves; cooling of the nerves to 8° C. abolishes both effects. On the other hand, positive-pressure breathing (which compresses the atria) or removal of 50 ml. of blood from a 10-kg. dog induces an antidiuresis and produces a decrease in impulse traffic in the vagus nerves. Thus, it has been suggested that stimulation of volume-sensitive stretch receptors within the walls of the left atrium produces a vagal afferent discharge which, in turn, leads to inhibition of the secretion of ADH and reduction in reabsorption of water in the distal tubules. Indeed, some in-

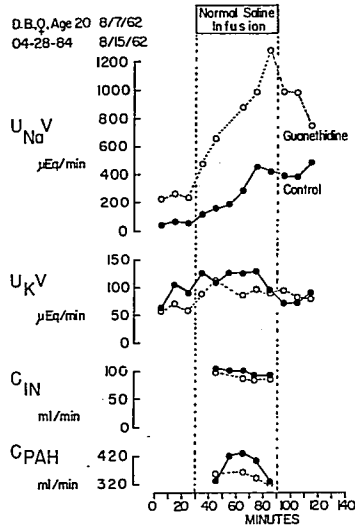


FIG. 4. Changes in renal sodium excretion ( $U_{Na}V$ ), potassium excretion ( $U_KV$ ), inulin clearance ( $C_{IN}$ ), and para-aminohippuric acid clearance ( $C_{PAH}$ ) with infusion of 2 liters of physiologic saline solution before (dots and solid lines) and during (open circles and broken lines) treatment with guanethidine in a normal subject. Adrenergic blockade resulted in a much greater excretion of the sodium load compared to the control infusion.<sup>42</sup>

investigators believe that this reflex control of ADH is the most important delayed means for regulating the blood volume, and that changes in aldosterone secretion and in adrenergic nervous activity are brought into action only in extreme circumstances.<sup>19</sup> It is of interest that *direct* measurement of the stimulation of ADH secretion by changes of blood volume has been made only in "extreme" circumstances. Thus, rapid loss of a large volume of blood was shown to elevate plasma ADH concentration in dogs.<sup>46</sup>

Considerable evidence relates the overall renal excretion of sodium to the autonomic nervous system. Thus, the infusion of physiologic saline solution into normal subjects in whom sympathetic blockade has been pro-

duced by guanethidine results in a much greater excretion of sodium than it did before treatment with the drug.<sup>47</sup> The glomerular filtration rate is often, but not always, greater after such sympathetic blockade (fig. 4) and the increase in sodium excretion must depend in part upon a decrease in tubular reabsorption. Similarly, an enhanced excretion of sodium during saline infusion is observed in patients with autonomic insufficiency.<sup>48</sup> During treatment with salt-retaining steroids in normal man, sodium retention and weight gain are less after than before adrenergic blockade.<sup>47</sup>

In normal subjects deprived of dietary sodium, the net urinary loss of sodium is greater with than without autonomic blockade.<sup>49</sup> Furthermore, anesthetized dogs with one kidney denervated excrete more sodium from the denervated than from the normal kidney.<sup>50</sup>

Studies with dog kidneys perfused from a donor dog, and retaining only nervous connections with the original owner, strongly support some role for the autonomic nervous system: such kidneys respond with sodium loss to infusion of saline into the original owner.<sup>51</sup>

The implication of left atrial mechanoreceptors in the mediation of diuresis has been especially attractive to clinical investigators. Thus, this mechanism has been evoked to account for the polyuria following paroxysmal atrial arrhythmias in patients.<sup>52, 53</sup> Conversely, the syndrome of inappropriate secretion of ADH and the resultant oliguria seen in some patients following the operative relief of severe mitral stenosis has been attributed to the sudden decrease in elevated left atrial pressure and volume.<sup>54</sup> Electrical pacing at high frequencies of the right atrium in dogs has produced diuresis.<sup>55</sup> On the other hand, in patients without heart disease and in cardiac patients with and without congestive failure studied in our laboratories, electrical pacing of the right atrium at fast rates for prolonged periods of time did not result in diuresis of sodium or water.

In congestive heart failure, there is evidence of sustained overactivity of the autonomic nervous system, presumably "in order to" support the circulation in the face of diminished cardiac contractility.<sup>5-8, 56</sup> In addition, despite

expansion of the extracellular and even the intravascular volume, there may be paradoxical elevation of secretion of renin and aldosterone. Finally, there may be inappropriate secretion of antidiuretic hormone,<sup>57</sup> preventing diuresis of water as well as of saline loads.

The precise mechanisms by which sodium and water are retained in cardiac failure are not clear. Because of this, and because of the apparently paradoxical effect of adrenergic blockade in this syndrome, the precise role of the autonomic nervous system has not been defined. It can best be assessed after a brief review of the mechanisms involved.

Retention of sodium in cardiac failure does not require a decrease in GFR and thus in filtered load; accordingly, it probably always depends upon abnormally large tubular reabsorption of sodium. This often includes distal reabsorption, as can be shown by the ready production of hypokalemia. There is often excessive production of renin, which has not been explained fully; it may depend upon autonomic impulses. There is often a corresponding increase in secretion of aldosterone, known to promote distal tubular sodium-for-potassium exchange. As with renin, the mechanism by which aldosterone secretion is increased has not been elucidated fully. There is considerable evidence that proximal tubular reabsorption of sodium and water is increased abnormally in cardiac failure. Thus, the defect in excretion of free water (dependent upon selective tubular reabsorption of sodium more distally) and of potassium (dependent upon sodium-for-potassium exchange more distally) can be overcome by infusion of non-reabsorbable solute, which "delivers" proximal tubular fluid to the distal nephron.<sup>58</sup> In some patients, maximal blockade of the action of aldosterone with spironolactone produces little or no sodium diuresis<sup>59</sup>; thus, most of the excess of sodium reabsorption is not that of distal, aldosterone-dependent sodium. A comparable renal situation can be produced by constriction of the aorta and by constriction of the inferior vena cava in animals "escaped" from aldosterone; in these experiments, proximal tubular reabsorption was shown to be excessive,<sup>43</sup> and some evidence for an hormonal basis was adduced.<sup>45</sup> Finally, in some pa-



tients with cardiac failure, there is evidence that antidiuretic hormone is secreted inappropriately,<sup>57, 60</sup> possibly because of an autonomic reflex dependent upon the cardiovascular abnormalities. This defect is difficult to assess without direct assay because of the aforementioned defect in excretion of free water, the only *in vivo* index to secretion of ADH.

Whereas the autonomic nervous system is clearly overactive in many patients with cardiac failure, attempts to define its precise role in the actual control of blood volume have not been successful. The overactivity may represent in part an "attempt" to restore central blood volume, which should be of benefit. It doubtless involves an "attempt" to repair cardiac functions as well.<sup>56</sup> The overall increase in blood volume might result both from early autonomic effects (decrease of overall post-capillary-to-precapillary resistance ratio) and from delayed effects: the excessive renal retention of sodium and water.

The question cannot be readily answered by the use of autonomic blockade. In contrast to normal subjects, patients with cardiac failure show further retention of sodium and water, an increase in blood volume and a worsening of the state of heart failure after blockade of the adrenergic nervous system. Retention of sodium has been induced by guanethidine<sup>61</sup> and by beta-receptor adrenergic blockade<sup>62</sup> in patients with heart disease who had been able to achieve normal balance prior to blockade.

Clearly, loss of adrenergic support results in deterioration of hemodynamic equilibrium in such patients. Any tendency for adrenergic blockade to enhance sodium excretion, as consistently observed in normal subjects, is overcome by its harmful effect in preventing compensatory cardiovascular reflexes. (For this reason it is clear that antiadrenergic drugs should not be administered to patients with heart disease and diminished cardiac reserve.)

The syndrome of inappropriate secretion of ADH appears in many patients with Addison's disease.<sup>60, 63</sup> These patients thus show a defect in excretion of free water. As the defect may be obviated by expansion of intravascular volume,<sup>64</sup> this syndrome may represent another "error" in control of intravascular volume, in which autonomic impulses, arising to

compensate for a steroid-dependent drop in pressure, lead to release of ADH as well.

### Integration of Autonomic Responses and the Control of Blood Volume

It is clear that a number of avenues exist through which autonomic influences may affect the volume of circulating blood. However, no well-defined scheme has been established to explain the manner in which these factors are synthesized into an integrated autonomic reflex system in order to maintain or to augment blood volume for optimal cardio-circulatory function. When arterial blood pressure falls markedly, central blood volume is enhanced by generalized reflex venoconstriction immediately. However, present evidence suggests that less severe degrees of hypotension are compensated for solely by reflex arterioleconstriction and by sympathetic stimulation of cardiac rate and contractility. With more prolonged adrenergic discharge, there are alterations of the postcapillary-to-precapillary resistance ratio: a decrease in the ratio will lower capillary pressure and increase intravascular volume by filtration from interstitial spaces.

There are further, poorly-understood reflex compensatory adjustments which attend losses of intravascular volume. The evidence suggests that small reductions in volume, sensed perhaps by stretch receptors in the low-pressure intrathoracic vascular chambers, restore volume through the secretion of ADH, perhaps without appreciable increase in adrenergic discharge to the vascular system. Large, rapid losses of blood, however, do excite arteriolar and venous reflexes. Activation of the high-pressure baroreceptors leads to activation of the renin-angiotensin-aldosterone system, but the point at which this occurs (in this sequence, ranging from mild to severe hemorrhage) is difficult to determine, since it is clear that much milder stimuli (e.g., a low-sodium diet) can activate the system, probably without the intervention of the high-pressure baroreceptors.

In any event, the ADH and the renin-angiotensin-aldosterone systems represent delayed, relatively slow reflex mechanisms for adjustment of blood volume. Evidence from experi-

ments in which blood volume is increased is consonant with these observations. Small infusions do not appear to decrease adrenergic discharge to the vasculature,<sup>19</sup> but the rapid administration of large amounts of fluid does induce venodilation.<sup>45</sup> Thus, the response to a small increment in intravascular volume may involve principally atrial stretch receptors and, perhaps, reflex inhibition of ADH, whereas the adjustment to a large infusion is more complex and may include the recruitment of higher-threshold atrial reflexes or high-pressure baroreceptors.

### Summary

Changes in blood volume lead the autonomic nervous system to respond with immediate direct, early, and delayed indirect reflexes which tend to oppose the changes. The more extensive and rapid the distortion of blood volume, the more the immediate reflexes are called upon; the smaller and slower the distortion, the greater the importance of the delayed, indirect reflexes.

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### Nervous System

**CSF DRAINAGE** Blue powder (particle size 100-200 mesh) was suspended in CSF and injected into the subarachnoid spaces of ten pigs and 9 sheep. Some of the suspension was also injected into the subdural spaces of these animals through surgically-placed polyethylene tubes. At the same time, a sciatic nerve of each animal was dissected and freed and subsequently ligatured above the knee joint. Animals were sacrificed four to 21 days after the procedure. Blue powder particles were found in peroneal, tibial and intact sciatic nerves, in muscles supplied by and still attached to these nerves, in thoracic nerves, and in branches of the brachial plexus. No particles were found in ligatured sciatic nerves from ligature to vertebral exit. Pigments injected in subdural spaces remained concentrated locally. When pigment was injected into the jugular veins of two control animals, particles accumulated in the lungs but not in other viscera or in nerve trunks. This excluded the possibility of blood spread of pigments in experimental animals. It is assumed that peripheral nerves are surrounded by membranes continuous with arachnoid mater and pia mater, and that CSF flows peripherally in the enclosed spaces towards muscles and integument. (Steer, J. C., and Horney, F. D.: *Evidence for Passage of Cerebrospinal Fluid Along Spinal Nerves*, *Canad. Med. Ass. J.* 98: 71 (Jan.) 1968.)