CARDIOVASCULAR ACTIONS OF VASOPRESSIN*

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IN 1895, *Oliver and Schafer*²²⁹ first reported that the posterior pituitary extract increases blood pressure in dogs. *Gaddum*¹²¹ found that vasopressin is a pressor principle whereas oxytocin is not only an oxytotic principle but also a depressor principle in chickens and cats. In 1953, *du Vigneaud et al.*^{198,199} identified the chemical structures and accomplished the synthesis of three natural peptides, i.e., lysine⁸-vasopressin, arginine⁸-vasopressin and oxytocin. Since 1960, many workers^{35,36,44,45,198,199,164,303} have synthesized a host of analogues of vasopressin and oxytocin. The cardiovascular effects of the crude posterior extracts, pitressin, pituitrin and vasopressins have been extensively studied in both experimental and clinical situations by many investigators and the results of the earlier and newer observations are reviewed in part elsewhere.^{7,114,217,219,257,278,293,294}

The purpose of the present communication is to review the results of the studies made on the cardiovascular effects of synthetic vasopressins and their analogues and to assess the underlying mechanism for their hemodynamic actions. These recent observations made with the synthetic vasopressins are integrated with the earlier observations made with the posterior pituitary

extracts, Pituitrin and Pitressin.

Vascular smooth muscle and microcirculation

Posterior pituitary extracts, Pituitrin, Pitressin, and synthetic vasopressins usually exert a vasoconstrictor action in nearly all of blood vessels of several mammals. However, the vasopressins were found to be possible vasodilators in some segments of the vascular bed of the heart, kidney and brain of certain species of animals.^{5,14,15,24,74,113,127} The vasoconstrictor action of the vasopressins appears to be mostly caused by direct contraction of the vascular smooth muscle and no nervous element or humoral mechanism may be involved in this action. Firstly, the vasoconstrictor action of vasopressin can be elicited in isolated arterial strips. Secondly, nicotine, ergotoxine, adrenergic blocking agents, anti-adrenergic agents and atropine cannot abolish the vasoactivity of vasopressin.^{131,189} Hence, it is logical to assume that the vascular action of the vasopressins is not mediated by mechanisms involving ganglionic stimulation, the release of transmitters from nerve endings or the combination with receptors for various humoral agents including catecholamines, acetylcholine, histamine, serotonin and prostaglandins.^{155,219} Pitressin or synthetic vasopressin contracts rat aorta, and dog and human femoral arteries, but not rabbit, dog or cat aortas.^{93,94,131} On the other hand, it was shown that vascular strips from the abdominal aorta are contracted by vasopressin with an increasing magnitude of contraction in the craniocaudal direction.^{8,276} Hence, *Somlyo et al.*⁷⁶ postulated not only the existence of considerable differences in the vascular responses to vasopressins but also that of the distribution of pharma-

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cologically heterogeneous blood vessel cells in a given species of animals. This difference in the segmental vascular responsiveness to vasopressin must be more or less peculiar to this hormone since no such difference was found in the responsiveness to norepinephrine and angiotensin between aortic segments. Similar small arteries and veins^{43,205} Isolated vascular strips from limb veins failed to respond to vasopressin in concentrations that produced a marked contraction of small artery strips taken from the same region.^{43,205,230}

In the isolated dog hind-limb and fore-limb preparation, Pitressin increases the perfusion pressure of the small artery but produces no significant change or only slightly decreases the small vein pressure.^{182,184,209} Furthermore, they found that vasopressin decreases the weight of the perfused denervated limb. Therefore it was concluded that vasopressin constricts predominantly the arterioles, as does angiotensin. Similarly, *Texter et al.*²⁸⁴ found that Pitressin and Octapressin markedly increase small vessel resistance whereas venous resistance of the same vascular bed is unaffected. Some of the earlier workers^{230,313} also found that Pitressin causes no significant effect on the venous vasculature of the ear in rabbits or on isolated veins from the cat, rabbit, dog or sheep. A similar observation with vasopressin was made by Bohr and Johansson⁴³ on the isolated subcutaneous artery or vein strips from dogs.

In contrast to these studies, others¹¹⁶ found that Pitressin constricts the veins of sheep and the venules in man. In the cat hindquarter preparation the i.a. injection of Octapressin causes a potent and prolonged constriction of the venous vessels and a moderate vasoconstriction of the arteries.⁶⁵ This observation demonstrated that Octapressin is different from angiotensin since angiotensin exerts a potent arterial constrictor action without producing any significant venoconstriction. Using similar preparations, however, vasopressin increases regional flow resistance, but practically no change occurs in vascular capacitance.²⁰⁵ This indicates a pattern of hemodynamic response compatible with the differing responses of small arterial and venous segments to vasopressin. Although it increases regional flow resistance, vasopressin does not produce a translocation of tissue fluid into the circulation. This is probably because the precapillary resistance increased *pari passu* with postcapillary resistance by proportional constriction

of both the arterioles and the post-capillary resistance vessels.

In the isolated perfused dog hind-leg preparation, Pitressin increases both arterial and venous pressure, and decreases the tissue weight of the perfused leg since the venous outflow exceeds the arterial inflow.^{8,9} In dogs Pitressin sometimes increases transiently systemic venous return¹⁰² possibly caused by the constriction of venous capacitance vessels. It is difficult to obtain a unitarian concept of the vascular responses to the vasopressins from the previous observations on the isolated limb preparations from dogs and cats. Conceivably these discrepancies arise because of differences in the vascular beds, studied, the experimental procedures employed and the hemodynamic status of the preparation prior to the injection of the peptides. In the isolated rat caudal artery, different vasopressins increase the perfusion pressure thus indicating a potent vasoconstrictor action.¹⁸⁴ The topical application of the posterior pituitary extract or Pituitrin constricts the capillaries in the frog web and in the small vessels of the dog ears,¹⁸⁶ whereas Pitressin briefly constriction in rabbits.³¹³ In rabbits, the intravenous injection of or the topical application of Pituitrin produces a dose-related constriction of the arterioles of the lungs and decreases or reverses the capillary blood flow.³⁰⁵ Topically applied Pitressin and arginine⁸-vasopressin constrict the arterioles in the vascular bed of the uterus omentum of the rat.¹⁸⁸ More recently, in the rat mesoappendix preparation, topical application of arginine⁸-vaso-pressin constricts arterioles, precapillaries, metaarterioles, and venules, and decreases overall capillary blood flow.^{10,11,150,151} Smaller doses do not constrict arterioles, but cause a vasoconstrictor action in some metaarterioles, precapillaries and venules, and decrease postcapillary outflow. A much smaller dose of Octapressin constricts only venules, whereas doses less than 0.25 ng are ineffective in all segments of the vessels. These results indicate that the magnitude of vascular responsiveness to arginine⁸-vasopressin decreases from the venular side toward the arteriolar side, whereas the trend is reversed with epinephrine and norepinephrine.^{10,11,33} The dose-graded constriction of various vessel types induced by locally applied lysine⁸-vasopressin or Octapressin¹⁰ closely resembled the effects observed with arginine⁸-vasopressin. In the same preparation, Octapressin transiently increases capillary circulation and constricts markedly the arteriolar vessels, while

systemic arterial pressure is not affected. Octapressin constricts small arteries and arterioles less than does norepinephrine.

In dogs with hemorrhagic shock Pitressin does not significantly change systemic arterial pressure but exerts a potent vasoconstrictor action on the terminal arterioles of the omentum, and improves blood flow through the omental vessels.³¹⁹ In rats with hemorrhagic or intestinal ischemic shock Octapressin increases microcirculatory blood flow and venous return by improving capillary inflow, decreasing responsiveness to catecholamines, and sustaining arteriolar and venular tone.^{150,151}

Myocardial Contractility and Cardiac Dynamics.

Several earlier investigators^{136,139,147,156,180-182,200} found that the posterior pituitary extract increases the amplitude of contraction of the isolated cat, rabbit, rat and human heart, whereas others^{71,135} showed a decrease or no change in contractility of the isolated dog and terrapin heart. It has been observed that Pituitrin constricts the coronary artery and dilates the ventricle in the dog heart-lung preparation,⁴² indicating evidence of myocardial failure due to hypoxia. Recently, in isolated guinea-pig and rabbit hearts, with no significant change in heart rate, vasopressin (0.5-1 u) decreases contractile force as coronary blood flow decreases.¹⁴⁸ Furthermore, 48 mU/ml of vasopressin produces no significant change in contractile force, but a larger concentration (480 mU/ml) exerts a positive inotropic action in both spontaneously beating guinea-pig atria and in the electrically driven papillary muscle. In contrast, lysine⁸-vasopressin, arginine⁸-vasopressin and Octapressin in concentrations less than 20 mU/ml do not produce any significant change in myocardial contractile force in the isolated electrically driven guinea-pig atria.²²⁰ On the other hand, the peptides in concentrations larger than 20 mU/ml (up to 320 mU/ml) cause a negative inotropic action essentially in proportion to the concentration. It is unlikely, however, that such high concentrations of vasopressin can be attained *in vivo* in plasma and tissue even after the administration of toxic doses of vasopressin.

Pituitary extract affects the heart by vagal stimulation through the cardio-inhibitory center and by direct action on the myocardium.^{37,243} Similarities have also been noted between the effects on the heart of pituitary extract and anoxemia. Fluoroscopic observations showed

that toxic doses of the pituitary extract cause a marked cardiac dilatation in dogs.¹⁷⁸ The *in vivo* effects of the vasopressins on myocardial contractility, cardiac dynamics and ventricular function have been studied mainly in dogs. The intracoronary injection of Pitressin causes intense constriction of the coronary vessels and reduction of coronary blood flow sufficient to depress myocardial contractile force.¹²⁹ Wang³⁰⁴ showed in dogs that Octapressin decreases myocardial contractile force markedly as coronary arterial blood flow decreases significantly. Nakano^{215,217} also found in dogs that lysine⁸-vasopressin (5-125 mU/kg, i.v.) produces prolonged dose-related depression of myocardial contractile force (as measured by a Walton-Brodie strain gauge arch) and in dp/dt values of the left ventricular pressure. It was also found that vasopressin shifts the ventricular function curve to the right, indicating depression of cardiac performance by this peptide. As vasopressin increases left ventricular systolic pressure and decreases myocardial contractile force, both left ventricular end-diastolic pressure and left atrial pressure increase progressively. On the other hand, vasopressin decreases both pulmonary arterial pressure and right ventricular systolic pressure whereas both right ventricular end-diastolic pressure and right atrial pressure remain essentially unchanged or slightly elevated.^{59,60,215,217} The i.v. injection of lysine⁸-vasopressin not only increases systemic arterial pressure but also causes myocardial contractility (dp/dt) and ECG in anesthetized dogs^{215,217} and in young, healthy men.⁴⁸ In anesthetized dogs, Octapressin decreases both left and right ventricular work since cardiac output decreases markedly.²⁰¹ Although these hemodynamic effects are associated with evidence of reflex vagal stimulation (bradycardia) due to the increased systemic arterial pressure, the negative inotropic action of vasopressin seems to be primarily related to constriction of the coronary arteries and consequent myocardial ischemia. Firstly, bilateral mid-cervical vagotomy abolishes the bradycardiac effect and elevates systemic arterial pressure more markedly. However, the magnitude of the negative inotropic action of vasopressin in dogs with intact innervation is essentially similar to that in vagotomized dogs. Furthermore, in dogs in which the coronary arterial inflow is regulated or kept constant by a Sigmamotor pump, both mechanically induced and vasopressin-induced reduction in the coronary arterial blood flow decreases myocardial

contractile force essentially in proportion to the magnitude of the constriction.^{215,216} In dogs in which the coronary arterial blood flow is kept constant, the i.a. injection of vasopressin increases the coronary arterial perfusion pressure, indicating an increase in the coronary resistance. However, in this situation, myocardial contractile force remains essentially unchanged. Furthermore, in a similar preparation, during a prolonged reduction in myocardial contractile force due to the coronary constriction by vasopressin, a single intra-coronary arterial injection of nitroglycerin resulted in an improvement of myocardial contractile force as the coronary arterial blood flow increases. These observations appear to infer that the decreased cardiac dynamics following the administration of vasopressin is due to its direct action on the coronary circulation.

Heart Rate

Earlier investigators^{79,139,147,206,308} found that the crude posterior pituitary extract decreases the frequency of contraction in the isolated dog, cat and rabbit heart or produces no significant change in the isolated cat heart. Likewise, vasopressin causes essentially no change in heart rate of the isolated guinea-pig heart.¹⁴⁸ On the other hand in various species of animals with intact circulation, the crude posterior pituitary extract was found to decrease heart rate moderately or markedly.^{126,159,192,247} Pitressin, synthetic vasopressins and their analogues have been shown to cause moderate to marked bradycardia under various clinical conditions in man^{134,287,198,226,236,246,247,289} and in different experimental preparations in dogs,^{36,59,76,95,102,192,198,201,215,290,299,308} cats,^{18,36,119} rabbits^{40,119} and rats.^{851,119} However, among the synthetic vasopressins studied in man, ornithine⁸-vasopressin usually causes a marked vasoconstriction without producing any significant change in heart rate or systemic arterial pressure.^{97,225} Since the bradycardiac effect of vasopressin is almost always associated with its hypertensive effect, the majority of the investigators have attributed the bradycardia to vagal stimulation mediated through the carotid sinus reflex mechanism. Although the causative mechanism responsible for the bradycardiac effect of vasopressin may be mainly due to reflex vagal stimulation, other factors may be involved. Several investigators^{18,125,137,159,192,211,266,295} found that the decrement in heart rate induced by posterior pituitary extract, Pitressin,

vasopressin and Octapressin is markedly reduced by pretreatment with atropine or by bilateral mid-cervical vagotomy, although the effect is not abolished completely by atropine or by vagotomy. *Yourmans et al.*^{317,318} also found that the bradycardiac effect of Pitressin in conscious rabbits is markedly greater and more prolonged than that in rabbits after excision of the carotid sinus and section of the aortic depressor nerve. Hence, they postulated that Pitressin may decrease heart rate not only by reflex vagal stimulation but also by a blocking action probably in the cardio-accelerator center. On the other hand, *Varma et al.*²⁹⁵ showed that the bradycardiac effect of Pitressin is diminished significantly by transection of the spinal cord at C₂ in dogs. Hence it was concluded that a direct stimulatory action of Pitressin on central cardio-inhibitory neurons plays a minor role in the genesis of bradycardia by the peptide in dogs. It was also postulated that vasopressin-induced bradycardia, which occurs after vagotomy and atropine, may be caused indirectly by coronary constriction and myocardial ischemia induced by vasopressin.^{243,278}

Electrocardiogram

Many investigators^{40,78,83,92,126,128,162,211,254,275} have found that the posterior pituitary extract, Pitressin, Pituitrin and synthetic vasopressins in sufficient doses could induce various cardiac arrhythmias and ECG changes in the T wave and the ST segment in animals and in man. Generally, smaller amounts (0.5-10 mU/kg/min) of Octapressin cause no ECG changes in dogs.¹⁹⁸ On the other hand, coronary arterial ligation or the administration of 6% oxygen increases the myocardial depressant action of vasopressins, hence resulting in more marked ECG changes.^{92,211}

The ECG changes induced by vasopressins are due mainly to (a) myocardial ischemia induced by coronary arterial constriction and/or to (b) vagal stimulation reflexly elicited by the pressor effect of the peptides. In rabbits,^{40,208} and in cats,³⁸ Pitressin caused biphasic changes in ECG. The first phase which lasted for 20-30 sec was manifested by large, elevated T waves and ST segments and shortened QT intervals. The second phase which lasted for several min was characterized by a depressed ST segment, depressed or inverted T waves and relatively normal or prolonged QT intervals, indicating evidence of sub-endocardial ischemia and injury.

In dogs and cats, posterior pituitary extract or Pitressin causes a marked bradycardia, shifting pacemaker, atrioventricular block, sinoatrial block, extra-systoles, bigeminy, a large T wave and depression of the ST segment.^{83,92,95,125,137,207,243} Although these ECG changes can be attributable to reflex vagal stimulation, pretreatment with atropine or vagotomy does not prevent these changes induced by vasopressin. Hence, these observations can be due in part to coronary vasoconstriction and subsequent myocardial ischemia induced by vasopressin. Similar observations were made in dogs after Pitressin²⁹⁹ lysine⁸-vasopressin or Octapressin³⁶ as well as after Pitressin⁹⁵ Lysine⁸-vasopressin causes transient ventricular extrasystole in dogs with myocardial infarction.^{21,59} On the other hand, Octapressin produces no arrhythmias in cats during halothane or cyclopropane anesthesia.¹⁶⁹

Many workers^{23,187,214,247,272,288} reported that pitressin and synthetic vasopressins induce little or no ECG changes during or after their administration to man. This can be explained partially by the fact that relatively small doses of vasopressins are generally given to patients with diabetes insipidus. When larger doses of Pitressin were injected into man, clinical evidence and ECG manifestations of cardiac arrhythmias and coronary insufficiency were clearly noticed by clinical investigators.²¹⁰ Myocardial ischemia has led to severe circulatory failure and even death.^{128,162,210,275} Hence, the coronary constrictor action of the vasopressins is one of the undesirable side effects. The so-called Pitressin test for coronary insufficiency should not be performed clinically.²⁵³

When used in patients receiving cyclopropane, Pituitrin caused circulatory failure probably due to the coronary vasoconstriction or to the existence of an unknown incompatibility between the two agents.³⁰ Octapressin caused no arrhythmias or infrequently caused supraventricular tachycardia in patients who received cyclopropane and halothane as general anesthetic agents.^{169,187} When larger doses of Pitressin were injected into man, the peptide invariably caused different types of cardiac arrhythmias due to myocardial anoxia along the conduction pathways in the myocardium. Vasopressin may induce a delay in A-V conduction mediated through reflex vagal stimulation or by a direct effect on the conduction system. Lysine⁸-vasopressin prevented the induction of ventricular

fibrillation which usually occurs in dogs under chloroform anesthesia after large doses of epinephrine.^{29,49} It was postulated that the vasopressins may exert a quinidine-like antiarrhythmic action. However, in this study²⁹ the vehicle solvent lengthened the refractory period of the ventricle by the same degree, indicating that most or all of the antiarrhythmic action could be attributed to the solvent rather than vasopressin.

Systemic Circulation-Systemic arterial pressure, cardiac output and total peripheral resistance:

As discussed previously the vascular responses to vasopressin are variable in species of animals. Sawyer²⁵⁷⁻²⁶⁰ and Wobley^{315,316} have studied extensively the effect of various vasopressins on systemic arterial pressure in a large number of species of animals. Vasopressins and their analogues may exert a pressor action in most of the mammals but may be either pressor or depressor substances in birds and amphibians. Since the majority of the previous studies on the vascular actions of vasopressins in many species of smaller animals has been made solely by the measurement of systemic arterial pressure without simultaneous determinations of cardiac output or blood flow, it is nearly impossible to assess precisely whether the peptides are vasoconstrictors or vasodilators in these animals. Since the distribution of vasopressin differs among species of animals,²⁵⁸ it can be said that the qualitative and quantitative differences in the hemodynamic effects of a given vasopressin may be partially or greatly influenced by the tissue and humoral responses to it, similar to that occurring with foreign protein in a given species of animals.

Numerous studies have been made on the pressor effect of the crude extract of posterior pituitary gland, Pitressin, lysine⁸-vasopressin, arginine⁸-vasopressin and Octapressin in rats^{10,36,39,85,119,194,196,261,294} rabbits^{119,171,176}, cats,^{24,36,119,169} dogs,^{36,59,76,86,95,102,103-107,117,126,137,149,178,198,201,215,235,238,251,256,261,292,299} monkey,⁶⁸ and man.^{46,47,55,82,91,100,109,134,138,149,169,187,226,231,234,246,247,265,266,272,289,297} Most of these studies show that the peptides increase systemic arterial pressure and total peripheral resistance. The magnitude of the hypertensive action of vasopressin is usually smaller than that of catecholamines or angiotensin.^{24,33,35} However, the duration of the pressor action of vasopressin is markedly longer than that of norepinephrine and slightly

longer than that of angiotensin. The magnitude of the pressor action of vasopressin appears to be greatly influenced by the hemodynamic and metabolic status of the individual prior to administration. Considerably larger doses (more than 150 mU/kg) of the vasopressins did not increase systolic pressure, but occasionally lowered it, even causing circulatory failure.^{162,173,185,210,275}

The i.v. injection of the vasopressins and Pitressin usually decreases stroke volume and cardiac output moderately to markedly in rats,^{127,241,342} in dogs^{47,59,74,76,86,95,103,106,107,109,198,201,209,215,235,292,299} and man.^{128,132-134,266} However, some workers have reported that therapeutic doses of the vasopressins did not change cardiac output in rats,^{85,240,241} cats²⁴ and man,^{82,128,247,289} and even increased it in man.⁴⁶ Several investigators found that the vasopressins produce a triphasic or biphasic response in systemic arterial pressure in rabbits,^{119,176} in cats,³⁶ in dogs^{36,59,126,149,168,192,215,240,246,251,256} and in man.^{37,38,82,169,203,297} This response is manifested by an initial transient slight rise, followed by a longer fall, and finally by a more prolonged and higher rise in systemic arterial pressure. The pressor phases of the response were obviously caused by an increase in total peripheral resistance since both myocardial contractile force and cardiac output were always decreased significantly in a monophasic pattern. The second (depressor) phase was caused by a maximal reduction in myocardial contractile force and a consequent reduction in cardiac output since total peripheral resistance was maximally increased during this phase.^{215,251} The pressor action of the vasopressins seen during the third phase was due solely to the increase in total peripheral resistance since systemic arterial pressure rises in spite of a concomitant decrease in cardiac output. During this phase, however, both myocardial contractile force and cardiac output recover slightly and very gradually after the maximum reduction during the second phase. Because of its potent myocardial depressant effect, the hemodynamic effects of the vasopressins are markedly influenced by the dose and velocity of the administration and by the cardiovascular status of the individual prior to the administration. Even with smaller doses (less than 25 mU/kg), when cardiac dilatation and/or hypertrophy are present, systemic arterial pressure increases only slightly or even decreases considerably below control due to more marked

reductions in myocardial contractility and cardiac output.^{215,217} Generally, as systemic arterial pressure increases, heart rate decreases reflexly through the cardiovascular baroreceptor mechanism, thereby resulting in continuous modulation of the various hemodynamic parameters. Since cardiac output decreases and systemic arterial pressure increases, total peripheral resistance increases markedly. Vasopressins always increase total peripheral resistance although some investigators^{10,82,149,247,292,297} found that the peptides produce no change, decrease or produce variable changes in systemic arterial pressure.

Pulmonary Circulation:

The effect of the vasopressins on the pulmonary circulation has been reviewed previously.^{17,114,254,278} Posterior pituitary extracts were found to constrict the pulmonary arteries in isolated, perfused cat, rabbit and dog lungs^{28,80,87,203,315} or produces no change in perfused cat and dog lungs.²⁵⁰ Posterior pituitary extract decreases pulmonary arterial pressure in the dog heart-lung preparation, but increases it in the cat heart-lung preparation.¹⁵⁶ In the angiographic study, Pituitrin decreases pulmonary vascular X-ray shadows in rabbits, indicating its vasoconstrictor action on the pulmonary vasculature.⁸⁴ With microscopic observations, Pituitrin also produced arteriolar constriction in cat lungs.³⁰⁵ In contrast, the posterior pituitary extract caused no significant change in pulmonary arterial pressure in the dog heart lung preparation or when the cardiac output was kept constant with a mechanical heart.²⁵¹

Many investigators found that the posterior pituitary extract, Pitressin, lysine⁸-vasopressin or Octapressin cause a decrease in pulmonary arterial pressure in anesthetized rabbits^{156,273} and dogs^{13,76,85,87,117,156,201,215,273,292,310,311} as cardiac output²¹⁵ flow⁸⁷ decreases significantly. On the other hand, a few workers found that the peptides increase both pulmonary arterial pressure and wedge pressure in dogs^{59,81,235,296,299} and in man.^{246,266,289,290} Still others, however, found that vasopressins cause variable changes or no change in either pulmonary or wedge pressure in dogs^{24,117,201} and in man.^{66,226,247} Both lysine⁸-vasopressin and Octapressin cause no change in pulmonary arterial pressure in healthy individuals but increase pulmonary arterial and wedge pressures in advanced lung diseases.^{246,247} Most in-

investigators found that pulmonary peripheral vascular resistance increases in dogs^{76,201,215,251} and in man^{246,266} or remains unchanged in dogs²⁹² and in man^{246,247}. Obviously, the hemodynamic changes in the pulmonary circulation are influenced by not only the pulmonary arteriolar resistance but also right ventricular output (pulmonary blood flow) and left atrial pressure. The increased pulmonary wedge pressure observed by some workers is most likely secondary to elevation of the left atrial pressure caused by the reduction of myocardial contractility by the peptide. The decreased pulmonary arterial pressure is most likely due to decreased right ventricular output secondary to the reduction in systemic venous return^{13,102,117,215,310,311} rather than the increase in pulmonary vascular resistance. The decreased right ventricular output may be due in part to decreased myocardial contractility in the right ventricle.^{179,200} When the cardiac input was kept constant by means of a Sigmamotor pump, lysine⁸-vasopressin significantly increases pulmonary arterial pressure in dogs.^{108,219} On the other hand, vasopressin decreases pulmonary arterial pressure in dogs with an intact circulation, even when the left atrial pressure increases significantly. Repeating the injection of lysine⁸-vasopressin, within 15-20 min after the first injection, causes an increase in pulmonary arterial pressure although the increment of systemic arterial pressure produced by the second injection is significantly smaller than that produced by the first injection.²¹⁵ The investigators,⁶⁶ who found an increase in pulmonary pressure after the vasopressins, postulated that pulmonary hypertension is caused directly by increased pulmonary vascular resistance and indirectly by increased left atrial pressure. The increases in left atrial pressure and in pulmonary arterial pressure coincide with the reduction in cardiac output in dogs.^{296,299} It is of interest that Pitressin and Octapressin increase cardio-pulmonary blood volume in man.^{108,289} On the other hand, in dogs, Pitressin reduces the pulmonary blood volume,¹⁵⁶ whereas the blood volume in the cardiopulmonary vasculature increases when cardiac input is kept constant by a Sigmamotor pump.^{108,205} Wiggers^{310,311} concluded that vasopressin would be hemodynamically the most ideal pharmacological agent in the treatment of patients with pulmonary hemorrhage since the peptide usually increases systemic pressure and decreases pulmonary arterial

pressure. A number of workers^{1,87,286,310} have successfully employed Pitressin, vasopressins, or Octapressin for this purpose.

Coronary Circulation and Myocardial Oxygen Metabolism:

The coronary vasoconstrictor effect of posterior pituitary extract was observed by many earlier workers in the isolated rabbit heart^{79,200,310,311} cat heart,^{139,206} dog heart^{145,203,221} terrapin heart^{135,136} human heart¹⁸⁰ and in the dog heart-lung preparation.^{12,42,145,156,250,251} A few workers,^{179,280} however, demonstrated that the extract may dilate the coronary artery in isolated cat and tortoise hearts, whereas it initially constricts and then dilates the artery in the isolated rabbit heart. Since Pitressin and synthetic vasopressins became available, many investigators concluded that the peptides are the most potent coronary vasoconstrictors in the isolated rabbit heart^{137,144} and in anesthetized cats and dogs.^{95,106-108,129,153,156,166,167,201,215,223,251,261,263,279,306,309} The coronary vasoconstrictor effect of the posterior pituitary extract or vasopressin is counteracted readily by various vasodilators including epinephrine, ephedrine, histamine, papaverine, nitroglycerin, PGE₁, bradykinin and eledoisin.^{193,206,218}

Synthetic vasopressins causes a significant constrictor effect in the coronary vasculature in dogs, resulting in a reduction in myocardial contractility and cardiac output essentially in proportion to the dose administered.^{95,215} Usually the second negative phase of the triphasic response of systemic arterial pressure to vasopressin coincides with a parallel phase of maximally reduced coronary blood flow. Although no studies have been reported on the effect of vasopressins on the coronary circulation in man, it is obvious that similar coronary vasoconstriction with subsequent decreases in myocardial contractility and cardiac output would take place in healthy human subjects and in patients. The occurrence of this hemodynamic change can be deduced from the indirect ECG evidence of myocardial ischemia or injury. It was reported that the subcutaneous injection of 20 IU of Pitressin resulted in myocardial infarction in a patient.²⁷⁵ Contrary to its effect on the coronary circulation, lysine⁸-vasopressin (6.7 mU/kg/min, i.v.) increases both cardiac output and coronary blood flow in dogs with hemorrhagic hypotension.¹⁰⁵⁻¹⁰⁹

Betz *et al.*³⁸ and Maxwell²⁰¹ showed that vasopressin or Octapressin increases systemic arterial pressure and markedly decreases myocardial blood flow, O₂ saturation and O₂ uptake in dogs. On the other hand, Nakano²¹⁵ showed that the i.v. infusion of lysine⁸-vasopressin decreases not only coronary blood flow and myocardial contractile force but also myocardial O₂ saturation and uptake essentially in proportion to the dose administered. The decrease in myocardial O₂ uptake occurs because of the reduced coronary blood flow and consequent reduction in O₂ availability. However, the coronary A-V O₂ difference and the myocardial O₂ extraction coefficient increase markedly. The increased coronary A-V O₂ difference is due mainly to the decrease in the O₂ content of the coronary sinus blood, since the arterial O₂ content remains essentially unchanged.^{76,215} The increased O₂ extraction coefficient in the myocardium is caused by the decrease in myocardial O₂ tension and capillary blood flow. Vasopressin also causes a negative lactate balance and increases "excessive lactate" together with the decreased coronary blood flow in dogs, indicating an evidence of significant myocardial ischemia.¹⁵³ Inosine significantly inhibits the increase in "excessive lactate".^{76,153} In dogs, Pituitrin decreases myocardial O₂ uptake and acetylcholinesterase activity essentially in proportion to the duration of myocardial ischemia.¹²⁰ In addition, Pituitrin increases the total glycolytic activity and lactate concentration in the myocardium. Although the coronary constrictor effect of vasopressin has been well established, Pitressin does not modify the size of the myocardial infarction induced experimentally by ligation of the anterior descending coronary artery in dogs.²¹¹

Cranial Circulation:

Using the angiographic technique, Aronsen *et al.*^{14,15} found in anesthetized dogs that vasopressin markedly decreases the external carotid arterial blood flow whereas the internal carotid arterial blood flow increases correspondingly. The cerebral arteries, and the orbital and external ophthalmic arteries are dilated by vasopressin. This observation indicates that the cerebral and ophthalmic blood flow improve at the expense of the remainder of the external carotid arterial vasculature. Vasopressin dilates the pial vessels in cats and dogs.¹¹³ On the other hand, vasopressin (30 mU/kg/min, i.v.) markedly decreases cardiac output but produces no significant change in the

posterior pituitary blood flow in unanesthetized rats.¹²⁷ In man, the posterior pituitary extract reduces markedly the blood flow to the face and ear for approximately 60 min and causes headache, fainting and discomfort.²⁸¹

Splanchnic, Hepatic and Portal Circulations:

A number of studies have been made on the effect of vasopressins on the splanchnic circulation in cats^{24,36,72} and dogs^{70,86,95,96,103,107,149,156,168,170,204,209,252,284,312} and in man.^{82,109,134,149,161,177,265,270,287} In cats, lysine⁸-vasopressin or Octapressin decreases mesenteric arterial blood flow markedly,^{24,36} whereas Pitressin constricts the mesenteric arteries but slightly dilates the mesenteric veins in dogs and cats.¹⁵⁶ Pitressin markedly decreases both intestinal and splenic arterial blood flow and slightly increases the hepatic arterial blood flow in anesthetized cats,⁷² indicating the vasoconstrictor and vasodilator actions of Pitressin in different vascular beds. In dogs, the infusion of infusion of the vasopressins into the superior mesenteric artery or the i.v. administration of the peptides decreases mesenteric arterial blood flow markedly and increases mesenteric arterial vascular resistance. Pitressin decreases the blood flows in the esophagus, stomach, duodenum, and pancreas in dogs.⁸⁶ The decrements in the gastrointestinal blood flows were significantly greater than that in total cardiac output. In patients with or without liver disease, the splanchnic vascular resistance, intrasplenic pressure greater than that in total cardiac output, In patients with or without liver disease, the splanchnic vascular resistance, intrasplenic pressure, wedge hepatic venous pressure and estimated hepatic blood flow, decreased during the i.v. infusion of Pitressin.²⁷⁰ On the other hand, Octapressin or lysine⁸-vasopressin decrease portal blood flow and portal pressure in patients with or without hepatic cirrhosis due to the reduction in splanchnic blood flow.^{161,287} Since the O₂ consumption in the splanchnic vascular bed did not change considerably, it was concluded that Octapressin impairs the splanchnic O₂ metabolism and organ functions.³⁹² Likewise, in patients with hepatic cirrhosis, Octapressin markedly reduces splanchnic blood flow.³⁵⁷ Since Octapressin reduced cardiac output by the same magnitude as the splanchnic blood flow, it was concluded that Octapressin has no greater constrictive effect upon the splanchnic blood vessels than elsewhere.²⁶⁶ Likewise, in dogs^{96,252} Pitres-

sin decreases both splanchnic blood flow and cardiac output by essentially the same degree. These studies on the hemodynamic effects in both dogs and man preclude the previous concept^{271,287} that the vasoconstrictor action of vasopressins is more or less selective for certain tissues or organs, and that vasopressins reduce the portal venous pressure by selective redistribution of blood from the splanchnic or portal circulation to other circulatory systems. The decreases in the splanchnic blood flow and in the portal venous pressure produced by vasopressins appear to reflect their effects on the overall cardiovascular system. The changes in splanchnic circulation during episodes of fainting in man mimic those following the i.v. injection of small doses of vasopressin^{28,282,312}. It was, postulated, therefore, that fainting and other hypotensive states which decrease the cerebral circulation result in an increase in the responsive secretion of vasopressin by a negative feedback mechanism^{28,67,283,297}.

Many studies have been made on the effect of vasopressins on the hepatic and portal circulations in cats,^{36,72,156} dogs^{36,70,95,103,149,156,168,170,204,209,239} and man^{24,28,52,100,109,265-267,270,274,287}. In dogs and cats, Pituitrin, Pitressin, lysine⁸-vasopressin and Octapressin decrease markedly hepatic arterial blood flow and also the portal venous pressure. Vasopressin decreases the portal pressure in dogs in which experimental portal hypertension was produced by constricting the inferior vena cava. Similarly in healthy man or in patients with hepatic cirrhosis,¹⁷⁰ Pituitrin, Pitressin, Octapressin or lysine⁸-vasopressin increases hepatic arteriolar resistance,²⁸⁷ decreases hepatic blood flow,^{28,82,103,270,287} hepatic wedge vein pressure,^{18,24,82,266,270,287} portal venous pressure^{100,265} and intrasplenic pressure.^{82,267} Pitressin does not change postsinusoidal resistance in man.²⁷⁰ From these observations in animals and man, it is evident that the vasopressins reduce the superior mesenteric and hepatic arterial blood flows by increasing peripheral vascular resistance in these vascular beds, and decrease markedly the portal venous blood flow. Because of these hemodynamic observations, and an actual observed therapeutic efficacy, the vasopressins have been employed frequently in the treatment of patients with bleeding esophageal varices secondary to the portal hypertension associated with hepatic cirrhosis.^{18,75,82,95,100,101,109,149,165,170,177,239,244,265,266,270,271,287-289} The reduction

in the portal venous pressure is due partly to a decrease in total cardiac output which results from the decreased myocardial contractility and systemic venous return.¹⁰² In addition, the reduction, in the portal pressure is caused by a decrease in the superior mesenteric and hepatic arterial blood flows due to the increased regional peripheral vascular resistance. The decrease in portal pressure induced by vasopressin was reversed by the subsequent injection of metaraminol.¹⁴⁹ Furthermore, other studies^{36,82,267} indicate that the decrease in the portal pressure may be caused not only by mesenteric vascular changes but also by splenic vascular changes, i.e., decreased splenic blood flow and splenic pulp pressure in man. In dogs, the magnitude and duration of the reduction in total hepatic venous return by vasopressin are less pronounced and shorter than in portal blood flow.¹⁴⁹ Hence, they ascribed this observation to an increase in hepatic blood flow from the hepatic artery during the infusion of vasopressin. Likewise, in the angiographic study dogs, vasopressin increases the distribution of the injected contrast medium to the liver, kidney and diaphragm whereas that to the spleen and intestine decrease.^{14,15,228} In guinea pigs Octapressin reduces gastric blood flow which previously has been increased by histamine.¹⁸³ In cats vasopressin decreases splenic blood flow and splenic peripheral capacitance and increases splenic peripheral resistance.¹³⁰ Vasopressin (30 mU/kg/min) also markedly or slightly decreases cardiac output but increases hepatic blood flow in rats as measured by Sapirstein's method.^{127,285} In contrast, measuring both hepatic arterial and portal blood flow in dogs directly with electromagnetic flowmeters, Pitressin reduces the hepatic arterial and portal venous blood flow as well as the splanchnic blood flow, although portal venous blood flow was reduced more than the hepatic arterial blood flow or the splanchnic arterial blood flow.⁹⁵ Free hepatic venous pressure is increased in man during and after the i.v. infusion of Octapressin, and suggested that this phenomenon reflects a rise in the right ventricular end-diastolic pressure, indicating relative right heart failure.²⁶⁶

Renal Circulation:

The effect of the vasopressins on the renal circulation has been studied in dogs,²⁴⁸ cats,^{24,25} rabbits,³⁰² dogs^{4,19,34,36,41,50,79,103,143,198,201,203,268,302,310} and in man.^{16,73,198,202} Posterior pituitary extract was found to reduce

the perfusion rate of the isolated cat and dog kidney^{4,7,9,203,310} or to increase the perfusion rate in the isolated sheep kidney.⁵⁸ The i.v. injection of posterior pituitary extract increases the kidney volume in dogs.¹⁹ It was ascribed this finding to passive congestion secondary to an increase in the peripheral vascular resistance in the splanchnic vascular bed since the extract decreased the kidney volume in the eviscerated dogs.¹⁹ Under microscopic observations the posterior pituitary extract stops renal blood flow through the glomeruli of the frog kidney.²⁴⁸ Likewise, Pituitrin reduces renal blood flow in dogs.³⁰² In dogs, Pitressin abruptly decreases renal blood flow.^{252,300} In dogs and humans, Octapressin slightly reduces renal blood flow whereas both carotid and femoral arterial blood flow decrease *pari passu* with aortic blood flow.¹⁹⁸ Vasopressin did not change renal blood flow in 18 dogs, but decreased it in 3 remaining dogs.⁵³ It was found, however, that the i.a. injection of the same dose of vasopressin decreases renal blood flow more markedly. In contrast, other workers^{50,88,268} found that neither Pitressin nor synthetic vasopressin in antidiuretic doses causes a significant change in the renal plasma flow in dogs. However, vasopressin prevented the powerful renal vasodilator action caused by oxytocin. Physiological doses (50–100 mU/hr) of Pitressin cause no significant change in renal blood flow whereas pharmacological doses (more than 500 mU/hr) of Pitressin reduce significantly the renal blood flow in man.²⁰² Rushmer *et al.*²⁵² found that the reduction in the renal arterial blood flow is of the same magnitude as that produced in a splanchnic artery or in the lower part of the abdominal artery. In contrast, Longo *et al.*¹⁹⁸ showed that, while the decrease in carotid and femoral blood flow is proportional to the decrease in cardiac output, the fall in renal flow is less marked.

The i.v. injection of posterior pituitary extract causes vasodilation in the renal artery and increases renal blood flow in dogs although urinary flow decreases markedly.^{143,264} Lysine⁸-vasopressin and Octapressin increase renal venous outflow in dogs while a higher dose (100 mU/kg) decreases renal venous outflow. Likewise, in rats¹²⁹ and cats³¹ lysine⁸-vasopressin, arginine⁸-vasopressin or Octapressin raises systemic arterial pressure slightly but increases renal arterial blood flow moderately. Furthermore, vasopressin partially or completely reverses the decrease of renal blood flow caused by a con-

tinuous i.v. infusion of angiotensin in cats. Vasopressin also increases renal blood flow in manitol-treated, water loaded dogs.⁴¹ In patients with hypotension or hepatic cirrhosis, Octapressin increases slightly both systemic arterial pressure and total peripheral resistance whereas it decreases cardiac output significantly.⁷³ With this dose of Octapressin, the renal blood flow increases as the renal peripheral resistance is decreased. A higher dose (20 mU/min) of Octapressin increases markedly systemic arterial pressure and total peripheral resistance while renal vascular resistance increases moderately and renal blood flow is maintained above control levels. Hence, it was concluded that Octapressin is a peculiar peptide which causes a vasodilator action on the renal vessels and a vasoconstrictor action on other vessels.^{24,25,73} However, the validity of this statement has been questioned by Saameli²⁵⁴ since their postulate is based on the observation that the increase in renal arterial blood flow occurs without any change in systemic arterial pressure. Berde *et al.*³⁶ concluded that the increase in renal blood flow is not due to vasodilation in the renal vascular bed, but rather to a redistribution of systemic blood flow caused by vasoconstriction in other regions of the body. With higher doses of vasopressin, the increased renal blood flow is preceded by a transient reduction due to the direct vasoconstrictor action of the vasopressins on the renal arteries.^{36,141} Octapressin increases renal arterial blood flow in dogs with hemorrhagic hypotension or with endotoxin shock.^{198,285} The increased renal blood flow in these animals caused by Octapressin may not be due to renal arterial dilatation but rather to increased renal arterial perfusion pressure secondary to increased systemic arterial pressure. Repeated injections of vasopressin causes renal arteriolar constriction, thereby causing renal cortical necrosis simulating necrotizing arteritis and eclampsia in pregnant rats.^{56,57} It was postulated that eclampsia patients are hypersensitive to vasopressin since they may have an overproduction of estrogens which may increase the vascular response to vasopressin. Few workers have studied the effect of physiological amounts of vasopressin on the renal circulation. Very recently, Fisher *et al.*¹¹⁰ showed in dogs with experimental diabetes insipidus that Pitressin (0.5–1 μ U/min, i.v. for 18 hrs) markedly increases total renal blood flow. Plethora increases systemic arterial pressure and renal plasma flow while plasma vasopressin levels

decrease in dogs.²²

Uterine Circulation:

In isolated human uterus *in vitro* vasopressin constricts the uterine arteries.²⁹⁸ Posterior pituitary extract decreases the uterine volume in pregnant rabbits, suggesting a constriction of the capacitance vessels.²¹³ Likewise, Pitressin constricts the uterine blood vessels and reduces the uterine blood flow in cats²⁴⁹ and in pregnant or post partum dogs.^{2,3} Since uterine blood flow is decreased by every uterine contraction, the decrease in uterine blood flow caused by vasopressin may be due not only to its direct vasoconstrictor action but also to an increase in extravascular resistance through its action on uterine contraction. In pregnant and non-pregnant rabbits, lysine⁸-vasopressin also markedly decreases the uterine (maternal placental and myometrial) blood flow.⁶¹⁻⁶⁴ The uterine veins are often visualized faster and their contrast density is somewhat greater after vasopressin suggesting that the contrast medium is by-passing the placenta through shunts. The vasoconstrictor action of vasopressin on the uterine artery is abolished or reversed by the subsequent injection of papaverine.⁶³ The reduction in uterine vein blood flow can be dissociated from the systemic pressor response of the animal, i.e., carotid pressure increase being of much shorter duration than the change in uterine blood flow. Hence, they postulated that the vascular bed of the uterus is particularly sensitive to the constrictor action of vasopressin.

Extremity Circulation:

In man,¹⁷⁴ dogs^{215,238} and cats,^{24,39} the i.a. injection of Pitressin (1.7 mU/min, i.a.) or vasopressin (0.1-0.5 mU or less than 5 mU/kg) increases peripheral vascular resistance and decreases femoral and brachial arterial blood flow without producing any significant change in systemic arterial pressure. The magnitude of the vasoconstrictor action of vasopressin is essentially in proportion to the dose administered.

The effect of the i.v. injection of vasopressin is more complicated, since it causes not only a direct vasoconstrictor action but also indirect vascular changes through the cardiovascular reflex mechanism. In man, Pitressin (170 mU/min, i.v.) causes vasoconstriction whereas the forearm blood flow increases in man.¹⁷⁴ In cats, lysine⁸-vasopressin or Octapressin (10 mU/kg or more, i.v.) increases femoral arterial blood flow.⁴⁹ In

dogs, however, the vasopressins, and Pitressin cause a biphasic change in femoral arterial blood flow, with an initial increase being followed by a secondary decrease.^{36,238,299} The initial increase in arterial blood flow may be related to a sudden change in distribution of cardiac output and possibly to reflex vasodilatation mediated through the baroreceptors. In contrast, in dogs, Octapressin does not produce a biphasic change but reduces femoral arterial blood flow essentially in proportion to the dose administered.¹⁹⁸ Likewise, in cats, vasopressin causes a slowly developing prolonged decrease in femoral venous blood flow.²⁴

Skin and Subcutaneous Circulation:

A number of investigators^{82,97,246,247,255,272,281,288} showed that Pitressin, Octapressin ornithine⁸-vasopressin causes skin pallor for one to several hours in man due to the decrease in the cutaneous blood flow. In rats, lysine⁸-vasopressin or Octapressin decreases markedly the cutaneous and muscular blood flows essentially in proportion to the dose administered.^{31,32} The decrement in the cutaneous and muscular blood flow is greater than that in total cardiac output. Likewise, lysine⁸-vasopressin or ornithine⁸-vasopressin reduces the cutaneous blood flow without producing any significant change in heart rate, cardiac output or other regional blood flows.^{97,283} Hence, Saameli²⁵⁴ suggested that vasopressin has a special affinity for skin vessels. Not only the i.v. but also the topical application of the vasopressins and Octapressin markedly constricts subcutaneous, mucous and serous membrane blood vessels. Hence, the vasopressins are used as hemostatic agents during surgical procedures or as vasoconstrictor agents for local anesthesia.^{23,46,154,169,175,187,212,227,231,272,291} When injected intradermally in man, the local vasoconstrictor action of lysine⁸-vasopressin and Octapressin is accompanied by an increased lymph flow in the superficial lymphatic vessels.⁵⁴

Tachyphylaxis:

Tachyphylaxis to the vasoconstrictor and hypertensive actions of vasopressin or Octapressin have been found in many species of animals including rats,²⁶² golden hamsters,¹⁹¹ rabbits,^{119,163,203,262,313} cats,^{39,189} dogs^{59,89,122,189,203,211,223,232,234,262,273} and man.²⁷² The circulatory effects of repeated doses of vasopressin are smaller than those of the initial dose. Frequently, repeated doses of vasopressin may produce

no or qualitatively different cardiovascular actions.^{215,223} For instance, the initial injection of vasopressin decreases pulmonary arterial pressure whereas the second injection increases it in dogs.²¹⁵

In rats, dogs and man, several workers^{36,119,149,254,288,289} showed that tachyphylaxis to the circulatory effects of vasopressin, Octapressin and other analogues is absent or not pronounced. Repeated short infusions of Octapressin produce approximately equal quantitative effects on hepatic blood flow in patients with bleeding esophageal varices.²⁸⁸

The pharmacodynamic mechanisms responsible for the genesis of tachyphylaxis remain uncertain. In spite of a short half life of the vasopressins,^{68,94} the cardiovascular effects of other than the pressor effect of vasopressin persist for a considerably longer period. Hence, it is tempting to speculate that vasopressin may well be attached to receptor sites in the cardiovascular system to interfere with the subsequent intrinsic actions of the peptide. The reduction in the pressor response to a continuous infusion or to frequently repeated injections of vasopressin can be explained on the basis of sustained coronary constrictor and subsequent myocardial depressant actions of repeated doses of vasopressin.^{215,217} The pressor response tachyphylaxis to vasopressin intervals is greatly diminished or abolished by pretreatment with ouabain in dogs.³¹⁴ It was concluded that vasopressin tachyphylaxis is due in part to prolonged pooling of blood in the splanchnic circulation by vasopressin and hence to a prolonged reduction in system venous return.^{102,215} Hence, overall cardiovascular responses including the pressor response to subsequent injections of vasopressin are markedly altered and the pressor response is diminished considerably. The increasing unresponsiveness of the extracardiac circulatory system to vasopressin may play an important role in the genesis of tachyphylaxis, since this phenomenon also was observed even when the circulation of animals was maintained by a mechanical heart.¹²⁴ Bilateral carotid sinus denervation increases the pressor response to vasopressin, but cannot prevent vasopressin tachyphylaxis.^{122,200} On the other hand, bilateral carotid sinus denervation and midcervical vagotomy not only increase the pressor response to vasopressin but also prevent vasopressin tachyphylaxis, suggesting that vasopressin tachyphylaxis may be due to increasing vagal activity

by repeated administration of vasopressin. In dogs, vasopressin tachyphylaxis is not significantly affected by vagotomy²⁴⁰ or by ganglionic blockade or by the section of the spinal cord at C₆.^{122,223} However, reserpine or pyrogallol prevents or diminishes markedly the development of vasopressin tachyphylaxis in dogs.^{222,223,234} In dogs, *Gardier et al.*¹²² showed that no vasopressin tachyphylaxis occurs if sympathetic activity is low initially and remains low. Likewise no tachyphylaxis is demonstrated if the sympathetic tone is initially high but remains depressed after the first dose of vasopressin. Subsequent doses give pressor responses equal to or greater than the original. On the other hand, vasopressin tachyphylaxis occurs if the sympathetic tone is initially high and recovery from the vasopressin-associated depression occurs prior to the succeeding injection.

Influences of the Autonomic Nervous Activities a) *Effects of vasopressin on the circulatory actions of catecholamines:*

Many investigators^{27,31,47,146,172,184,215,224,232,262,277} showed that vasopressin modulates the cardiovascular actions of catecholamines. The hypertensive action of epinephrine or norepinephrine is potentiated by physiological or pharmacological doses of vasopressin in rats, cats and dogs. Doses as low as 20 μ U/kg/min of arginine⁸-vasopressin, i.e., a dose far below threshold for its pressor effect, has been sufficient for this potentiation. Since an enhanced pressor response to catecholamines by vasopressin is demonstrated not only in intact animals but also in isolated organs including the aortic strip,^{26,27} atrium, papillary muscle and isolated heart,²⁰⁰ this is a direct action on the vascular smooth muscle or myocardium, and not mediated through the central nervous system. *Nakano*²¹⁵ showed that vasopressin increases the pressor action of norepinephrine but does not influence the positive inotropic action of the amine in vagotomized dogs. Contrary to other workers, *Louis and Doyle*¹⁹⁹ showed that the pressor effect of norepinephrine is not affected by the administration of Pitressin in dogs. The reason for this discrepancy remains unclear. Pitressin reverses the hypotensive action of isoproterenol to a hypertensive action.²²⁴ It was postulated that vasopressin blocks the peripheral vasodilator receptors without antagonizing the positive inotropic action of isoproterenol. Octapressin potentiates the vasoconstrictor action of locally

applied epinephrine in the meso-appendix of control rats.^{12,150} In contrast, Octapressin decreases the extremely high reactivity to epinephrine in rats with intestinal ischemic shock.^{11,150}

The underlying mechanism responsible for the potentiation of the pressor action of catecholamines by vasopressin remains controversial. *Bartelstone* and *Naysmyth*^{26,27} postulated that both vasopressin and catecholamines synergistically catalyze adenylyl cyclase and increase the cellular concentrations of cyclic 3',5'-AMP. However, no conclusive evidence has been shown to substantiate their hypothesis. Since adenylyl cyclase activity is enhanced mainly by stimulation of beta-adrenergic receptors and inhibited by that of alpha-adrenergic receptors, the experimental observations made by the previous workers are not entirely in agreement with the hypothesis.²¹⁵

b) Effects of sympathetic activities on the circulatory actions of vasopressin:

Sympathomimetic drugs, pharmacological stimulation or blockade of the sympathetic nervous pathways alter considerably the cardiovascular actions of vasopressin. Splenic nerve stimulation potentiates the vasoconstrictor action of vasopressin in the isolated perfused cat spleen preparation.³⁷ Ephedrine and epinephrine augment the pressor action of the posterior pituitary extract²⁰⁸ but this does not occur if the circulation is maintained by an artificial heart. *Chenoweth et al.*⁶⁹ found that hydroxyamphetamine, norepinephrine, amphetamine and ephedrine potentiate the pressor action of Pitressin and vasopressin in dogs with or without vagotomy.^{69,74}

It has been shown that the pressor response to Octapressin or Pitressin is enhanced in rats pretreated with phenoxybenzamine, dibenamine, dihydroergotamine, propranolol, bretylium, chlorpromazine or tetraethylammonium (TEA)^{85,190,197}. Furthermore, pretreatment with phenoxybenzamine, dibenamine, tolazoline, Hydergine, chlorpromazine or reserpine was found to increase the pressor action of vasopressin in dogs.^{74,118,223,282,307} Likewise, the pressor action of the initial or repeated doses of vasopressin is usually associated with a concomitant decrease in sympathetic tone.¹²² Higher sympathetic tone results in a weaker pressor action to vasopressin, whereas lower tone results in a greater pressor action. An inverse relationship between the initial blood pressure and the

magnitude of the pressure rise to vasopressin in rats.²²⁷ The pressor action of vasopressin in pithed golden hamsters is greater than that in anesthetized animals.¹⁷⁷ In contrast, pretreatment with TEA or spinal cord section does not augment the pressor response to Pitressin in dogs.²³³ Likewise, postganglionic sympathetic denervation does not modify the splenic arterial vasoconstrictor action of vasopressin in the isolated cat spleen preparation.¹⁵² Phentolamine decreases the preparation pressor action of vasopressin in healthy young male subjects.⁴⁸ On the other hand, in the isolated aorta, phentolamine does not influence the contractile response to vasopressin.¹³¹ Either reserpine or bretylium diminishes the T wave change in the ECG by Pitressin in rats.²⁶⁹

Amphetamine- or ephedrine-induced potentiation of vasopressin is not blocked by chlorisodamine, but is abolished by phenoxybenzamine or pretreatment with reserpine. Hemodynamically, the amphetamine-induced potentiation of the pressor action to Pitressin is most likely due to its enhanced vasoconstrictor action, thereby increasing total peripheral resistance rather than to cardiac output changes. Hence, it was concluded that the potentiation of the pressor action to vasopressin is caused partly by the release of catecholamines from the sympathetic nerve endings induced by amphetamine or ephedrine, thus interacting synergistically with vasopressin at a peripheral vascular bed.⁷⁴ In patients with orthostatic hypotension caused by primary autonomic nerve disturbance, the doses of vasopressin required to produce an increase in systemic arterial pressure are much lower than in normal individuals.²⁹⁷ When a hemodynamic state similar to hypotension is induced in normal subject by TEA or sodium nitrate, the vascular responsiveness to vasopressin is greatly increased.²⁷⁹

c) Effect of cholinergic blockade on the circulatory actions of vasopressin:

Earlier workers^{18,125,137,159,192,211,215,295} showed that the posterior pituitary extract slows heart rate significantly partially because of reflex vagal stimulation. However, bilateral vagotomy or the administration of atropine decreases but does not completely abolish the bradycardiac action of vasopressin. Similarly, the heart-rate slowing action of Octapressin in man is less pronounced when atropine is given before.²⁶⁶ In contrast, atropine does not interfere with fe-

moral arterial blood flow changes caused by vasopressin in the cat.³⁹ Furthermore, the pressor action of Octapressin is increased by atropine in anesthetized rats whereas its bradycardiac action is not affected.⁸⁵ Larson¹⁸⁹ and Gardier *et al.*^{122,123} showed that bilateral carotid sinus denervation and mid-cervical vagotomy or the administration of atropine increases the pressor response to vasopressin although veratrum does not modify it in dogs.

Influence of the Vasoactive Agents:

The responsiveness to the pressor action of vasopressin is reduced in male and female rats treated with DOCA prior to the development of hypertension.^{157,158} Cortisone decreases the sensitivity to vasopressin of estrous females but increase that of males and diestrous females.^{157,158} Most of the DOCA or Cortisone-treated rats respond to oxytocin by a pressure rise, usually preceded by a fall in systemic arterial pressure.¹⁵⁷ Prostaglandin inhibits the pressor action of vasopressin in pithed rats.¹⁵⁵ Since this antagonism exists also for the pressor action of angiotensin and catecholamines, it is believed to be a nonspecific mechanism. The prolonged coronary vasoconstrictor action and subsequent myocardial depressant action of the intra-coronary injection of vasopressin is temporarily reversed by the intra-arterial injection of nitroglycerin and PGE₁ in dogs.²¹⁸ During the period of the coronary vasodilator action of the two agents, the coronary blood flow increases above control values, and then decreases to levels below controls as the action of both nitroglycerin and PGE₁ disappears, but as the action of vasopressin persists. Likewise, the uterine arterial constriction induced by vasopressin is abolished or reversed by the consequent injection of papaverine in rabbits.⁶³ These observations indicate that the vasoconstrictor action of vasopressin can be easily reversed by non-specific vasodilators. The vasodilator action of histamine is neutralized by the vasoconstrictor action of vasopressin in cats and dogs.²⁰ However, in rats, histamine, acetylcholine and serotonin do not influence the pressor response to vasopressin.¹⁹⁶ Bulbocapnine, a potentiator of the effects of histamine, increases the pressor action of vasopressin in dogs.³⁰¹ The vasoconstrictor action of vasopressin is altered by an anti-histaminic agent, mepyramine, in cats.³⁹ The hypertensive effect of the posterior pituitary extract in dogs with renal hypertension is greater than that in normo-

tensive dogs.⁵¹ On the other hand, vasopressin reduces the pressor response to angiotensin in dogs.^{199,232} Since vasopressin does not alter the pressor response to norepinephrine, it was suggested that vasopressin and angiotensin may compete for a common receptor site in the blood vessels. Both vasopressin and angiotensin inhibit the release of renin induced in dogs by lowering renal perfusion pressure.⁵³ As in some experiments with vasopressin, inhibition of renin release occurs without changes in systemic arterial pressure, the inhibitory action could not be related to hemodynamic alterations.

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