ANTAGONISM OF HISTAMINE EDEMA FORMATION BY NOREPINEPHRINE IN THE CANINE FORELIMB

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DOUGLAS LEE MARCINIAK

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ABSTRACT

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By

Douglas Lee Marciniak

There is clearly a route-dependent differential action of histamine on forelimb transvascular fluid flux. Local (intra-arterial) infusions of histamine (4 to 64μg base/min) into the brachial artery of the forelimb causes marked increases in transvascular fluid flux and forelimb weight owing to an increased capillary hydrostatic pressure gradient and an increased permeability to plasma proteins. Massive visible edema is seen with dosages of 15 to 60μg base/minute. In contrast, systemically (intravenously) infused histamine at rates that produce blood concentrations calculated to equal or exceed those achieved during local infusions, results in sustained net extravascular fluid reabsorption.

Possible explanations for this route-dependent differential action of histamine are: the lungs may actively destroy histamine since it must first pass through the pulmonary circuit before reaching the systemic microvessels during intravenous infusion; that factors within the blood may destroy or inactivate histamine before it reaches the systemic microvasculature during systemic infusions; that substances

released (e.g., catecholamines) during a sympathoadrenal discharge, subsequent to a marked and immediate hypotension produced only with the systemic infusions (20 to 800µg base/min), may effectively antagonize the edemogenic actions of histamine by a direct blockade of histamine's permeability increasing effects on the microvessels, a shunting of blood to non-nutritional channels or a combination of both.

Forelimb weight and hemodynamic studies were conducted during systemic histamine infusions (400 to 800µg base/min) into the vena cava, the left ventricle of the heart and during local infusion into the brachial artery of the forelimb (4 and 64µg base/min). This allowed for comparisons of systemic and local infusions and evaluation of the possible role the lungs may have upon the route-dependent differential actions of histamine.

To test the hypothesis that substances liberated during a hypotensive induced sympathoadrenal discharge antagonize histamine's action on the microvasculature, systemic histamine, acetylcholine, and hemorrhagic hypotension were produced for 60 minutes. This was followed by a 30 or 60 minute infusion of histamine (4 and 64µg base/min,I.A.) into forelimbs perfused at constant inflow during the systemic hypotension.

To further test the hypothesis that substances released during a sympathoadrenal discharge antagonize histamine at the size of the microvasculature, weight and hemodynamic studies were conducted in which norepinephrine (4µg base/min) was simultaneously infused with histamine (4µg base/min) into the forelimb brachial artery.

Histamine (400 and 800µg base/min) infused into the vena cava and left ventricle of the heart for 90 minutes produced marked

hypotension and only very slight increases in forelimb skin lymph flow rate and total protein concentration. Forelimb weight continually decreased during these infusions. There was no discernable differences in any of the hemodynamic parameters during intravenous or left heart infusions. Thus, the route-dependent differential actions of histamine cannot be attributed to uptake or destruction of histamine by the lungs.

The greater transit time required for histamine to reach the microvasculature during systemic infusions than during local infusions, which would allow more time for factors within the blood to destroy or inactivate histaime, cannot account for the route-dependent differential actions of histamine either. This is demonstrated by the fact that large increases in lymph flow rate and total protein concentration are witnessed during local histamine infusions into forelimbs perfused at constant inflow. In these preparations, histamine must travel through about 3 feet of polyethylene tubing before reaching the forelimb. Since this distance is equal to or greater than the distance histamine must travel during systemic infusions, if factors within the blood were destroying histamine than such profound histamine effects (increased lymph flow and total protein concentration) would not be expected during the local infusions into forelimbs perfused at constant inflow.

Histamine infused locally (4 and 64μg base/min) into forelimbs perfused at constant inflow completely prevented the increase in total protein contentration of lymph following 60 minutes of systemic histamine, acetylcholine or hemorrhagic hypotension. This indicates that hypotension results in the release of substances (e.g.,

catecholamines) that effectively antagonizes histamine's actions on the microvasculature.

The stimultaneous infusion of norepinephrine (4μg base/min) with histamine (4μg base/min) into forelimbs perfused at constant inflow prevented the usual large increases in lymph flow and total protein concentration seen during histamine infusions alone. This convincingly demonstrates the antagonistic action of norepinephrine on histamine at the site of the microvasculature.

In conclusion, the failure of systemically infused histamine to exert effects on the microvasculature similar to those produced by locally infused histamine is related to hypotension per se and to antagonism of the microvascular actions of histamine subsequent to the release of substances (e.g., catecholamines) in response to the hypotension produced by systemically infused histamine.

This antagonism of histamine by norepinephrine and/or other substances released during a sympathoadrenal discharge could be due to a direct blockage of histamine's permeability increasing effect or to a shunting of blood flow to non-nutritional channels or a combination of both.

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Douglas Lee Marciniak

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DEDICATION

This thesis is dedicated to my parents and grandmother. Without their love, understanding, encouragement and willing support, my education and this thesis would never have been possible.

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LIST OF SYMBOLS AND ABBREVIATIONS

NF	=	Naturally perfused forelimb.
CF	=	Forelimb perfused at constant inflow.
LH	=	Drug infusion into the left ventricle of the heart.
IA	=	Drug infusion intra-arterially into the forelimb.
IV	=	Drug infusion into the vena cava.
µg	=	Microgram.
min	=	Minute.
ml	=	Milliliter.
l	=	litter.
g	=	grams.
Kg	=	Kilograms
mmHg	=	Millimeters of mercury pressure.
A^4	=	Acetylcholine infused intravenously along with 4µg/min of histamine base.
Hm^4	=	Hemorrhage along with 4µg/min of histamine base.
Hm^{64}	=	Hemorrhage along with 64µg/min of histamine base.
H4	=	4µg/min of histamine base.
H64	=	64µg/min of histamine base.
H400	=	400µg/min of histamine base.
H800	=	800µg/min of histamine base
N4	=	4µg/min of norepinephrine base.

N16 = 16μg/min of norepinephrine base.

* = $P \leq 0.01$ Relative to 0 minute control.

† = $P \leq 0.05$ Relative to 0 minute control.

ω = $P \leq 0.01$ Relative to 60 minute value.

Ω = $P \leq 0.05$ Relative to 60 minute value.

INTRODUCTION

Histamine (β-imidazolylethylamine) was first subjected to scientific investigation in 1910 by Dale and Laidlow (8). They found that it stimulated a variety of smooth muscle and markedly depressed blood pressure when injected intravenously. In 1927 Best et al. (4) determined that histamine was actually an autocoid and at the same time Lewis (37) showed that it was liberated in response to tissue injury and antigen-antibody reactions. The work by these investigators led to histamine being one of the most studied compounds in the history of biomedical sciences.

Over the past 50 years histamine has been implicated in many pathophysiological conditions such as anaphylaxis, allergy, tissue injury and shock. When histamine release is confined to localized areas such conditions may be associated with tissue edema. It is now becoming apparent that histamine may be involved in various normal physiological mechanisms such as microcirculatory regulation, tissue growth and repair, central nervous system function and possibly gastric secretory responses (33). Of primary interest in this study are those actions of histamine relevant to pathological conditions which are manifested by abnormal transvascular fluid fluxes.

Local (intra-arterial) infusions of histamine in large doses (15-60 μg base/min) increases transvascular fluid filtration leading to massive edema formation. This edema is attributable to both a rise in the transmural capillary hydrostatic pressure gradient subsequent to arteriolar vasodilation and a fall in the transmural colloid osmotic pressure gradient owing to an increased microvascular permeability to plasma proteins. Even if capillary hydrostatic pressure is mechanically prevented from increasing, edema still occurs indicating that the fall in the transmural colloid osmotic pressure gradient exerts the dominant effect, at least with the higher doses (15-60 μg base/min). In contrast, histamine administered systemically (intravenously), at rates that produce concentrations estimated to equal or exceed those achieved locally, not only fails to promote edema formation but rather leads to sustained net reabsorption of extravascular fluid (19). The mechanism of these little noted route-dependent differential actions of histamine on transvascular fluid fluxes is unknown.

Although the estimated blood concentrations of histamine may be equal during both local and systemic administration of this agent, there are other obvious differences that may account for the observed route-dependent differential actions of histamine on fluid filtration. First of all, during local infusions of histamine capillary hydrostatic pressure (Pc) increases whereas it decreases during systemic infusions of this agent. Also during intravenous infusions, histamine passes first through the pulmonary circuit before reaching the systemic microvessels. Thus it is possible that passage through the pulmonary circuit may result in uptake, metabolism, or biotransformation of

histamine by the lungs. During local administration histamine first enters the microcirculation and then, upon recirculation, enters the lung. The transit time from the point of introduction to the microcirculation is also greater during systemic than during local infusions, possibly resulting in destruction by factors within the blood. Additionally, systemic pressure is little affected during local administration of histamine (5 to 60μg base/min) or falls only slightly after edema has already developed (20). In contrast, during systemic administration there is an immediate and sustained fall in systemic pressure which, at least initially, appears to be dose related within a range of 20 to 800μg of histamine base/min (19). The fall in arterial blood pressure is undoubtedly associated with a marked sympathoadrenal discharge. It is conceivable that substances liberated subsequent to the hypotension effectively antagonize the usual edemogenic action of histamine.

It is, therefore, the aim of this study to elucidate the mechanism(s) of the route-dependent differential actions of histamine on transvascular fluid fluxes. These findings may lead to a more complete understanding of the microcirculatory actions of histamine, and may also have relevance to the pathophysiology of certain anaphylactic and circulatory shock states which are associated with extremely high blood levels of histamine (up to 1μg/ml whole blood [28]) but persistent net extravascular fluid reabsorption occurs.

LITERATURE REVIEW

The movement of fluid across the capillaries was first proposed in 1653 by Bartholinus (3) and again in 1753 by Hales (25). The first definitive theory concerning capillary filtration was proposed in 1861 by C. F. Ludwig (38) and it was not until 1896, when Starling published an article entitled "On the absorption of fluids from the connective tissue spaces" (62), that the physical determinants of fluid exchange across the capillaries began to be understood.

The physical basis of fluid filtration is expressed by the following equation: F.M. = K (Pc - Pi - πp + πi) where F.M. represents fluid movement across the capillary wall. When the equation is positive, filtration occurs (movement of fluid into the interstitium from the vasculature) and when negative, fluid reabsorption (movement of fluid from the interstitium into the vasculature) occurs. Pc represents capillary hydrostatic pressure and Pi represents the hydrostatic pressure of the interstitial fluid. Colloid osmotic pressure (oncotic pressure) is symbolized by πp for plasma and πi for interstitial fluid. The symbol K is a proportionality constant representing the capillary filtration coefficient. It is a measure of the permeability of the capillary wall to isotonic fluids (relative to plasma) and is determined by the product of capillary permeability and surface area available for diffusion.

Capillary hydrostatic pressure (Pc) is the force acting to move fluid outward into the interstitium across the capillary wall. Its immediate determinants are capillary blood volume and capillary compliance. Since the capillaries are relatively stiff, compliance is usually not considered to significantly change. Clough et al. (7) reported changes in radius of only about 0.1 micrometer during systole in capillaries of cat mesentery. This rigidity may be due to elastic properties of the capillary wall (5) or to the incompressible nature of the surrounding gel preventing capillary distention (15). Hence, capillary hydrostatic pressure is determined by capillary blood volume which is regulated by several physical factors affecting both inflow and outflow. These factors are related by the equation:

$$\bar{P}c = (\bar{P}a - Pv) \frac{Rv}{Ra+Rv} + Pv$$

where: $\bar{P}c$ = mean capillary hydrostatic pressure

$\bar{P}a$ = mean arterial blood pressure

Pv = venous or outflow pressure

Rv = venous resistance to outflow

Ra = arterial resistance to inflow

Thus, capillary hydrostatic pressure is directly related to changes in mean arterial blood pressure, venous outflow pressure and venous resistance; and is indirectly related to arterial resistance. Arterial and venous resistances are related to vessel caliber which is determined by active changes (vascular smooth muscle activity), passive changes (transmural pressure) and blood viscosity.

The hydrostatic pressure of interstitial fluid (Pi) is analogous to the capillary hydrostatic pressure but is that pressure

found in the interstitial spaces. The classical view is that interstitial tissue pressure is positive and consequently opposes fluid movement out of the capillaries. Recently, however, new information has come forth challenging this viewpoint suggesting that interstitial fluid hydrostatic pressure is slightly negative in a variety of tissues (21). If this is the case then fluid movement out of the capillaries would be enhanced by interstitial hydrostatic pressure since there would be no opposing force to even the minimal capillary hydrostatic pressure. This issue remains to be resolved.

Plasma colloid osmotic pressure (πp) is the pressure resulting from the concentration of dissolved proteins in the plasma and other physical-chemical factors not completely understood. The plasma proteins are a mixture containing albumins, globulins and fibrinogen. Albumin has an average molecular weight of 69,000 and its concentration is normally found to be about 4.5 grams %. The globulins average molecular weight is 140,000 with a concentration of about 2.5 grams %. Fibrinogen is the largest with a molecular weight of about 400,000 and is found in concentrations of approximately 0.3 grams %. This yields a total plasma protein concentration of 7.3 grams % and a normal plasma colloid osmotic pressure of around 28 mm Hg of which 19 mm Hg is attributable to the proteins themselves and 9 mm Hg to charged ions being held by electronegative forces from the plasma proteins. (The values stated are human plasma values; the values for a dog tend to be slightly less.) Since albumin is only about half the size of the globulins and its concentration is almost twice as much, the osmotic effect of albumin is about 70% of the total colloid osmotic pressure.

Colloid osmotic pressure of interstitial fluid depends upon the amount of protein dissolved within the interstitium. Small amounts of plasma proteins normally cross the microvascular wall usually at the immediate postcapillary venule (41). Albumin, since it is smaller, crosses at about 1.5 times the rate of the globulins. The total quantity (grams) of the interstitial proteins is about equal to that of plasma but since interstitial fluid water volume is about 4 times greater than plasma, the effective protein concentration (grams %) and hence, osmotic pressure, is much less. Normal concentration of total interstitial proteins is about 2.0 grams % which gives an interstitial colloid osmotic pressure of about 4.5 mm Hg in tissues such as skin and skeletal muscle. This pressure is disproportionately less compared to plasma because at low concentrations of protein the colloid osmotic pressure becomes mostly a function of concentration alone. The electronegative forces become minimal. More recent findings suggest that the total protein concentration of interstitial fluid is about 3 grams % and the colloid osmotic pressure about 10 mm Hg (66). Protein concentration and colloid osmotic pressure will vary from one vascular bed to another depending upon the capillary permeability. An example is in the liver where the heptic sinuses are extremely permeable to proteins thereby allowing for a very rapid and an effective exchange of nutrients between blood and liver cells.

When discussing tissue colloid osmotic pressure certain reservations must be kept in mind especially concerning absolute values. Measurements using implantable devices such as perforated capsules that theoretically equilibrate with interstitial fluid, may be inaccurate because of the possiblity of contamination by plasma or

that sampled fluid may not contain all the various osmotically active particles. Lymph fluid analysis, the most common method, makes the assumption that it is a true reflection of interstitial fluid. However, there could be drastic changes in lymph composition as it flows from terminal lymphatics upwards to larger vessels and/or that gradients of protein concentration exist within the interstitial spaces.

Mayerson and associates (45, 49) and Garlick and Renkin (17) have performed studies showing exchange occurs only at lymph nodes, not in the lymphatic trunks. Therefore, if lymph is sampled before it reaches a node it should be a true reflection of what is at the terminal lymphatic vessel. Furthermore, Renkin and Garlick (53) using dextran molecules of known molecular weight and size found that the concentrations were equal between lymph and interstitial fluid for the dextran molecules and presumably for albumins. Their conclusion was that there is no substantial protein concentration gradients within the interstitial spaces beyond the capillaries. So at least under normal conditions, it appears that lymph protein concentration is a satisfactory reflection of interstitial fluid protein concentration. However, there is the possibility that under abnormal conditions the lymph proteins may not remain in equilibrium with the interstitium.

The capillary filtration coefficient is actually a composite of several variables affecting transcapillary fluid movement. These variables are the surface area of the capillary wall available for filtration (Am), thickness of the capillary wall (Δx), fluid viscosity (η) and the specific filtration constant of the membrane (Km). Looking at these factors in terms of an equation we see:

$$\text{Capillary filtration coefficient (K)} = \frac{Km\ Am}{\eta\ \Delta x}$$

Since viscosity of the fluid and capillary wall thickness remains fairly constant, the primary determinants for the capillary filtration coefficient is the actual permeability of a given vascular bed and the surface area available for diffusion. Furthermore, within a given capillary bed, permeability remains fairly constant under normal conditions. Hence in normal physiological conditions it is usually changes in surface area available for diffusion that alters the capillary filtration coefficient and consequently affects net fluid movement.

In many pathophysiological states, such as anaphalaxis, allergy, tissue injury and shock, all of the parameters affecting fluid movement may be markedly altered and subsequently cause drastic changes in transcapillary fluid movement. Histamine, released in such conditions is one agent that could be involved in at least some of the cardiovascular alterations associated with these pathophysiological states. Hinshaw found that mean blood levels of histamine increase linearly from a control of 0.1 μg/ml to about 1.0 μg/ml over a time span of 180 minutes after intravenous administration of a lethal dose of endotoxin to anesthetized dogs (28). Similar changes were observed in monkeys under the same experimental conditions, however mean values were much lower. Histamine increased from control values of nearly zero to about 0.4 μg/ml of blood within one hour after endotoxin administration (29). Schayer (57, 58) demonstrated that in response to not only endotoxin shock but to stress induced shock (achieved by intramuscular injections of 20 or 40 μg epinephrine in

mice) that there was a threefold increase in skin and lung tissue histidine decarboxylase activity. Norepinephrine produced similar results in skin at the same dosages but with 3 separate subcutaneous injections. Histidine decarboxylase is the enzyme involved with the conversion of histidine to histamine. An increase in its activity presumably reflects an increase in the rate of histamine synthesis. Dekanski observed in mice that the total body histamine content almost doubled from a control of about 8.6 μg/gram of tissue within 10 minutes after being plunged into 60°C water for 30 seconds (10). Schayer and Ganley repeated these experiments and found a threefold increase in histidine decarboxylase (59). When the stimulus for histamine release is a localized condition such as a burn, bee sting, etc., the amount of histamine released is extremely variable being dependent not only upon the nature and severity of the insult but upon the sensitivity of the individual. Consequently, to study the local effects of histamine, investigators usually administer doses of histamine that produce effects similar to those seen clinically.

In most vascular beds the local administration of histamine in doses ranging from 3-64 μg base/min intra-arterially or 1.0 to 28.0 μg injected subcutaneously greatly increases net transvascular fluid filtration (6, 9, 20, 24, 32, 35). Massive visible edema, similar to that observed clinically, is produced with the medium to high infusion rates (16-64 μg base/min). This increased net fluid filtration is attributable to both a rise in the transmural capillary hydrostatic pressure gradient and a fall in the transmural colloid osmotic pressure gradient. The rise in the transmural hydrostatic pressure gradient is due to an increased capillary hydrostatic

pressure subsequent to arteriolar vasodilation. The fall in the transmural colloid osmotic pressure gradient is attributable to an increased microvascular permeability to plasma proteins and exerts the dominant edemogenic effect with the higher doses of histamine. The alterations of these two determinants of fluid filtration is witnessed by marked increases in organ weight, volume and circumference, and both flow rate and total protein concentration of lymph draining the vascular bed. The latter approaches plasma values with high doses of histamine (6, 20, 23, 32, 52). The increased protein efflux is usually attributable to an increased pore size subsequent to a direct action of histamine on the postcapillary microvascular membrane (39, 40, 41, 42, 67). These microscopic studies offer evidence that gaps appear between the endothelial cells of the microvasculature, primarily in venules of 20 to 30 micra diameter. It has been postulated that histamine may actually cause contraction of actomyosin-like fibrils within the endothelial cells resulting in their "rounding up," thereby effectively creating a larger than normal intercellular cleft, i.e., pore (42).

The concept of histamine causing an increased pore size has recently been challenged by Renkin and co-workers (6, 32, 51, 52). Rather than an increased microvascular pore size, allowing for an increased outward diffusion of proteins, they postulate that histamine is a stimulus for an increased vesicular transport of proteins across the capillary membrane thereby accounting for the increased protein efflux witnessed with histamine administration. Vesicular transport, or pinocytosis, is a process whereby the capillary endothelial cell invaginates and subsequently engulfs a small portion of plasma. An intracellular, or pinocytotic vesicle is then formed which diffuses

to the other side of the cell, where its contents are released into the interstitium. Definitive support for this hypothesis being the major protein transport mechanism stimulated by histamine is still lacking.

Controversy surrounds the possibility of capillary hydrostatic pressure contributing to an increased microvascular permeability and, if so, how important a role it may play. Shirley et al. (60) have postulated the concept of the "stretched pore phenomenon" based on the fact that investigators have found that increasing capillary hydrostatic pressure leads to an increase in the size of the macromolecules appearing in lymph (36, 44, 60). Haddy et al. (23) have shown that mechanical increases in blood flow and small vein pressures for 30 minutes to levels identical with those seen during local histamine infusions results in a slight increase in albumin concentration in lymph while globulin concentration was unchanged. When venous pressure alone was increased for 90 minutes they found slight increases in total concentration of lymph protein within the first 10 minutes after elevation (12). This was attributable to an increased albumin concentration and no change in globulin concentration. The initial increase in lymph total protein may be a result of a washout of protein from the free fluid phase of the interstitial space. Apparently passive stretching of microvasculature pores occurs but its importance seems to be relatively minor based on the available data, especially in the presence of histamine (20).

Of the many publications of the effects of histamine on fluid filtration there is surprisingly only a small number concerning the effects of systemically administered (intravenous) histamine on

transcapillary fluid exchange (9, 11, 19, 22, 50). In general these studies show that, in contrast to locally administered histamine, systemic administration promotes sustained net reabsorption of extravascular fluid.

Daugherty et al. (9) noted that in comparing intra-arterial and intravenous infusions of histamine that large increases in hindlimb weight occurred during intra-arterial administration whereas during intravenous infusions, weight was increased only very slightly with the lowest dose employed (20.6 μg base/min) and was reduced with higher doses, falling below control with the highest dose used (82.4 μg base/min). Haddy (22) offered evidence indicating that differences in capillary hydrostatic pressure contributed, at least partially, to the failure of intravenous histamine to increase transcapillary fluid filtration. During local administration of histamine, skin small vein pressure (which represents a minimum for capillary hydrostatic pressure) increases to levels just slightly lower or equal to normal colloid osmotic pressure (22). Hence, net fluid filtration is favored across the vascular bed in question. In contrast, during intravenous infusion of histamine small vein pressures increased slightly with a small dose of 5μg base/min. This may explain the increase in forelimb weight that Daugherty et al. observed with their lowest dose. With a higher dose (34μg base/min) small vein pressures decreased well below control suggesting a reduction in microvascular pressure which would favor net extravascular fluid reabsorption. Remington and Baker (50), using changes in specific gravity of blood and plasma as indicators found no evidence for leakage of plasma proteins (indicating an increased capillary permeability) during intravenous infusions of histamine.

Deyrup (11), injecting histamine subcutaneously in the thigh of the dog hindlimb, used changes in plasma volume as an indicator of histamine's effects on transcapillary fluid flux. She found during the first 30 to 90 minutes after histamine injection (3 to 12 mg base/kg), when blood pressure was markedly reduced, that plasma volume was unchanged or moderately increased and in a few cases slightly reduced. There was no evidence for increased capillary permeability since the escape of the albumin-bound dye T-1824 from the vasculature did not increase significantly.

In a study performed by Grega et al. (19) using isolated, naturally perfused, innervated canine forelimbs, it was found that instead of the typical large increases in forelimb weight seen with the medium to high doses of locally infused histamine (20-60 μg base/min) (20), there was a persistent dose-dependent (20-800 μg base/min) weight loss of a magnitude that could not be accounted for solely by decreased intravascular volume when infused intravenously. This was best demonstrated by the fact that during the time period of the greatest forelimb weight loss, the total forelimb small vessel and large vein (capacitance vessels) resistances were not changing. This implies that vessel caliber and consequently intravascular blood volume was constant during this time. Hence, extravascular fluid reabsorption must have occurred to account for the observed weight loses. Most likely this was a result of a decreased transmural capillary hydrostatic pressure gradient. This is suggested because all vascular pressures, including small vein pressures, and forelimb blood flow fell markedly below control. Unfortunately flow rate and total protein concentration of lymph were not measured in any of the systemic studies.

Thus only speculations can be made concerning any permeability changes and consequently the transmural capillary colloid osmotic pressure gradient. If systemically administered histamine does increase microvascular permeability and hence decrease transmural colloid osmotic pressure gradients, it must be effectively counteracted by an even greater fall in the transmural capillary hydrostatic pressure gradient. Local histamine increases permeability sufficiently to increase forelimb weight significantly even when capillary hydrostatic pressure (Pc) is mechanically prevented from increasing above normal plasma colloid osmotic pressure (20). In this situation, fluid filtration still occurs when perfusion pressure is kept at or below normal plasma colloid osmotic pressure. Capillary hydrostatic pressure then must certainly have been well below normal plasma colloid osmotic pressure.

Since locally administered histamine increases microvascular permeability and subsequently causes net fluid filtration even when perfusion pressure and capillary hydrostatic pressure are exceedingly low, it is perplexing why fluid filtration does not occur during systemic administration of histamine when perfusion pressure, blood flow and calculated blood concentrations (assuming no degradation) are at least equal or exceed the minimal dosage that produces fluid filtration when infused locally (see Appendix A for calculations). There are, however, several differences that may account for the route-dependent differential actions of histamine on transvascular fluid flux. First of all, during local infusions of histamine, capillary hydrostatic pressure (Pc) increases, whereas Pc decreases during systemic infusions of histamine (19, 20). Also during systemic infusions, histamine first passes through the pulmonary circuit before reaching

the systemic capillary beds. This passage through the pulmonary circuit may result in the uptake, metabolism, or biotransformation of histamine by the lungs. During local administration, histamine first passes through the microvasculature and then, upon recirculation, enters the lung. The transit time from the point of administration to the microvessels is also greater during systemic administration than during local intra-arterial infusions. This added time may possibly allow destruction of histamine by factors within the blood. Additionally, systemic pressure is little affected during local administration of histamine or falls only slightly after edema has already developed. In contrast, during systemic administration there is an immediate precipitous and sustained fall in systemic arterial blood pressure. Hence, the latter response is most likely associated with a marked sympathoadrenal discharge subsequent to the hypotension. It is conceivable that substances liberated from the sympathoadrenal discharge such as the glucocorticoids and catecholamines, effectively antagonize the usual edemogenic action of histamine seen with local histamine administration. Schayer proposed that there exists a balance between catecholamines and histamine which subsequently forms a component of circulatory homeostasis in stressful conditions (57). Hence, the catecholamines are very likely candidates.

Evidence for adrenal gland discharge subsequent to histamine administration is offered by Weiss et al. (65). While studying the effects on blood pressure in normal human subjects they observed that upon termination of a prolonged histamine infusion (several hours) of 25 to 50 μg base/min that there was a significant increase in systemic blood pressure above normal control levels. Also, skin (such as of

the face) that was previously flushed appeared very pale. They contributed these opposite responses to "antagonistic substances" and/or "vasomotor reflexes" having been developed which are antagonistic to histamine. Their hypothetical substance and vasomotor reflex had actions very similar to the catecholamines, norepinephrine and epinephrine which are released from sympathetic nerve fibers and the adrenal gland, respectively. Further evidence for an adrenal gland discharge subsequent to histamine administration is offered by Roth and Kvale who used histamine as a test for pheochromocytoma (56). The intravenous injections of histamine into patients suspected of having the disease resulted in marked increases in blood pressure which was identical to the typical paroxysmal hypertension (a result of hypersecretion of adrenal catecholamines) often seen in such patients. Furthermore, Robinson and Jochim (54) found that during histamine induced hypotension from intravenous administration that there was marked increases in blood levels of catecholamines (from a control of 0.035 μg/kg/min up to 0.25 μg/kg/min), leaving the adrenal glands via the lumboadrenal vein in dogs. Hökfelt, using rats, found that the suprarenal content of norepinephrine was significantly reduced following subcutaneous injections of histamine (30). It has also been shown that adrenalectomized rats and mice (26, 27, 43) are rendered hypersensitive to histamine. This hypersensitivity (measured by comparisons of mortality rates to dose levels between normal and adrenalectomized animals) is at least partially reversible when epinephrine is given prior to histamine administration (27).

The primary stimulus for catecholamine release from the adrenal gland appears to be the hypotension produced regardless of the

causative mechanism. Rosenberg et al. (55) produced hypotension by two different methods in dogs. Within 5 minutes after an intravenous injection of endotoxin (7.5 mg/kg) they found venous plasma epinephrine concentration had increased to 20μg/l. A 30-fold increase above control. Norepinephrine increased to about 17 μg/l representing a 9-fold increase above control. Hemorrhagic hypotension, produced by an acute loss of 36% of total blood volume, within 5 minutes resulted in epinephrine increasing to 35 μg/l and norepinephrine to 14 μg/l, a 70 and 5 fold increase above control, respectively. The discrepancy between concentrations achieved by these two different mechanisms are most likely a result of the arterial blood pressure values. Within 5 minutes after endotoxin administration, arterial blood pressure fell to about 80 mm Hg whereas during hemorrhage it fell to about 50 mm Hg. Furthermore, this hypotension induced release of catecholamines appears to function via a neurogenic mechanism as demonstrated by Nykiel and Glaviano (48) and Egdahl (13) who observed no change in adrenal catecholamine output following intravenous administration of sublethal doses of endotoxin in dogs with their splanchnic nerves sectioned or spinal cord transected between C-7 and T-1, respectively.

Without question, the catecholamines are released during hypotension, however, much disagreement exists within the literature concerning the catecholamines effects upon the various vasculature sites and subsequently transvascular fluid flux. In general, the catecholamines are believed to be vasoconstrictors of both resistance and capacitance vessels except for epinephrine which in low concentrations is said to dilate the precapillary vessels of skeletal muscle (18). In studies of naturally perfused forelimbs and ileum segments

(14, 24) small vein pressures are sometimes seen to rise, sometimes fall, or remain unchanged in response to norepinephrine. The organ weight (forelimbs or ileum segment) was found to vary directly with small vein pressure in these studies. This association between small vein pressure and consequently organ weight can be best explained in terms of varied effects upon the pre/post capillary resistance ratio. If the venous segment of the vascular bed constricts more than the arterial segment, capillary outflow would be impeded and hence capillary hydrostatic pressure will increase, thereby favoring an increase in filtration and consequently an increased organ weight. If the arterial segment was constricted proportionately more than the venous segment, then capillary inflow would be impeded, thus capillary hydrostatic pressure would decrease, thereby favoring net fluid reabsorption which would account for the observed weight decreases.

Kaiser and Diana (34) found no significant alteration in isogravimetric capillary pressure nor the capillary filtration coefficient during infusions of norepinephrine (0.9 to 2.9 μg base/min/kg tissue) under both constant flow and constant perfusion pressure conditions in isolated dog hindlimbs. Mellander and Nordenfelt (46) studying the human hand (skin) and calf (skeletal muscle) also found no significant effects upon the capillary filtration coefficient by norepinephrine administered intravenously at dosages of 0.05 to 0.3 μg base/kg/min for 30 minutes. The results of these two studies indicate that both capillary surface area available for diffusion (determined by the precapillary sphincters) and capillary permeability were uneffected by norepinephrine. However, Järhult (31) has reported that under constant perfusion pressure conditions, in denervated

skeletal muscle of the lower leg of cat hindlimbs, that norepinephrine (mean dosage of 2.7 μg base/kg/min) increases the capillary filtration coefficient indicating an increased capillary surface area available for diffusion. In contrast, Appelgren and Lewis (1) reported a decreased capillary permeability-surface area product (PS) in naturally perfused human skeletal muscle when solutions of 0.04 mg/ml norepinephrine were injected locally.

Uptake of ^{86}Rb, used as an index of capillary surface area available for diffusion, has been shown to increase (indicative of an increased surface area) during constant inflow conditions in isolated dog forelimbs during intra-arterial infusion of 0.015 to 0.03 μg epinephrine/min (2) and in isolated dog hindlimbs following an intra-arterial injection of 2 μg epinephrine or norepinephrine (16). However, in an isolated, pump perfused, canine gracilis muscle preparation, Szwed and Freedman (63) have reported a decreased in ^{86}Rb uptake reflecting a decreased capillary surface area available for diffusion during intra-arterial infusion of 0.0012 to 0.06 μg/min/gram of tissue of epinephrine or norepinephrine.

STATEMENT OF THE PROBLEM

The objective of this study was to attempt to determine the mechanism(s) of the route-dependent differential actions of histamine on forelimb transvascular fluid flux. Local (intra-arterial) infusions of histamine (4 to 64μg base/min) into the forelimb increase transvascular fluid flux and forelimb weight producing massive visible edema with the medium to high infusion rates (16-64μg base/min). The increased fluid flux and consequently edema is attributable to both a rise in the transmural capillary hydrostatic pressure gradient (due to arteriolar vasodilation) and a fall in the transmural colloid osmotic pressure gradient (due to an increased microvascular permeability to plasma proteins). In contrast, systemically (intravenously) infused histamine at rates that produce histamine blood concentrations calculated to exceed those achieved by local infusion, results in sustained net extravascular fluid reabsorption.

Since during intravenous infusions, histamine must first pass through the pulmonary circuit before reaching the systemic microvasculature, the possibility exists that the lungs may remove, destroy or inactivate histamine. It is also possible that since the transit time during systemic administration is much greater than during local infusions, that factors within the blood may destroy or inactivate histamine before it reaches the forelimb microvasculature.

During local infusions of histamine (3 to 64μg base/min) systemic arterial blood pressure is minimally affected or falls only slightly after edema has already developed. In contrast, there is an immediate and sustained fall in aortic pressure during systemic administration of histamine which is, at least initially, dose related (20-800μg base/min). This marked reduction in systemic blood pressure is undoubtedly associated with a sympathoadrenal discharge. Hence, it is conceivable that substances released subsequent to the hypotension (e.g., catecholamines) effectively antagonize the usual edemogenic actions of histamine. This antagonism may be a result of a direct blockade of histamine's permeability increasing effects upon the microvasculature, or a shunting of blood flow to non-nutritional channels or a combination of both.

These possibilities will be systematically evaluated to determine if and if so, to what extent, they may affect the route-dependent differential actions of histamine.

METHODS

Mongrel dogs weighing approximately 18 kilograms were anesthetized with sodium pentobarbital (30mg/kg). Normal saline was administered at 15ml/kg to assure good hydration and ample time was allowed for equilibration. Blood clotting was prevented by administering 10,000 U.S.P. units of Sodium Heparin.

Small incisions were made in the right forelimb over the brachial artery, cephalic vein (above the elbow), second superficial dorsal metacarpal vein in the paw and also over the femoral triangle. In all experiments a lymph vessel in the area of the cephalic vein above the elbow was isolated and cannulated. The lymph vessels in this area drain primarily the forelimb skin and paw (47). As many vessels as could be found (usually 2 or 3) were tied off and one of them was then cannulated distally with PE-10 polyethylene tubing about 10cm. in length and beveled at the cannulating end. Initial puncture of the lymph vessel was accomplished by using a 23 gauge hypodermic needle. Lymph was collected over 10 minute periods in miniature graduated cylinders (about 0.3ml capacity) constructed from narrow plastic pipettes to minimize evaporation. Lymph total protein concentration was measured by the spectrophotometric method of Waddel (64) on a Beckman DB spectrophotometer (Model 24, Beckman Instruments, Inc., Fullerton, California).

In all experiments the femoral vein was cannulated to allow administration of saline, heparin and nembutal as needed. Pressures in skin small veins were obtained by cannulating upstream one of the small surface veins on the dorsal side of the paw with PE-60 polyethylene tubing. All pressures were measured with Statham pressure transducers (Model P23Gb, Statham Instruments, Inc., Oknard, California). connected to a direct writing Sanborn oscillograph (7700 series, Hewlett Packard Co., Palo Alto, California).

Drugs utilized were histamine diphosphate, levarterenol-bitartrate (norepinephrine) and acetycholine hydrochloride in solutions of isotonic saline which were administered with a Harvard Apparatus infusion/withdrawal pump (Harvard Apparatus Co., Inc., Millis, Maryland). The volume delivery rate of the infusate was either 0.2cc/min or 0.4 cc/min depending on the dose being used.

In those experiments utilizing a naturally perfused forelimb, a small side branch of the brachial artery above the level of the elbow was isolated and cannulated upstream with PE-50 polyethylene tubing for local (intra-arterial) infusion of drugs. In cases where both histamine and norepinephrine were simultaneously infused, two small side branches were isolated and cannulated. Systemic arterial blood pressure was measured by a cannula inserted upstream through the femoral artery into the descending aorta.

In experiments utilizing a forelimb perfused at constant inflow, the brachial artery was isolated, tied off and transected about 2 inches above the level of the elbow. Blood was obtained from a cannula in the femoral artery and pumped at constant but controllable flow into the transected brachial artery by a Sigmamotor pump

(Model T68H, Sigmamotor Inc., Middleport, New York). Perfusion pressure was monitored by cannulating a small side branch of the brachial artery distal to the site of transection. Systemic arterial blood pressure was measured by inserting a cannula upstream through the brachial artery, proximal to the transection, to approximately the subclavian artery. Local (intra-arterial) administration of drugs in these experiments was achieved by infusion into the pump circuit behind the Sigmamotor pump.

In four series (the number of animals per series is reported in the tables) of experiments, a PE-240 polyethylene tubing was inserted down the right common carotid artery into the left ventricle of the heart. The catheter was initially connected to a pressure transducer and successful placement was confirmed by a typical left ventricular pressure tracing. Drug administration was then achieved by infusion into this catheter.

In three series of experiments, systemic drug administration was accomplished by infusion into the femoral vein. In these experiments the saphenous vein of one of the hindlimbs was isolated and cannulated in case supplemental nembutal was necessary after beginning intravenous drug infusion into the femoral vein.

In all experiments, arterial blood samples of about 3ml were withdrawn from the cannula used to obtain aortic pressure. A sample was taken during the control period and at 30 minute intervals during the experiments. Hematocrits and total plasma protein concentration in grams % were determined from these samples.

In three series of experiments, histamine (4 and 64μg base/min) was infused locally for 60 minutes into forelimbs perfused at constant

inflow during or following acetylcholine or hemorrhagic induced hypotension. Acetylcholine hypotension was produced by intravenous infusions of dosages necessary to lower and maintain aortic pressure at or near 60 mmHg for 60 minutes. The dosage at 60 minutes was then continued for the remainder of the experiment (total duration 120 minutes). Hemorrhagic hypotension was produced by removing the necessary quantity of blood (through a PE-360 polyethylene catheter inserted into the femoral artery) to lower and maintain aortic pressure near 40 mmHg for 60 minutes. Vascular pressures, lymph flow rate, plasma and lymph total protein concentrations and hematocrits were obtained as described above during the control period, hypotensive period, and the drug infusion period during the last hour of the 120 minute experimental period.

In five series weight and hemodynamic measurements were made in collateral-free, innervated canine forelimbs. The surgical procedure consisted of sectioning the skin circumferentially about 1-2 inches above the elbow of the right forelimb. The forelimb nerves (median, ulnar, radial, and musculocutaneous), brachial artery, and brachial and cephalic veins were isolated and coated with an inert silicone spray to prevent drying. The muscles and connective tissue in this area were then sectioned by electrocautery. The humerus was cut with a bone saw and the ends of the marrow cavity were packed tightly with bone wax to prevent bleeding. At this point blood entered the forelimb only through the brachial artery and exited only via the brachial and cephalic veins. The brachial and cephalic veins were partially transected at about the level of the elbow. They were then cannulated with short sections of PE-320 polyethylene

tubing. The sections of tubing were about 6 inches in total length with a 90° bend at about the 5 1/2 inch mark. The short 1/2 inch section of the bent tubing was then inserted into the veins. The cannulas were secured such that the outflow tips were at the same level as the veins. The venous outflow was directed into a reservoir and returned the dog via the jugular vein by a variable speed Holter pump (Model RE161, Extracorporeal Medical Specialties, King of Prussia, Pennsylvania) at a rate that kept reservoir volume constant. Blood flow was determined by timed collections of the venous outflows into graduated cylinders and calculated as ml of flow/min/100 grams of forelimb tissue. The median cubital vein (the major anastomosis between the brachial and cephalic veins) was tied off in these experiments. This provided a more accurate mean for comparing resistance changes between muscle and skin vascular beds since the cephalic vein drains primarily skin and the brachial vein primarily muscle (47). The brachial and cephalic venous pressures were measured by inserting PE-60 polyethylene tubing through side branches found at a level of about 1-2 inches below the elbow. Aortic, perfusion (constant inflow conditions) and skin small vein pressures were all obtained by the methods described above.

When surgery was completed, the forelimb was suspended on a wire mesh tray that was attached to a sensitive strain gauge I-beam balance. The balance was wired to the Sanborn oscillograph thereby allowing changes in forelimb weight to be continuously monitored throughout the experiment. This system was calibrated by the addition of a 2 gram weight to the center of the isolated forelimb which produced a pen deflection of about 10-22 mm. Total skin and muscle vascular

resistances were calculated by dividing cephalic or brachial blood flows into their respective pressure gradients.

The data was analyzed by Analysis of Variance utilizing a Randomized Complete Block Design (61). All means were compared to the 0 minute control mean and significant difference was determined for P equal to or less than both 0.05 and 0.01 by the Least Significant Difference Test (61). When applicable, means were compared back to minute 60 and control.

RESULTS

Table 1

In naturally perfused forelimbs intravenously infused histamine (400 + 800µg base/min) produced a continuous decrease in forelimb weight. Aortic pressure and forelimb cephalic and brachial vein pressures and outflows were all markedly reduced. Total skin resistance was only minimally affected being statistically greater than control only at minutes 30, 35, and 90. Total muscle resistance was significantly increased throughout the infusion period. The local infusion of histamine (64µg base/min) produced no further alterations in any of the measured parameters.

In forelimbs perfused at constant inflow there was a rapid marked increase in forelimb weight within 5 minutes. The peak of the weight increase was reached within 15 minutes and remained elevated throughout the infusion period. Aortic pressure fell markedly whereas perfusion and cephalic vein pressures were only modestly reduced, the latter declining slowly with time. Brachial vein pressure was uneffected whereas skin small vein pressure was moderately increased throughout the experiment. No effect was observed upon cephalic venous outflow but a slight reduction was seen in brachial venous outflow during the first 35 minutes. There was no appreciable effect on total skin resistance. Total muscle resistance increased slightly

during the first 15 minutes, returned to control, and was then significantly reduced from 60 minutes on. Local histamine, as in naturally perfused forelimbs, produced no further changes in any of the parameters measured.

Table 2

In naturally perfused forelimbs histamine (400 + 800µg base/min) infused either intravenously or into the left ventricle markedly reduced aortic pressure and either failed to alter or only slightly decreased skin small vein pressure. Lymph flow rate and lymph total protein concentration were moderately increased. Plasma protein concentration was not changed and hematocrits were greatly elevated. The simultaneous local infusion of histamine (64µg base/min, I.A.) during the last 30 minutes of systemic infusion produced no further alterations in any of the measured parameters relative to minute 60. In forelimbs perfused at constant inflow the systemic infusions of histamine either intravenously or into the left ventricle resulted in a moderate reduction of perfusion pressure. All other responses were similar to those seen in naturally perfused forelimbs except skin small vein pressure was increased and the rise in lymph flow rate and lymph total protein concentration was markedly greater. The simultaneous local histamine infusion produced no further alterations as in naturally perfused forelimbs.

Table 3

In forelimbs perfused either at natural or constant inflow the simultaneous infusion of histamine (400µg base/min) into the left ventricle and locally (64µ base/min, I.A. initiated 3 minutes after

beginning systemic infusion) markedly reduced aortic pressure, produced no significant change in perfusion pressure and plasma protein concentration and increased hematocrits. Skin small vein pressure was significantly reduced in naturally perfused forelimbs and was markedly increased in forelimbs perfused at constant inflow. In naturally perfused forelimbs, lymph flow and lymph total protein concentration were unaltered whereas in forelimbs perfused at constant inflow they were significantly increased.

Table 4

Hypotension induced by hemorrhage resulted in lower aortic pressures than that produced by acetylcholine infusion. Acetylcholine hypotension produced no effect upon perfusion pressure, skin small vein pressure, lymph flow or lymph and plasma total protein. The simultaneous infusion of local histamine (4μg base/min, I.A.) initiated at minute 60 failed to produce any further alterations of aortic pressure, skin small vein pressure, plasma protein and hematocrits. It did, however, produce a significant reduction in perfusion pressure relative to control and minute 60. Lymph flow rate and lymph protein concentration were slightly increased; however, the latter was not significantly elevated until the last 20 minutes of histamine infusion. Hemorrhagic hypotension produced a marked increase in perfusion pressure, either a slight reduction or no change in skin small vein pressure and a slight but not significant increase in lymph flow rate. Lymph total protein was either unchanged or modestly increased whereas plasma protein concentration was either unchanged or slighly reduced. Local histamine (4μg base/min) produced no further change in aortic

pressure, a moderate reduction in perfusion pressure and a slight increase in skin small vein pressure relative to minute 60. Although skin small vein pressure was increased by local histamine it still remained below control. No further alterations were observed in lymph flow rate or lymph and plasma protein concentration. The high dose of histamine (64µg base/min) produced a significant reduction relative to minute 60 in aortic and perfusion pressure. Skin small vein pressure was increased relative to minute 60 and was also significantly greater than control. Lymph flow rate was moderately increased being significantly greater than both control and minute 60. No further changes were observed in lymph or plasma total protein concentration. In all three series the hematocrits were significantly elevated with no further change produced by either dose of histamine.

Table 5

Table 5 shows the effects of histamine alone (4µg base/min, I.A.) and in combination with norepinephrine (4µg base/min, I.A. of each) in naturally perfused forelimbs on forelimb weight, vascular pressures and resistances and blood flows. The effects of histamine alone and in combination with norepinephrine produced no effect upon aortic pressure and markedly increased skin small vein pressure. Histamine alone produced a continuous increase in forelimb weight throughout the infusion period. Venous pressures and outflows were all increased by histamine alone whereas both skin and muscle total resistances were reduced.

The combination of histamine and norepinephrine in contrast, produced an initial fall in forelimb weight during the first 5 minutes

which then slowly increased to a value slightly above control at the end of the infusion period. Cephalic vein pressure and outflow and brachial venous outflow were all markedly reduced whereas brachial venous pressure was significantly increased. Both skin and muscle total resistances were greatly elevated throughout the infusion period.

Table 6

Table 6 shows the effects of histamine and norepinephrine (4μg base/min, I.A. of each) in forelimbs perfused at constant inflow on forelimb weight, vascular pressures, resistances and blood flows. Aortic pressure was significantly increased during the first 30 minutes whereas perfusion and skin small vein pressures remained markedly elevated throughout the entire 60 minute infusion period. Forelimb weight was significantly increased by 15 minutes and then continued to rise slowly throughout the remainder of the infusion period. Cephalic and brachial venous pressures were both significantly increased initially but then returned towards control with cephalic pressure returning slowly with time and brachial pressure returning abruptly. Both cephalic and brachial venous outflows were only minimally affected being slightly reduced when statistically significant. Total skin and muscle resistances were increased and fairly well maintained throughout the infusion period.

Table 7

In naturally perfused forelimbs, local histamine (4μg base/min, I.A.) alone or in combination with norepinephrine (4μg base/min, I.A.) produced no effect upon aortic pressure and markedly increased skin small vein pressure. Histamine alone caused marked increases in

lymph flow and lymph protein concentration but with the simultaneous infusion of norepinephrine no change was observed in either of these parameters. During the simultaneous infusion of histamine and norepinephrine no change in plasma protein concentration and a slight increase in arterial hematocrit was observed. These parameters were not monitored for histamine infusion along.

In forelimbs perfused at constant inflow, histamine (4μg base/min, I.A.) failed to alter aortic or skin small vein pressure and significantly reduced perfusion pressure. Histamine infused simultaneously with norepinephrine (4μg base/min, I.A. of each) or norepinephrine alone (4μg base/min) produced marked increases in these vascular pressures. Histamine alone greatly increased lymph flow and lymph total protein concentration but failed to alter plasma protein concentration or arterial hematocrit. Only a slight increase in lymph flow and no change in lymph or plasma total protein concentration was observed during the combination infusion. Norepinephrine alone did not alter lymph flow rate or plasma total protein concentration but produced a slight decrease in lymph total protein concentration during the last 30 minutes of infusion. Arterial hematocrits were slightly elevated during the infusion of norepinephrine.

In naturally perfused forelimbs the local infusion of the high dose of histamine (64μg base/min, I.A.) alone or in a combination with norepinephrine (4μg base/min, I.A.) resulted in decreased aortic pressures and increased skin small vein pressures. The magnitude of the increased small vein pressure was much lower during the combination infusion. Histamine alone produced marked increases in both flow rate and total protein concentration of lymph. Plasma proteins and

arterial hematocrits were not monitored in this series. The simultaneous infusion of norepinephrine with histamine prevented the large increases in flow and protein concentration of lymph. Only slight increases were seen relative to control. The combination infusion produced no effect upon plasma protein concentration but significantly increased arterial hematocrits.

In forelimbs perfused at constant inflow the high dose of histamine (64μg base/min, I.A.) significantly reduced both aortic and perfusion pressures but failed to alter skin small vein pressure. Lymph flow and lymph total protein concentration were markedly increased throughout the infusion period. The simultaneous infusion of norepinephrine (4μg base/min, I.A.) with the high dose of histamine failed to prevent the fall in aortic pressure but caused significant increases in both perfusion and skin small vein pressure. There was a large increase in lymph flow rate throughout the infusion period being much more pronounced than with histamine alone. Lymph total protein concentration was increased throughout the infusion period with values being similar to those seen during histamine infusion alone. However, the change from control was much less. The simultaneous infusion of norepinephrine (16μg base/min, I.A.) with the high dose of histamine produced significant increases in aortic, perfusion and skin small vein pressures, the latter two being profound. Lymph flow rate was markedly increased but the magnitude was not nearly as great as that seen with the low dose of norepinephrine infused simultaneously with the high dose of histamine. The values were similar to those seen during infusion of the high dose histamine alone but the rate of increase was much greater with the combination infusion. The combination of the

high dose of norepinephrine with histamine attenuated the increase in lymph total protein concentration seen with both the combination of the low dose of norepinephrine with histamine and histamine alone. In all three series no change was observed in plasma total protein concentration except for histamine alone which caused a slight decrease at minute 60. Arterial hematocrits were significantly increased in all cases.

In comparing the high to low dose of histamine alone in both natural and constant flow conditions it is apparent that the magnitude of the increased lymph flow is dose dependent (being directly related) and is markedly greater in naturally perfused forelimbs. The increase in lymph total protein concentration is better maintained by the high dose of histamine in both natural and constant inflow conditions.

Table 1.--Effects of histamine base infused intravenously for 90 minutes plus histamine infused intra-arterially into the forelimb during the last 30 minutes on forelimb weight, vascular pressures, blood flow and vascular resistances (n = 6 each).

		Control		Infusion Period								
				H400			H800			H800 + H64		
Time (minutes)		-5	0	5	15	30	35	45	60	65	75	90
Change in Weight	NF	0	0.5	-1*	-4*	-7*	-9*	-12*	-15*	-15*	-16*	-18*
(grams)	CF	0	0.2	17*	22*	22*	22*	22*	21*	21*	19*	16*
Systemic Arterial Blood	NF	130	130	45*	41*	38*	36*	39*	42*	45*	45*	44*
Pressure (mm Hg)	CF	119	120	34*	36*	34*	30*	33*	33*	29*	29*	29*
Perfusion Pressure (mm Hg)	CF	112	113	104	112	91*	86*	87*	86*	83*	82*	83*
Skin Small Vein Pressure	NF	--	--	--	--	--	--	--	--	--	--	--
(mm Hg)	CF	9	10	21*	18*	15†	16†	18*	17*	16†	15†	15†
Cephalic Vein Pressure	NF	7	7	3*	2*	1*	1*	2*	2*	2*	2*	2*
(mm Hg)	CF	5	5	5	4	4	4	3†	3†	3†	3†	3†
Brachial Vein Pressure	NF	8	8	4*	3*	3*	3*	4*	4*	4*	4*	4*
(mm Hg)	CF	8	7	8	8	8	8	8	9	9	9	10
Cephalic Flow	NF	14	14	7*	5*	3*	3*	3*	4*	4*	4*	4*
(ml/min/100 grams)	CF	16	16	16	16	17	17	15	15	14	15	14
Brachial Flow	NF	9	9	2*	2*	1*	1*	1*	1*	2*	2*	2*
(ml/min/100 grams)	CF	13	13	11†	10*	11†	11†	12	13	13	13	12

Table 1.--Continued.

		Control		Infusion Period								
				H400			H800			H800 + H64		
Time (minutes)		-5	0	5	15	30	35	45	60	65	75	90
Total Skin Resistance	NF	11	10	7	9	15†	15†	14	12	14	14	16*
(mm Hg_1 x min x ml^{-1} x 100 g^{-1})	CF	10	10	9	14	8	7	8	10	8	8	8
Total Muscle Resistance	NF	15	16	28†	30*	35*	31*	36*	33*	31*	27†	26
(mm Hg_1 x min x ml^{-1} x 100 g^{-1})	CF	8	9	11†	11†	8	8	8	7†	6*	6*	7†

* = $p \leq 0.01$ relative to control.

† = $p \leq 0.05$ relative to control.

No mean values for 65, 75 or 90 minutes were significantly different from the 60 minute values.

Table 2.--Effects of histamine base infused systemically for 90 minutes plus histamine infused intra-arterially into the forelimb during the last 30 minutes on lymph flow, protein concentration of lymph and plasma, vascular pressures and hematocrit.

			Control		Infusion Period								
					H400			H800			H800 + H64		
Time (minutes)			-10	0	10	20	30	40	50	60	70	80	90
Systemic Arterial Blood Pressure (mm Hg)	LH	NF (n=7)	120	122	34*	34*	37*	36*	36*	35*	35*	34*	41*
		CF (n=6)	117	118	30*	31*	35*	30*	30*	29*	29*	29*	28*
	IV	NF (n=6)	113	113	34*	32*	33*	31*	33*	32*	30*	31*	29*
		CF (n=6)	112	111	31*	29*	34*	31*	33*	32*	32*	32*	32*
Perfusion Pressure (mm Hg)	LH	CF (n=6)	109	109	68*	90*	98†	96†	96†	94*	93*	93*	91*
	IV	CF (n=5)	101	101	72*	78*	80*	78*	79*	75*	75*	79*	80*
Skin Small Vein Pressure (mm Hg)	LH	NF (n=7)	11	11	9	11	11	12	11	11	11	11	12
		CF (n=6)	14	14	19	17	18	17	18	17	14	15	15
	IV	NF (n=6)	10	9	8†	8†	7*	8†	7*	7*	7*	7*	6*
		CF (n=6)	13	13	21*	22*	20*	20*	26*	22*	21*	21*	21*
Lymph Flow Rate (ml/10 min)	LH	NF (n=7)	.03	.02	.07†	.14*	.11*	.08†	.08†	.07†	.05	.03	.06
		CF (n=6)	.02	.02	.16*	.31*	.24*	.19*	.15*	.13*	.09†	.08	.06
	IV	NF (n=6)	.02	.02	.06*	.06*	.06*	.05†	.04	.03	.02	.02	.03
		CF (n=6)	.02	.02	.17*	.31*	.22*	.17*	.14*	.11†	.12†	.09	.10

Table 2.--Continued.

			Control		Infusion Period								
					H400			H800			H800 + H64		
Time (minutes)			-10	0	10	20	30	40	50	60	70	80	90
Lymph Total Protein (grams %)	LH	NF (n=6)	1.9	2.2	2.7†	2.7†	2.8†	3.0*	3.0*	3.0*	3.0*	3.1*	3.2*
		CF (n=6)	1.9	1.9	3.1*	4.0*	4.2*	4.4*	4.4*	4.5*	4.2*	4.2*	4.4*
	IV	NF (n=6)	1.9	2.1	2.3	2.3	2.6*	2.9*	3.0*	3.0*	3.0*	3.2*	3.2*
		CF (n=6)	2.3	2.3	2.8	4.1*	3.9*	3.8*	3.8*	3.7*	3.8*	3.7*	3.7*
Plasma Protein (grams %)	LH	NF (n=6)		5.6			5.1			5.2			5.1
		CF (n=6)		5.6			5.6			5.6			5.4
	IV	NF (n=6)		5.0			5.4			4.9			4.9
		CF (n=6)		5.3			5.3			5.4			5.0
Hematocrit	LH	NF (n=7)		40			50*			54*			55*
		CF (n=6)		38			51*			55*			56*
	IV	NF (n=6)		34			48*			53*			51*
		CF (n=6)		37			56*			60*			59*

* = $p \leq 0.01$ relative to control. † = $p \leq 0.05$ relative to control.

No mean values for 70, 80 or 90 minutes were significantly different from the 60 minute values.

Table 3.--Effects of histamine base infused into the left ventricle of the heart and intra-arterially (after a 3 minute delay) into the forelimb for 60 minutes on lymph flow, protein concentration of lymph and plasma, vascular pressures and hematocrit.

		Control		Infusion Period H400 + H64					
Time (minutes)		-10	0	10	20	30	40	50	60
Systemic Arterial Blood Pressure (mm Hg)	NF (n=6)	123	123	34*	33*	35*	41*	44*	45*
	CF (n=6)	106	107	34*	33*	34*	34*	35*	36*
Perfusion Pressure (mm Hg)	CF (n=6)	100	100	91	101	98	90	84	83
Skin Small Vein Pressure (mm Hg)	NF (n=6)	11	11	6*	7*	6*	7*	7*	7*
	CF (n=6)	10	10	22*	19*	16*	14	13	12
Lymph Flow Rate (ml/10 min)	NF (n=6)	.02	.02	.02	.03	.03	.04	.04	.04
	CF (n=6)	.02	.02	.29*	.35*	.27*	.17*	.12†	.09
Lymph Total Protein (grams %)	NF (n=6)	2.7	3.0	3.0	2.9	3.1	3.2	3.4	3.4
	CF (n=6)	2.4	2.5	3.2†	3.5*	3.8*	3.8*	4.2*	4.0*
Plasma Protein (grams %)	NF (n=6)		6.5			6.3			6.3
	CF (n=6)		5.7			5.6			5.2
Hematocrit	NF (n=6)		41			51*			55*
	CF (n=6)		34			51*			48*

* = $p \leq 0.01$ relative to control. † = $p \leq 0.05$ relative to control.

Table 4.--Effects of locally infused histamine (4 or 64 μg base/min, I.A.) for 60 minutes following 60 minutes of hypotension produced by either acetylcholine base infused intravenously at a concentration necessary to lower and maintain aortic pressure near 60 mm Hg for the first 60 minutes or following 60 minutes of hemorrhagic hypotension with aortic pressure maintained near 40 mm Hg. Constant inflow (n=6 each).

		Control		Acetylcholine Infusion											
				Hemorrhage						Histamine Infusion					
		-10	0	10	20	30	40	50	60	70	80	90	100	110	120
Systemic Arterial	A4	118	118	57*	61*	58*	59*	58*	57*	58*	59*	60*	62*	62*	62*
Blood Pressure	Hm4	115	117	45*	44*	43*	47*	41*	40*	46*	45*	43*	41*	41*	39*
(mm Hg)	Hm64	120	121	43*	43*	43*	43*	45*	53*	39*Ω	38*ω	40*Ω	39*Ω	40*Ω	37*ω
Perfusion	A4	107	108	93	103	95	93	93	92	65*ω	66*ω	67*ω	67*ω	68*ω	68*ω
Pressure	Hm4	105	107	173*	168*	155*	160*	160*	156*	138†	133†	133†	128 Ω	124 Ω	119 ω
(mm Hg)	Hm64	111	111	171*	190*	194*	179*	186*	186*	93 ω	108 ω	106 ω	102 ω	100 ω	100 ω
Skin Small Vein	A4	13	13	12	12	12	12	12	12	12	13	13	13	13	13
Pressure	Hm4	14	13	9*	9*	8*	8*	8*	8*	9*	10*Ω	10*Ω	10*Ω	10*Ω	10*Ω
(mm Hg)	Hm64	13	13	11	12	13	12	13	14	21*ω	21*ω	21*ω	19†Ω	19†Ω	19†Ω
Lymph Flow Rate	A4	.02	.02	.02	.02	.02	.02	.02	.02	.03	.05†Ω	.05†Ω	.06*ω	.06*ω	.05†Ω
(ml/10 min)	Hm4	.02	.02	.03	.04	.04	.03	.04	.04	.04	.05	.04	.03	.03	.03
	Hm64	.02	.02	.02	.03	.04	.05	.06	.06	.13*	.24*ω	.28*ω	.21*ω	.17*ω	.14*Ω
Lymph Total	A4	2.3	2.3	2.4	2.3	2.3	2.4	2.2	2.3	2.2	2.2	2.3	2.5	2.7*ω	2.8*ω
Protein	Hm4	2.1	2.1	2.2	2.2	2.2	2.2	2.1	2.4	2.2	2.2	2.1	2.0	2.0	1.9
(grams %)	Hm64	2.1	2.2	2.2	2.5	2.7†	2.5	2.5	2.7†	2.8†	3.0*	2.9*	2.8†	2.8†	2.6
Plasma	A4		5.3			5.3			5.2			5.3			5.4
Protein	Hm4		4.8			4.2*			3.9*			3.9*			3.8*
(grams %)	Hm64		4.8			4.6			4.5			4.5			4.3
	A4		35			38†			39*			40*			41*
Hematocrit	Hm4		34			37†			39*			38*			38*
	Hm64		37			39			42*			43*			43*

* = $p \leq 0.01$ relative to control.

† = $p \leq 0.05$ relative to control.

ω = $p \leq 0.01$ relative to minute 60.

Ω = $p \leq 0.05$ relative to minute 60.

Table 5.--Effects of histamine (4 μg base/min, I.A.) and histamine plus norepinephrine (4 μg base/min, I.A. of each) infused locally into naturally perfused forelimbs on weight, vascular pressures, blood flows and vascular resistances (n = 6 each).

Time (minutes)		Control		Infusion Period				
		-5	0	5	15	30	45	60
Change in Weight (grams)	H4	0	0.2	18*	27*	34*	40*	44*
	H4+N4	0	0.3	-10*	-5*	-2	2	5*
Systemic Arterial Blood Pressure (mm Hg)	H4	127	128	128	128	127	126	127
	H4+N4	127	128	129	132	128	132	131
Skin Small Vein Pressure (mm Hg)	H4	10	10	20*	19*	18*	18*	17*
	H4+N4	10	9	24*	23*	25*	25*	24*
Cephalic Vein Pressure (mm Hg)	H4	5	6	11*	11*	10*	10*	10*
	H4+N4	6	6	2*	2*	2*	2*	2*
Brachial Vein Pressure (mm Hg)	H4	5	5	10*	10*	9*	9*	8*
	H4+N4	8	8	15*	14*	13*	14*	16*
Cephalic Flow (ml/min/100 grams)	H4	15	15	24*	25*	25*	26*	24*
	H4+N4	15	15	4*	7*	5*	4*	2*
Brachial Flow (ml/min/100 grams)	H4	10	10	16*	17*	16*	26*	24*
	H4+N4	7	7	3*	5	3*	3*	3*
Total Skin Resistance (mm Hg x min x ml^{-1} x 100 g^{-1})	H4	9	9	5*	5*	5*	5*	5*
	H4+N4	9	9	44*	33†	36*	47*	58*

Table 5.--Continued.

Time (minutes)		Control		Infusion Period				
		-5	0	5	15	30	45	60
Total Muscle Resistance (mm Hg x min x ml^{-1} x 100 g^{-1})	H4	12	13	8*	7*	8*	5*	5*
	H4+N4	20	20	52*	36	44†	51*	44†

* = $p \leq 0.01$ relative to control. † = $p \leq 0.05$ relative to control.

Table 6.--Effects of histamine plus norepinephrine (4 μg base/min, I.A. of each) infused locally into forelimbs perfused at constant inflow on forelimb weight, vascular pressures, blood flows and vascular resistances (n = 6).

Time (minutes)	Control		Infusion Period				
	-5	0	5	15	30	45	60
Change in Weight (grams)	0	0.3	1	7*	11*	14*	15*
Systemic Arterial Blood Pressure (mm Hg)	123	123	153*	147*	139†	130	133
Perfusion Pressure (mm Hg)	109	108	194*	159*	177*	182*	176*
Skin Small Vein Pressure (mm Hg)	13	13	34*	26*	27*	24*	21*
Cephalic Vein Pressure (mm Hg)	5	6	14*	12†	11	9	7
Brachial Vein Pressure (mm Hg)	7	7	15*	10	10	11†	11†
Cephalic Flow (ml/min/100 grams)	14	14	11*	14	14	13	12*
Brachial Flow (ml/min/100 grams)	9	9	11	10	9	11	11
Total Skin Resistance (mm Hg x min x ml^{-1} x 100 g^{-1})	9	9	20*	13	16*	18*	17*
Total Muscle Resistance (mm Hg x min x ml^{-1} x 100 g^{-1})	13	13	17†	18*	20*	19*	17†

* = $p \leq 0.01$ relative to control.

† = $p \leq 0.05$ relative to control.

Table 7.--Effects of histamine base and/or norepinephrine base infused intra-arterially into the forelimb for 60 minutes on lymph flow, protein concentration of lymph and plasma, vascular pressures and hematocrit.

Time (minutes)				Control -10	Control 0	Infusion Period 10	20	30	40	50	60
Systemic Arterial Blood Pressure (mm Hg)	NF	H4	(n=6)	120	119	115	115	114	114	114	113
	NF	H4+N4	(n=6)	110	108	124	121	121	117	114	119
	CF	H4	(n=6)	118	119	116	120	120	122	122	121
	CF	H4+N4	(n=6)	115	116	140*	135*	136*	135*	132*	130*
	CF	N4	(n=6)	119	120	153*	149*	145*	145*	144*	143*
	NF	H6	(n=7)	118	118	82*	78*	75*	78*	79*	79*
	NF	H64+N4	(n=7)	112	111	62*	59*	62*	61*	64*	64*
	CF	H64	(n=6)	118	119	92*	86*	84*	87*	87*	89*
	CF	H64+N4	(n=6)	103	104	86†	87†	86†	85†	85†	83†
	CF	H64+N16	(n=7)	121	121	142*	123	130	132†	131†	131†
Perfusion Pressure (mm Hg)	CF	H4	(n=6)	112	117	65*	67*	69*	70*	70*	69*
	CF	H4+N4	(n=6)	110	112	168*	165*	170*	178*	183*	184*
	CF	N4	(n=6)	113	113	208*	203*	208*	216*	220*	221*
	CF	H64	(n=6)	108	109	78*	90†	86*	84*	85*	83*
	CF	H64+N4	(n=6)	94	94	101	114†	128*	135*	140*	135*
	CF	H64+N16	(n=7)	110	110	190*	208*	241*	259*	274*	289*

Table 7.--Continued.

Time (minutes)				Control -10	Control 0	Infusion Period 10	20	30	40	50	60
Skin Small Vein Pressure (mm Hg)	NF	H4	(n=6)	14	15	26*	25*	26*	26*	26*	25*
		H4+N4	(n=6)	11	10	33*	32*	30*	29*	29*	28*
	CF	H4	(n=6)	10	10	10	11	11	11	11	11
		H4+N4	(n=6)	10	9	32*	31*	31*	32*	31*	30*
		N4	(n=6)	12	11	23*	21*	21*	22*	22*	21*
	NF	H64	(n=7)	13	13	25*	25*	23*	23*	22*	22*
		H64+N4	(n=7)	9	9	19*	12	13†	14*	15*	14*
	CF	H64	(n=6)	11	10	12	11	11	10	10	10
		H64+N4	(n=6)	9	9	43*	33*	32*	32*	32*	31*
		H64+N16	(n=7)	12	12	55*	50*	50*	51*	51*	53*
Lymph Flow Rate (ml/10 min)	NF	H4	(n=6)	.01	.01	.21†	.29*	.38*	.30*	.31*	.32*
		H4+N4	(n=6)	.02	.01	.03	.03	.04	.04	.03	.03
	CF	H4	(n=6)	.02	.02	.10†	.17*	.18*	.18*	.19*	.19*
		H4+N4	(n=6)	.02	.02	.06†	.07*	.06†	.04	.03	.03
		N4	(n=6)	.02	.02	.03	.02	.02	.02	.03	.02
	NF	H64	(n=7)	.02	.02	.63*	.90*	.65*	.44*	.33*	.28*
		H64+N4	(n=7)	.01	.01	.08	.07	.04	.04	.04	.04
	CF	H64	(n=6)	.01	.01	.19*	.42*	.34*	.27*	.23*	.20*
		H64+N4	(n=6)	.04	.04	.67*	.77*	.51*	.43*	.35*	.29*
		H64+N16	(n=7)	.03	.03	.40*	.41*	.30*	.27*	.24*	.26*

Table 7.--Continued.

Time (minutes)				Control -10	Control 0	Infusion Period 10	20	30	40	50	60
Lymph Total Protein (grams %)	NF	H4	(n=6)	2.7	2.8	4.2*	4.6*	4.6*	4.2*	4.0*	3.9*
		H4+N4	(n=5)	2.9	3.3	3.4	3.5	3.2	3.4	3.3	3.2
	CF	H4	(n=6)	2.4	2.5	3.1*	3.5*	3.9*	4.2*	4.3*	4.7*
		H4+N4	(n=6)	3.9	4.0	4.0	4.2	4.2	4.1	4.1	4.0
		N4	(n=5)	2.2	2.3	2.5	2.4	2.1	1.9†	1.9†	1.8*
	NF	H64	(n=7)	2.8	3.0	4.4*	4.6*	4.6*	4.6*	4.6*	4.4*
		H64+N4	(n=7)	3.6	3.8	4.2†	4.3†	4.3†	4.5*	4.6*	4.5*
	CF	H64	(n=6)	2.0	2.1	3.4*	4.8*	4.9*	4.6*	4.7*	4.8*
		H64+N4	(n=6)	3.2	3.3	4.2*	4.8*	4.5*	4.4*	4.0*	3.8†
		H64+N16	(n=7)	2.7	2.8	3.6*	3.7*	3.7*	3.3†	3.3†	2.9
Plasma Protein (grams %)	NF	H4	(n=6)		5.9			--			--
		H4+N4	(n=5)		6.2			6.1			6.1
	CF	H4	(n=6)		5.6			5.5			5.5
		H4+N4	(n=6)		6.2			6.5			6.4
		N4	(n=6)		5.2			5.5			5.6
	NF	H64	(n=7)		4.8			--			--
		H64+N4	(n=7)		6.8			6.8			6.7
	CF	H64	(n=6)		5.4			5.4			5.1*
		H64+N4	(n=6)		5.9			6.0			5.9
		H64+N16	(n=7)		5.5			5.8			5.9

Table 7.--Continued.

Time (minutes)				Control -10	Control 0	Infusion Period 10	20	30	40	50	60
Hematocrit	NF	H4	(n=6)		--			--			--
		H4+N4	(n=6)		36			38†			39*
	CF	H4	(n=6)		32			33			33
		H4+N4	(n=6)		33			38*			39*
		N4	(n=6)		39			42†			45*
	NF	H64	(n=7)		--			--			--
		H64+N4	(n=7)		35			42*			47*
	CF	H64	(n=6)		36			41*			43*
		H64+N4	(n=6)		33			42*			43*
		H64+N16	(n=7)		35			46*			47*

* = $p \leq 0.01$ relative to control.

† = $p \leq 0.05$ relative to control.

DISCUSSION

The data clearly demonstrates that the effects of histamine on transvascular fluid flux is route-dependent. Systemic administration of histamine (400 to 800μg base/min, I.V.) in naturally perfused forelimbs produces a continuous decine in forelimb weight throughout the infusion period (Table 1). In contrast, during the local infusion of histamine (4μg base/min, I.A.) in naturally perfused forelimbs, there is a continuous increase in forelimb weight (Table 5). Furthermore, systemic histamine (infused either intravenously or into the left heart) produced only minimal increases in lymph flow and total protein concentration (Table 2) when compared to local histamine (Table 7). These differences occur despite the fact that the calculated blood concentration of histamine during systemic infusion (assuming no degradation) greatly exceeds or is at least equal to that which produces profound effects on the above parameters when infused locally.

There is the possibility that the lungs destroy or inactivate histamine, thereby accounting for the route-dependent differential action of histamine by drastically reducing the effective concentration at the site of forelimb microvasculature. Such a function being served by the lungs is disproved by comparison of systemic histamine infusions into the vena cava which first must pass through the

pulmonary circuit before entering the general circulation, and into the left ventricle of the heart whereby histamine bypasses the pulmonary circuit (Table 2). There is no discernable difference between either route of systemic histamine administration upon any of the measured parameters. There still existed the possibility that histamine may be inactivated by factors within the arterial blood before reaching the studied vascular bed. This possibility was ruled out since, in forelimbs perfused at constant inflow the local infusion of histamine (4 and 64μg base/min, I.A.) produced marked increases in flow rate and total protein concentration of lymph. The increases in these two parameters is attributable to an increased microvascular permeability since they occurred in the face of unaltered skin small vein pressure and slightly reduced perfusion pressure (a minimum and maximum for capillary hydrostatic pressure respectively). During constant inflow the locally infused histamine must travel through about three feet of polyethylene tubing before reaching the forelimb. This distance is as much or more than histamine would travel during left ventricular infusion. Consequently, if factors within the blood were destroying histamine then one would not expect to see such large increases in flow and total protein concentration of lymph during local infusions at constant inflow. This should not imply that histamine destruction does not occur to some extent. It does however, imply that whatever the degradation rate may be, it is not sufficient to account for the route-dependent differential actions of histamine.

In naturally perfused forelimbs the systemic administration of histamine caused marked reductions in forelimb blood flow, either no effect or slight reductions in skin small vein pressure and increased

total resistances in the skin and muscle vascular beds. Consequently, the observed forelimb weight loss can be attributed to both a decreased intravascular blood volume (inferred from increased resistances) and to a reduced capillary hydrostatic pressure (inferred from flow and skin small vein pressure decreases) which would favor tissue fluid reabsorption. However, these hemodynamic changes alone cannot solely account for the failure of histamine to produce marked increases in forelimb weight and flow rate and total protein concentration of lymph as seen during local administration. This conclusion is drawn from three different observations. First of all, Grega et al. (20) demonstrated that in forelimbs perfused at constant inflow at a pressure at or below normal colloid osmotic pressure (thereby greatly favoring tissue fluid reabsorption) that histamine (60μg base/min, I.A.) produced a weight gain of 19 grams within 10 minutes. This indicated that histamine acts, at least partially via a pressure independent mechanism, i.e., an increase in capillary permeability. Secondly, the fact that histamine is present in the naturally perfused forelimbs during systemic administration is evidenced by the slight increases in lymph flow rate and total protein concentration seen. This occurs in spite of a reduced capillary hydrostatic pressure inferred from the marked fall in skin small vein pressure. Hence, these observed increases must be due to a slight increase in microvascular permeability. In contrast to the local infusion of histamine in naturally perfused forelimbs, the increased flow and total protein concentration of lymph are quite small during systemic infusion compared to the lowest dose of histamine (4μg base/min, I.A.) infused locally. This attenuation is not likely due to a proportionally

decreased histamine blood concentration in the forelimb, since during systemic administration it is calculated to be higher or at least equal to the concentration during local histamine infusion (assuming even distribution of the infused histamine) even though forelimb blood flow is reduced. Thirdly, during systemic infusions of histamine (400 to 800μg base/min) into forelimbs perfused at constant inflow (Table 1 and 2) the increase in forelimb weight, lymph flow and lymph total protein concentration is actually less than that produced by equal concentrations of histamine infused locally (64μg gase/min) in forelimbs perfused at constant flow. These changes during systemic administration occur in the presence of an increased microvascular pressure (inferred from the increased skin small vein pressure) whereas microvascular pressure is unchanged relative to control during the local infusion of histamine. Based on these observations, one would expect substantially greater increases in these three parameters during systemic administration.

The above observed differences between local and systemic histamine infusions on weight and lymph hint to the possibility that the effects of histamine during systemic infusion are being antagonized at the site of the microvessels by some endogenous factor. Support of this possibility is offered by the fact that after 60 minutes of systemic histamine infusion (400 to 800μg base/min) the initiation of a 30 minute local infusion of histamine (64μg base/min, I.A.) produces no further alterations in any of the observed parameters (Table 2). One possible explanation for this is that the responsiveness of the microvasculature to histamine diminished with time, thereby making the local infusion of histamine ineffective. This possibility is ruled out

though since systemic infusion of histamine (400μg base/min) into the left heart simultaneously with local histamine (64μg base/min, I.A.) in which, after a delay of only three minutes, the local histamine infusion failed to produce any major differences in results when compared to the other systemic studies (Table 3). From this it is obvious that some factor(s) are present that effectively antagonize the local actions of histamine upon the microvascular.

One readily observable difference between systemic and local infusions of histamine is the effect upon systemic arterial blood pressure. During local histamine infusions (4 or 64μg base/min, I.A.) there is either no effect or only a moderate decrease in aortic pressure. The latter occurring with the high dose of histamine. In contrast, during systemic infusions of histamine (400 to 800μg base/min) there is a large precipitous fall in aortic pressure. This hypotension would elicit a generalized sympathoadrenal discharge which may effectively antagonize the effects of histamine via catecholamines and/or other substances released in response to hypotension. To test the hypothesis that endogenous catecholamine release, subsequent to hypotension, may antagonize the microvasculature actions of histamine, three series of experiments were performed in which hypotension was produced by means other than histamine (Table 4). Hypotension was produced by both hemorrhage and acetylcholine for 60 minutes prior to initiation of a local infusion of histamine (4 or 64μg base/min, I.A.) into forelimbs perfused at constant inflow. Following 60 minutes of hemorrhagic induced hypotension, the local infusion of histamine (4μg base/min, I.A.) for 60 minutes failed to produce any further alterations in lymph flow or total protein concentration. The increased perfusion

pressure prior to initiating the local histamine infusion is indicative of a sympathoadrenal discharge which would tend to compensate for the loss of blood and blood pressure. In contrast, the high dose of histamine (64μg base/min, I.A.) produces moderate increases in lymph flow rate, but even in the face of an increased microvasculature pressure (inferred from the increased skin small vein pressure) this increase was greatly attenuated compared to local infusion of the same dose of histamine alone in forelimbs perfused at constant inflow. No further change was observed in lymph total protein concentration in spite of the increased lymph flow rate thereby indicating that the local action of histamine on the microvasculature was effectively antagonized. Acetylcholine hypotension did not produce as severe a reduction in aortic pressure as hemorrhage did. The local infusion of histamine (4μg base/min, I.A.) following 60 minutes of acetylcholine hypotension produced only a very slight increase in lymph flow rate and essentially no change in lymph total protein concentration. Hence, by comparison of all three types of hypotension and both doses of local histamine, it appears that the same antagonist is present (i.e., the catecholamines) regardless of how hypotension is produced and that it antagonizes histamines microvascular actions.

To test the hypothesis that the catecholamines are antagonistic to histamine's action on the microvasculature, experiments were performed to compare differences in forelimb weight changes, hemodynamics, lymph flow and lymph total protein concentration between local histamine infusions alone and in combination with norepinephrine. The doses of histamine employed were 4 and 64μg base/min, the former being a more physiological dose. The dosage of norepinephrine employed

was 4μg base/min except in one series where 16μg base/min was infused.

In naturally perfused forelimbs, histamine (4μg base/min, I.A.) infused locally produced a continuous increase in forelimb weight, reaching 44 grams by minute 60 (Table 5). Forelimb vascular pressures and blood flows were all significantly increased and forelimb resistances decreased throughout the infusion period. Lymph flow rate and lymph total protein concentration were both markedly increased within the first 10 minutes of infusion and continued to rise modestly or remained fairly constant throughout the infusion period (Table 7). In one series of experiments norepinephinre (4μg base/min, I.A.) was infused into forelimbs perfused at constant inflow. There was no observable effect upon lymph flow rate and a slight decrease in lymph total protein concentration during the last 30 minutes of infusion (Table 7).

The simultaneous infusion of norepinephrine with histamine (4μg base/min, I.A. of each) into naturally perfused forelimbs, in contrast to histamine alone, produced an initial decline in forelimb weight which then slowly increased reaching +5 grams by minute 60. There was no change in lymph flow or lymph protein concentration. Thus, the effects of local histamine on forelimb weight, lymph flow and lymph total protein concentration were effectively antagonized by norepinephrine.

To determine possible contributions of reduced forelimb blood flow per se during the simultaneous infusions of histamine and norepinephrine into naturally perfused forelimbs, these infusions were repeated in forelimbs perfused at constant inflow (Tables 6 and 7).

An increase in forelimb weight was observed, reaching 15 grams by minute 60, and only slight increases in lymph flow rate which was significantly less than that seen during histamine infusion alone. Lymph total protein concentration did not change. Hence, the increase in forelimb weight and lymph flow must have been a result of an increased fluid filtration due to an increased microvascular hydrostatic pressure (inferred from the increased skin small vein pressure). Since forelimb inflow is held constant, and there was no significant shunting of blood flow between skin and muscle, the increased microvascular pressure can be attributed to a venoconstriction (skin large vein resistance markedly increases) produced by norepinephrine. This data illustrates that the simultaneous infusion of norepinephrine with histamine (4μg base/min, I.A. of each) completely prevents the normal histamine effect upon the microvessels, i.e., histamine failed to produce an increase in microvascular permeability (inferred from the failure of lymph protein concentration to change).

The local infusion of the high dose of histamine (64μg base/min, I.A.) produces drastic increases in both lymph flow rate and lymph total protein concentration. The latter approaching plasma protein values. These effects are largely pressure independent since at constant inflow microvascular pressure remains constant (inferred from the unaltered skin small vein pressure) but lymph total protein concentration still increases (relative to control) to about the same values as seen during natural flow.

The simultaneous infusion of norepinephrine (4μg base/min, I.A.) with histamine (64μg base/min, I.A.) in naturally perfused forelimbs appeared to produce a slight increase in lymph flow rate

(although not statistically significant) and lymph total protein concentration. These dosages in forelimbs perfused at constant inflow produced an increased lymph flow rate greater than that produced by histamine alone at constant inflow and similar to that seen at natural inflow. This large increase occurred however, in the face of an increased microvascular pressure (inferred from the increased skin small vein pressure) substantially greater than that seen in natural flow. Hence, much of this increase can be attributed to fluid filtration across the capillary membrane due to an increased capillary hydrostatic pressure. The fact that lymph total protein concentration failed to increase relative to control as much as with histamine alone, in the constant inflow experiments indicates at least some antagonistic action of norepinephrine even though such a disproportionate concentration ratio exists.

The higher dose of norepinephrine (16μg base/min, I.A.) infused simultaneously with histamine in forelimbs perfused at constant inflow, prevented as marked an increase in lymph total protein concentration, relative to control, as seen during histamine infusion alone. Lymph flow rate increased substantially more than during histamine infusion alone but was less than that seen during simultaneous infusion with the low dose of norepinephrine even though microvascular pressure is inferentially greater. Thus, it appears that the antagonism of histamine's microvascular effects by norepinephrine is dose dependent. This conclusion is in line with Schayer's proposed balance of histamine and catecholamines producing a degree of circulatory homeostasis during shock or stressful states (57).

This antagonism of the microvascular actions of histamine by norepinephrine could be due to a complete shunting of blood from nutritional to non-nutritional channels and/or a direct antagonism of the action of histamine on the microvascular membrane by norepinephrine. Additional experimentation is needed to resolve this point.

SUMMARY AND CONCLUSIONS

It is clearly demonstrated that a route-dependent response exists concerning histamine's microvascular effects. In naturally perfused forelimbs during systemic histamine administration (400 to 800μg base/min) there is a continuous decline in forelimb weight. In contrast, local histamine (4μg base/min, I.A.) produces a continuous increase in forelimb weight throughout the infusion period. This differential action cannot be explained on the basis of destruction or inactivation of histamine by the lungs or factors within the blood since infusions upstream and downstream to the lung produce essentially identical effects on the forelimb microvasculature.

Prior hypotension for 60 minutes produced by either systemic histamine, acetylcholine or hemorrhage completely prevented the marked rise in lymph total protein concentration during local infusions of histamine (4 and 64μg base/min, I.A.). These data suggest that substances liberated subsequent to hypotension (e.g., catecholamines) effectively antagonize the local microvascular actions of histamine.

At constant inflow, the combined infusion of histamine and norepinephrine (4μg base/min, I.A. of each) prevented the increase in lymph flow and total protein concentration seen during infusion of histamine alone (4μg base/min, I.A.) and did not produce any significant

shunting of blood flow between skin and skeletal muscle. These data demonstrate that norepinephrine effectively antagonizes the action of histamine on the microvasculature. This antagonism of histamine by norepinephrine could either be due to a direct blockade of histamine's effect on the microvascular membrane or a drastic shunting of blood flow to non-nutritional channels. Further experimentation is necessary to completely resolve this matter.

In conclusion, it seems likely that the severe hypotension produced by systemic infusions of histamine functions as a stimulus for a sympathoadrenal discharge, and that the released catecholamines (and perhaps other substances) effectively antagonize the microvascular actions of histamine. This would account, at least in part, for the route-dependent differential actions of histamine on the microvasculature.

APPENDICES

APPENDIX A

SAMPLE CALCULATIONS FOR BLOOD CONCENTRATIONS OF HISTAMINE

APPENDIX A

SAMPLE CALCULATIONS FOR BLOOD CONCENTRATIONS OF HISTAMINE

Preliminary Information:

1. About 8% of total body weight in grams equals the total blood volume of the dog in milliliters. Thus a 20 Kg dog has a total blood volume of 1600 ml.
2. Forelimb blood flow (control) is about 25 ml/min/100 grams of forelimb. The average forelimb weight for the dogs used in these studies is about 600 grams. Thus, the control blood flow through a 600 gram forelimb would be 150 ml/min.

Calculations:

A. Systemic Administration

general formula: infusion rate ÷ total blood volume = blood concentration after one minute

1. Histamine infusion = 400 µg base/min.

   Blood concentration = 0.25 µg/ml after one minute.

2. Histamine infusion rate = 800 µg base/min.

   Blood concentration = 0.50 µg/ml after one minute.

B. Local Administration

general formula: infusion rate ÷ ml/min forelimb blood flow = forelimb blood concentration.

1. Histamine infusion rate = 4 µg base/min.

   Blood concentration = 0.03 µg/ml.

2. Histamine infusion rate = 16 µg base/min.

   Blood concentration = 0.11 µg/ml.

3. Histamine infusion rate = 64 µg base/min.

   Blood concentration = 0.43 µg/ml.

These calculations are for comparative purposes only. It is not intended that these calculations represent actual blood concentrations since degradation rate and distribution within the blood volume will obviously affect the concentration of histamine at any given site.

APPENDIX B

TABLES

APPENDIX B

TABLES

Appendix B lists, in the form of tables, all the individual observations for the experiments performed in this study. Also listed are the means, standard error of the mean, and statistical significance.

The data in the appendix tables corresponds to the mean values in Tables 1-7 as follows:

Table Number	Appendix Table Number
1	A1, A2
2	A3, A4, A5, A6
3	A7, A8
4	A9, A10, A11
5	A12, A13
6	A14
7	A15, A16, A17, A18, A19, A20, A21, A22, A23, A24

Table A1.--Effects of histamine base infused intravenously for 90 minutes plus histamine infused intra-arterially into naturally perfused forelimbs during the last 30 minutes on forelimb weight, vascular pressures, blood flow and vascular resistances.

	Control		Infusion Period								
			H400			H800			H800 + H64		
Time (minutes)	-5	0	5	15	30	35	45	60	65	75	90
Change in Weight	0	1	-8	-6	-9	-11	-15	-19	-21	-23	-25
(grams)	0	0	-6	-10	-16	-17	-19	-21	-22	-24	-28
	0	1	9	9	7	4	2	0	0	0	-2
	0	0	5	5	2	2	0	-3	-3	-4	-4
	0	0	-10	-16	-18	-24	-28	-28	-29	-26	-28
	0	1	2	-3	-8	-9	-12	-16	-16	-16	-18
means	0	.5	-1*	-4*	-7*	-9*	-12*	-15*	-15*	-16*	-18*
standard error	±0	±.2	±3	±4	±4	±4	±5	±4	±5	±5	±5
Systemic Arterial Blood	114	115	35	30	30	30	30	30	37	37	43
Pressure (mm Hg)	130	127	40	45	33	35	38	35	35	35	32
	131	133	42	35	30	27	27	35	37	37	30
	117	117	36	35	45	35	40	45	45	47	47
	148	150	65	45	37	43	50	52	56	57	57
	140	140	50	55	53	47	50	55	57	55	55
means	130	130	45*	41*	38*	36*	39*	42*	45*	45*	44*
standard error	±5	±6	±5	±4	±4	±3	±4	±4	±4	±4	±5
Cephalic Vein Pressure	11	11	4	2	1	1	2	2	2	2	1
(mm Hg)	4	4	1	1	0	0	0	0	0	0	0
	5	5	3	3	1	2	2	3	3	4	4
	10	10	6	4	2	2	2	3	2	3	3

Table A1.--Continued.

	Control		Infusion Period								
			H400			H800			H800 + H64		
Time (minutes)	-5	0	5	15	30	35	45	60	65	75	90
	3	3	1	1	2	2	2	2	2	3	3
	8	8	3	3	1	1	2	2	1	1	1
means	7	7	3*	2*	1*	1*	2*	2*	2*	2*	2*
standard error	±1	±1	±1	±1	±.3	±.3	±.3	±1	±.4	±1	±1
Brachial Vein Pressure	11	11	3	4	4	4	4	4	4	5	3
(mm Hg)	8	8	6	4	4	4	3	3	3	2	3
	7	7	5	1	2	2	3	3	3	3	3
	12	12	7	5	5	5	7	9	10	9	8
	4	4	1	1	1	1	1	1	1	1	1
	8	8	3	3	3	3	3	3	3	3	3
means	8	8	4*	3*	3*	3*	4*	4*	4*	4*	4*
standard error	±1	±1	±1	±1	±1	±1	±1	±1	±1	±1	±1
Cephalic Flow	8	8	4	2	1	1	2	2	2	2	2
(ml/min/100 grams)	12	12	9	7	5	4	4	5	5	6	6
	13	13	8	5	4	4	4	5	5	6	5
	7	7	3	4	2	2	2	2	2	2	2
	29	29	9	6	4	3	3	4	4	3	2
	14	14	6	4	4	3	3	4	4	4	4
means	14	14	7*	5*	3*	3*	3*	4*	4*	4*	4*
standard error	±3	±3	±1	±1	±1	±1	±.4	±1	±1	±1	±1

Table A1.--Continued.

	Control		Infusion Period								
			H400			H800			H800 + H64		
Time (minutes)	-5	0	5	15	30	35	45	60	65	75	90
Brachial Flow	8	8	4	2	1	1	1	2	3	3	3
(ml/min/100 grams)	6	6	2	2	1	2	1	2	2	3	3
	10	10	2	2	1	1	1	1	2	2	2
	10	10	2	1	1	1	1	1	1	1	1
	6	6	1	1	1	1	1	1	1	1	1
	11	11	1	1	1	1	1	1	1	2	2
means	9	9	2*	2*	1*	1*	1*	1*	2*	2*	2*
standard error	±1	±1	±1	±.2	±0	±.2	±0	±.2	±.3	±.4	±.4
Total Skin Resistance	13	13	8	14	29	29	14	14	18	18	21
(mm Hg_1 x min x ml^{-1} x	11	10	4	6	7	9	10	7	7	6	5
100 g^{-1})	10	10	5	6	7	6	6	6	7	6	5
	15	15	10	8	22	17	19	21	22	22	22
	5	5	7	7	9	14	16	13	14	18	27
	9	9	8	13	13	15	16	13	14	14	14
means	11	10	7	9	15†	15†	14	12	14	14	16*
standard error	±1	±1	±1	±2	±4	±3	±2	±2	±2	±3	±4
Total Muscle Resistance	13	13	8	13	26	26	26	13	11	11	13
(mm Hg_1 x min x ml^{-1} x	20	20	17	21	29	16	35	16	16	11	10
100 g^{-1})	12	13	19	17	28	25	24	32	17	17	14
	11	11	15	30	40	30	33	36	35	38	39

Table A1.--Continued.

Time (minutes)	Control		Infusion Period								
			H400			H800			H800 + H64		
	-5	0	5	15	30	35	45	60	65	75	90
	24	24	64	44	36	42	49	51	55	56	56
	12	12	47	52	50	44	47	52	54	26	26
means	15	16	28†	30*	35*	31*	36*	33*	31*	27†	26
standard error	±2	±2	±9	±6	±4	±4	±4	±7	±8	±7	±7

* = $p \leq 0.01$ relative to control.

† = $p \leq 0.05$ relative to control.

No mean values for 65, 75 or 90 minutes were significantly different from 60 minute values.

Table A2.--Effects of histamine base infused intravenously for 90 minutes plus histamine infused intra-arterially into forelimbs perfused at constant inflow during the last 30 minutes on forelimb weight, vascular pressures, blood flow and vascular resistances.

	Control		Infusion Period								
			H400			H800			H800 + H64		
Time (minutes)	-5	0	5	15	30	35	45	60	65	75	90
Change in Weight	0	.5	20	26	22	20	20	26	30	26	20
(grams)	0	-1	8	12	14	18	22	18	15	11	6
	0	1	14	14	10	4	-2	-6	-10	-14	-16
	0	.2	4	8	6	6	4	4	4	4	4
	0	0	21	27	33	34	36	40	42	44	48
	0	.7	36	44	47	49	49	46	45	41	36
means	0	.2	17*	22*	22*	22*	22*	21*	21*	19*	16*
standard error	±0	±.3	±5	±5	±6	±7	±8	±8	±9	±9	±10
Systemic Arterial Blood	129	130	40	40	35	33	45	43	40	35	40
Pressure (mm Hg)	120	121	30	30	30	30	30	30	15	15	15
	133	135	42	47	55	35	30	27	25	27	27
	105	105	35	25	20	20	23	20	20	20	20
	83	85	25	35	31	25	27	30	25	25	25
	145	144	33	40	35	37	40	45	50	50	45
means	119	120	34*	36*	34*	30*	33*	33*	29*	29*	29*
standard error	±9	±9	±3	±3	±5	±3	±3	±4	±5	±5	±5
Perfusion Pressure	115	116	90	85	65	65	65	60	65	75	75
(mm Hg)	115	115	85	85	75	85	85	85	80	80	80
	107	110	90	105	85	85	75	75	65	65	68
	119	121	155	120	110	90	100	90	90	82	85
	140	140	155	210	140	120	125	135	125	125	125

Table A2.--Continued.

	Control		Infusion Period								
			H400			H800			H800 + H64		
Time (minutes)	-5	0	5	15	30	35	45	60	65	75	90
	75	77	50	67	70	70	70	72	70	67	65
means	112	113	104	112	91*	86*	87*	86*	83*	82*	83*
standard error	±9	±8	±17	±21	±12	±8	±9	±11	±9	±9	±9
Skin Small Vein Pressure	7	7	6	8	7	7	6	5	4	4	4
(mm Hg)	8	8	12	12	7	7	7	7	11	14	10
	11	10	25	15	13	15	30	22	18	11	15
	3	4	6	4	4	5	4	4	4	4	3
	15	19	49	40	30	35	35	37	37	32	33
	12	12	30	30	27	27	27	27	23	23	23
means	9	10	21*	18*	15†	16†	18*	17*	16†	15†	15†
standard error	±2	±2	±7	±6	±5	±5	±6	±6	±5	±5	±5
Cephalic Vein Pressure	9	9	9	7	7	6	5	7	7	7	6
(mm Hg)	3	3	3	3	3	3	2	1	1	1	1
	3	2	5	3	3	2	2	2	2	1	2
	11	11	12	10	9	7	3	3	3	3	5
	1	1	2	2	2	2	2	1	1	1	1
	1	1	0	1	1	1	1	2	2	2	3
means	5	5	5	4	4	4	3†	3†	3†	3†	3†
standard error	±2	±2	±2	±1	±1	±1	±1	±1	±1	±1	±1

Table A2.--Continued.

	Control		Infusion Period								
			H400			H800			H800 + H64		
Time (minutes)	-5	0	5	15	30	35	45	60	65	75	90
Brachial Vein Pressure	10	9	12	15	15	13	13	14	14	13	15
(mm Hg)	5	5	5	4	6	6	6	6	7	7	7
	12	11	15	8	8	10	5	10	10	10	10
	8	8	7	8	8	7	7	7	9	9	9
	5	4	5	5	4	4	4	4	4	4	5
	7	7	6	8	8	8	10	13	11	12	11
means	8	7	8	8	8	8	8	9	9	9	10
standard error	±1	±1	±2	±2	±2	±1	±1	±2	±1	±1	±1
Cephalic Flow	25	24	21	23	25	27	17	20	20	22	20
(ml/min/100 grams)	6	6	7	7	9	8	5	4	6	6	5
	19	19	18	17	14	17	18	17	15	15	15
	27	27	30	29	28	27	27	27	25	23	23
	7	7	6	4	6	7	8	6	6	7	7
	13	13	15	18	17	16	15	15	14	15	14
means	16	16	16	16	17	17	15	15	14	15	14
standard error	±4	±4	±4	±4	±4	±4	±3	±4	±3	±3	±3
Brachial Flow	13	13	9	6	7	9	9	9	11	12	10
(ml/min/100 grams)	15	15	14	17	16	14	13	15	15	15	14
	14	14	10	10	13	13	13	14	14	15	14
	8	8	6	7	8	7	6	8	8	8	7

Table A2.--Continued.

	Control		Infusion Period								
			H400			H800			H800 + H64		
Time (minutes)	-5	0	5	15	30	35	45	60	65	75	90
	13	13	13	13	12	12	14	12	12	13	13
	16	16	13	9	9	10	19	17	17	13	15
means	13	13	11†	10*	11†	11†	12	13	13	13	12
standard error	±1	±1	±1	±2	±1	±1	±2	±2	±1	±1	±1
Total Skin Resistance	14	5	4	3	2	2	4	3	3	3	4
(mm Hg_1 x min x ml^{-1} x	19	19	12	12	8	10	17	21	13	13	16
100 g^{-1})	6	6	5	6	6	5	4	4	4	4	4
	4	4	5	4	4	3	4	3	4	3	4
	20	20	26	52	23	17	15	22	21	18	18
	6	6	3	4	4	4	5	5	5	4	4
means	10	10	9	14	8	7	8	10	8	8	8
standard error	±3	±3	±4	±8	±3	±2	±3	±4	±3	±3	±3
Total Muscle Resistance	8	8	9	12	7	6	6	5	5	5	6
(mm Hg_1 x min x ml^{-1} x	7	7	6	5	4	6	6	5	5	5	5
100 g^{-1})	7	7	8	10	6	6	5	5	4	4	4
	14	14	25	16	13	12	16	14	10	9	11
	10	11	12	16	11	10	9	10	10	9	9
	4	4	3	7	7	6	3	3	4	4	4
means	8	9	11†	11†	8	8	8	7†	6*	6*	7†
standard error	±1	±1	±3	±2	±1	±1	±2	±2	±1	±1	±1

* = $p \leq 0.01$ relative to control. † = $p \leq 0.05$ relative to control.

No mean values for 65, 75 or 90 minutes were significantly different from 60 minute values.

Table A3.--Effects of histamine base infused into the left ventricle of the heart for 90 minutes plus histamine infused intra-arterially into naturally perfused forelimbs during the last 30 minutes on lymph flow, protein concentration of lymph and plasma, vascular pressures and hematocrit.

	Control		Infusion Period								
			H400			H800			H800 + H64		
Time (minutes)	-10	0	10	20	30	40	50	60	70	80	90
Systemic Arterial Blood Pressure (mm Hg)	137	137	35	30	30	45	43	37	35	30	30
	125	125	33	27	37	30	33	33	30	30	30
	120	120	55	50	50	50	50	55	60	65	65
	125	125	25	35	35	33	30	27	25	20	20
	130	130	30	32	37	30	27	18	17	18	15
	80	100	27	27	27	29	35	37	35	37	37
	120	120	35	35	42	37	37	37	40	40	90
means	120	122	34*	34*	37*	36*	36*	35*	35*	34*	41*
standard error	±7	±4	±4	±3	±3	±3	±3	±4	±5	±6	±10
Skin Small Vein Pressure (mm Hg)	13	13	11	11	12	13	13	13	12	11	11
	9	10	7	13	13	22	12	12	11	12	13
	11	11	11	10	10	10	10	11	12	12	13
	11	11	7	11	7	8	10	9	10	10	11
	12	12	8	10	12	11	11	11	13	12	13
	9	9	9	9	9	8	8	8	6	7	7
	12	10	13	11	12	12	12	12	13	14	15
means	11	11	9	11	11	12	11	11	11	11	12
standard error	±1	±1	±1	±1	±1	±2	±1	±1	±1	±1	±1

Table A3.--Continued.

	Control		Infusion Period								
			H400			H800			H800 + H64		
Time (minutes)	-10	0	10	20	30	40	50	60	70	80	90
Lymph Flow Rate	.05	.05	.24	.36	.28	.20	.21	.18	.07	.02	.02
(ml/10 min)	.03	.03	.03	.02	.08	.02	.04	.05	.04	.04	.05
	.02	.01	.02	.24	.15	.13	.09	.07	.06	.04	.03
	.02	.02	.04	.05	.03	.03	.04	.03	.02	.02	.01
	.02	.02	.06	.14	.16	.11	.08	.09	.10	.05	.21
	.02	.02	.03	.02	.03	.02	.05	.02	.03	.04	.04
	.02	.02	.07	.13	.05	.03	.02	.03	.04	.02	.03
means	.03	.02	.07†	.14*	.11*	.08†	.08†	.07†	.05	.03	.06
standard error	±.004	±.01	±.03	±.05	±.03	±.03	±.02	±.02	±.01	±.01	±.03
Lymph Total Protein	1.6	1.8	2.3	3.0	3.3	3.6	3.3	3.0	2.8	3.0	3.0
(grams %)	1.5	1.9	2.1	2.4	2.2	2.2	2.3	2.7	3.0	3.1	3.5
	2.2	2.2	3.2	2.3	3.6	3.8	3.7	3.7	3.8	4.0	4.0
	2.3	2.8	3.1	3.2	2.3	2.2	2.3	2.2	2.3	2.4	2.4
	2.1	2.5	2.8	2.6	2.5	2.8	3.0	3.2	3.1	3.2	3.4
	1.5	1.9	2.5	2.8	3.1	3.3	3.1	3.0	3.0	2.9	2.7
means	1.9	2.2	2.7†	2.7†	2.8†	3.0*	3.0*	3.0*	3.0*	3.1*	3.2*
standard error	±.2	±.2	±.2	±.1	±.2	±.3	±.2	±.2	±.2	±.2	±.2
Plasma Protein		6.0			6.0			5.8			5.5
(grams %)		6.3			6.1			6.1			5.9
		5.6			5.2			5.3			5.3
		5.8			3.7			3.4			3.8

Table A3.--Continued.

	Control		Infusion Period								
			H400			H800			H800 + H64		
Time (minutes)	-10	0	10	20	30	40	50	60	70	80	90
		5.3			5.2			5.4			5.4
		4.4			4.4			5.0			4.5
means		5.6			5.1			5.2			5.1
standard error		±.3			±.4			±.4			±.3
Hematocrit		40			55			57			59
		40			52			55			56
		45			55			58			60
		40			41			41			43
		44			62			64			62
		32			43			50			52
		37			44			52			54
means		40			50*			54*			55*
standard error		±2			±3			±3			±2

* = $p \leq 0.01$ relative to control.

† = $p \leq 0.05$ relative to control.

No mean values for 70, 80 or 90 minutes were significantly different from 60 minute values.

Table A4.--Effects of histamine base infused intravenously for 90 minutes plus histamine infused intra-arterially into naturally perfused forelimbs during the last 30 minutes on lymph flow, protein concentration of lymph and plasma, vascular pressures and hematocrit.

	Control		Infusion Period								
			H400			H800			H800 + H64		
Time (minutes)	-10	0	10	20	30	40	50	60	70	80	90
Systemic Arterial Blood	115	115	37	32	32	32	32	27	25	23	23
Pressure (mm Hg)	93	90	30	30	33	27	27	25	20	17	7
	120	120	35	32	27	27	32	35	40	42	45
	120	120	30	27	30	25	23	20	20	20	20
	110	110	35	35	37	37	40	40	37	40	37
	120	125	35	37	37	37	42	42	40	42	42
means	113	113	34*	32*	33*	31*	33*	32*	30*	31*	29*
standard error	±4	±5	±1	±2	±2	±2	±3	±4	±4	±5	±6
Skin Small Vein Pressure	9	9	9	10	10	10	9	8	8	8	8
(mm Hg)	12	11	9	8	8	8	8	7	6	6	4
	7	7	7	8	5	6	5	5	5	5	2
	10	10	9	6	8	8	7	6	7	6	6
	11	10	8	7	8	8	8	8	9	9	9
	9	9	6	7	5	5	5	5	5	5	5
means	10	9	8†	8†	7*	8†	7*	7*	7*	7*	6*
standard error	±1	±1	±1	±1	±1	±1	±1	±1	±1	±1	±1
Lymph Flow Rate	.02	.02	.01	.04	.04	.04	.03	.02	.02	.03	.03
(ml/10 min)	.02	.02	.13	.18	.14	.09	.04	.03	.03	.04	.03
	.02	.02	.02	.02	.04	.07	.10	.08	.02	.01	.01
	.02	.02	.08	.04	.06	.07	.06	.05	.05	.03	.06

Table A4.--Continued.

	Control		Infusion Period								
			H400			H800			H800 + H64		
Time (minutes)	-10	0	10	20	30	40	50	60	70	80	90
	.02	.02	.11	.07	.07	.02	.02	.01	.01	.01	.01
	.01	.01	.01	.01	.01	.01	.01	.01	.01	.01	.01
means	.02	.02	.06*	.06*	.06*	.05†	.04	.03	.02	.02	.03
standard error	±.001	±.001	±.02	±.03	±.02	±.01	±.01	±.01	±.01	±.01	±.01
Lymph Total Protein	1.7	1.7	2.0	2.0	1.9	2.6	3.1	3.1	2.8	3.0	3.2
(grams %)	2.4	2.4	2.7	3.4	3.5	3.5	3.8	3.5	3.8	3.8	3.7
	2.1	2.2	2.2	2.3	2.7	3.5	3.2	3.5	3.5	3.4	3.3
	1.4	2.3	2.2	2.1	2.7	3.0	3.3	3.6	3.4	3.6	3.5
	2.4	2.1	2.9	2.6	3.0	3.0	3.1	2.9	2.6	3.1	3.2
	1.6	1.7	1.7	1.4	1.5	1.6	1.6	1.5	2.0	2.0	2.0
means	1.9	2.1	2.3	2.3	2.6*	2.9*	3.0*	3.0*	3.0*	3.2*	3.2*
standard error	±.2	±.1	±.2	±.3	±.3	±.3	±.3	±.3	±.3	±.3	±.2
Plasma Protein		5.0			4.7			4.6			4.3
(grams %)		4.1			4.8			5.0			5.2
		5.0			5.4			5.1			4.9
		5.4			6.4			5.0			4.6
		4.9			5.5			4.6			4.9
		5.4			5.4			5.2			5.3
means		5.0			5.4			4.9			4.9
standard error		±.2			±.3			±.1			±.2

Table A4.--Continued.

	Control		Infusion Period								
			H400			H800			H800 + H64		
Time (minutes)	-10	0	10	20	30	40	50	60	70	80	90
Hematocrit		33			59			62			60
		31			40			47			46
		33			48			52			51
		37			45			49			46
		37			52			54			52
		35			44			51			50
means		34			48*			53*			51*
standard error		±1			±3			±2			±2

* = $p \leq 0.01$ relative to control.

† = $p \leq 0.05$ relative to control.

No mean values for 70, 80 or 90 minutes were significantly different from 60 minute values.

Table A5.--Effects of histamine base infused into the left ventricle of the heart for 90 minutes plus histamine infused intra-arterially into forelimbs perfused at constant inflow during the last 30 minutes on lymph flow, protein concentration of lymph and plasma, vascular pressures and hematocrit.

	Control		Infusion Period								
			H400			H800			H800 + H64		
Time (minutes)	-10	0	10	20	30	40	50	60	70	80	90
Systemic Arterial Blood Pressure (mm Hg)	125	125	35	37	50	37	40	40	40	43	37
	120	120	35	30	30	30	27	25	25	25	25
	107	107	25	20	30	23	23	20	20	18	18
	100	100	27	30	35	30	35	37	40	40	40
	125	130	27	27	30	27	27	27	25	23	23
	125	125	30	40	37	32	25	26	25	26	26
means	117	118	30*	31*	35*	30*	30*	29*	29*	29*	28*
standard error	±4	±5	±2	±3	±3	±2	±3	±3	±4	±4	±4
Perfusion Pressure (mm Hg)	120	115	90	95	110	110	120	110	100	93	75
	115	115	75	80	90	95	95	90	87	90	90
	100	100	50	115	115	95	95	95	95	95	100
	100	100	57	75	77	83	80	80	75	65	65
	105	110	70	87	100	93	95	95	95	97	103
	115	115	65	90	97	100	90	93	105	120	110
means	109	109	68*	90*	98†	96†	96†	94*	93*	93*	91*
standard error	±4	±3	±6	±6	±6	±4	±5	±4	±4	±7	±7
Skin Small Vein Pressure (mm Hg)	17	15	50	29	31	28	36	33	18	20	15
	14	14	12	14	14	15	15	16	14	14	15
	15	15	12	12	17	13	14	12	12	12	15
	13	13	14	17	16	18	18	18	16	15	15

Table A5.--Continued.

	Control		Infusion Period								
			H400			H800			H800 + H64		
Time (minutes)	-10	0	10	20	30	40	50	60	70	80	90
	15	15	12	17	17	17	17	16	16	15	16
	12	12	12	12	12	11	9	8	9	14	11
means	14	14	19	17	18	17	18	17	14	15	15
standard error	±1	±1	±6	±3	±3	±2	±4	±4	±1	±1	±1
Lymph Flow Rate	.01	.01	.08	.22	.16	.08	.05	.13	.06	.12	.08
(ml/10 min)	.01	.01	.06	.26	.22	.20	.18	.09	.05	.05	.04
	.03	.03	.17	.36	.35	.27	.24	.17	.18	.15	.11
	.02	.02	.08	.20	.07	.06	.03	.03	.03	.02	.03
	.02	.02	.40	.36	.25	.18	.15	.16	.11	.08	.10
	.01	.01	.19	.45	.40	.32	.25	.19	.11	.04	.02
means	.02	.02	.16*	.31*	.24*	.19*	.15*	.13*	.09†	.08	.06
standard error	±.01	±.01	±.05	±.04	±.05	±.04	±.04	±.02	±.02	±.02	±.02
Lymph Total Protein	1.2	1.5	2.0	3.5	3.5	3.6	3.8	3.6	3.7	3.6	3.8
(grams %)	1.2	1.1	1.8	3.8	4.0	3.7	4.1	3.9	3.6	3.8	3.7
	2.4	2.7	2.9	3.6	4.4	4.3	4.4	5.2	5.0	4.9	5.4
	1.0	1.3	2.4	3.0	3.6	3.3	3.4	3.0	2.9	2.9	3.0
	1.4	1.1	2.5	4.0	4.2	5.0	4.4	4.5	3.4	3.5	4.0
	3.7	3.8	7.0	5.8	5.6	6.3	6.1	6.8	6.5	6.3	6.4
means	1.9	1.9	3.1*	4.0*	4.2*	4.4*	4.4*	4.5*	4.2*	4.2*	4.4*
standard error	±.4	±.5	±.8	±.4	±.3	±.5	±.4	±.6	±.5	±.5	±.5

Table A5.--Continued.

	Control		Infusion Period								
			H400			H800			H800 + H64		
Time (minutes)	-10	0	10	20	30	40	50	60	70	80	90
Plasma Protein (grams %)		5.8			5.7			5.9			5.9
		5.3			5.3			5.2			4.6
		6.0			5.9			6.1			5.7
		4.5			4.7			4.9			4.8
		5.0			5.6			5.5			4.9
		7.1			6.6			6.1			6.5
means		5.6			5.6			5.6			5.4
standard error		±.4			±.3			±.2			±.3
Hematocrit		44			55			61			62
		40			50			53			50
		38			45			52			56
		31			40			45			46
		38			48			52			54
		37			67			68			67
means		38			51*			55*			56*
standard error		±2			±4			±3			±3

* = $p \leq 0.01$ relative to control. † = $p \leq 0.05$ relative to control.

No mean values for 70, 80 or 90 minutes were significantly different from 60 minute values.

Table A6.--Effects of histamine base infused intravenously for 90 minutes plus histamine infused intra-arterially into forelimbs perfused at constant inflow during the last 30 minutes on lymph flow, protein concentration of lymph and plasma, vascular pressures and hematocrit.

	Control		Infusion Period								
			H400			H800			H800 + H64		
Time (minutes)	-10	0	10	20	30	40	50	60	70	80	90
Systemic Arterial Blood	103	103	33	27	25	20	25	25	25	25	25
Pressure (mm Hg)	120	120	30	30	43	40	50	50	55	55	55
	130	125	40	35	40	43	47	43	45	45	50
	120	120	30	30	33	30	27	25	25	25	23
	95	95	25	25	35	27	25	23	20	20	20
	105	105	25	25	27	23	23	23	23	23	20
means	112	111	31*	29*	34*	31*	33*	32*	32*	32*	32*
standard error	±5	±5	±2	±2	±3	±4	±5	±5	±6	±6	±7
Perfusion Pressure	90	90	75	85	85	90	93	83	83	83	85
(mm Hg)	110	110	70	80	85	80	83	77	83	80	80
	115	115	90	95	95	85	85	90	85	100	95
	100	100	70	75	67	70	70	70	70	70	75
	90	90	57	55	67	63	63	57	55	60	65
means	101	101	72*	78*	80*	78*	79*	75*	75*	79*	80*
standard error	±5	±5	±5	±7	±6	±5	±5	±6	±6	±7	±5
Skin Small Vein Pressure	14	14	27	31	26	31	47	38	31	34	31
(mm Hg)	16	16	21	24	25	23	25	25	26	25	25
	14	12	31	23	24	20	19	19	19	21	19
	15	15	25	22	19	21	21	18	16	17	17

Table A6.--Continued.

	Control		Infusion Period								
			H400			H800			H800 + H64		
Time (minutes)	-10	0	10	20	30	40	50	60	70	80	90
	10	10	10	11	13	11	11	11	10	12	12
	11	11	11	22	11	16	31	18	25	19	22
means	13	13	21*	22*	20*	20*	26*	22*	21*	21*	21*
standard error	±1	±1	±4	±3	±3	±3	±5	±4	±3	±3	±3
Lymph Flow Rate	.01	.01	.06	.39	.09	.08	.10	.05	.05	.05	.05
(ml/10 min)	.02	.02	.44	.60	.44	.34	.30	.27	.20	.16	.14
	.02	.02	.19	.37	.27	.21	.22	.14	.15	.09	.05
	.02	.02	.17	.28	.23	.11	.04	.09	.15	.03	.22
	.01	.01	.12	.19	.23	.19	.12	.06	.13	.14	.05
	.02	.02	.03	.05	.07	.06	.07	.07	.05	.07	.07
means	.02	.02	.17*	.31*	.22*	.17*	.14*	.11†	.12†	.09	.10
standard error	±.002	±.002	±.06	±.08	±.06	±.04	±.04	±.03	±.03	±.02	±.03
Lymph Total Protein	2.7	2.4	2.6	6.3	4.4	3.9	4.0	3.7	3.7	4.1	3.9
(grams %)	2.2	2.5	3.1	4.2	4.0	4.1	4.3	4.4	3.8	3.5	3.4
	2.1	1.9	2.7	3.7	3.4	3.7	3.8	3.7	3.7	3.5	3.4
	1.7	1.9	2.1	3.7	3.5	3.6	3.6	3.7	4.1	3.4	4.3
	3.1	3.1	3.9	4.1	5.4	5.2	4.2	3.9	4.3	4.8	4.2
	2.0	2.1	2.3	2.3	2.4	2.5	2.6	2.7	2.9	2.8	3.0
means	2.3	2.3	2.8	4.1*	3.9*	3.8*	3.8*	3.7*	3.8*	3.7*	3.7*
standard error	±.2	±.2	±.3	±.5	±.4	±.4	±.3	±.2	±.2	±.3	±.2

Table A6.--Continued.

	Control		Infusion Period								
			H400			H800			H800 + H64		
Time (minutes)	-10	0	10	20	30	40	50	60	70	80	90
Plasma Protein (grams %)		5.3			5.8			4.4			3.3
		5.3			5.2			5.5			5.7
		5.5			5.2			5.4			5.4
		5.4			5.2			6.2			5.9
		5.3			5.5			5.9			5.7
		5.0			4.6			4.7			3.9
means		5.3			5.3			5.4			5.0
standard error		±.1			±.2			±.3			±.5
Hematocrits		42			75			69			68
		41			55			65			64
		42			57			63			59
		36			55			62			62
		33			47			58			57
		28			44			42			42
means		37			56*			60*			59*
standard error		±2			±4			±4			±4

* = $p \leq 0.01$ relative to control. † = $p \leq 0.05$ relative to control.

No mean values for 70, 80 or 90 minutes were significantly different from 60 minute values.

Table A7.--Effects of histamine base infused into the left ventricle of the heart and intra-arterially (after a 3 minute delay) into naturally perfused forelimbs for 60 minutes on lymph flow, protein concentration of lymph and plasma, vascular pressures and hematocrit.

	Control		Infusion Period					
			H400 + H64					
Time (minutes)	-10	0	10	20	30	40	50	60
Systemic Arterial Blood Pressure (mm Hg)	100	95	28	26	30	38	40	40
	115	115	40	45	45	45	45	45
	130	135	40	30	45	47	50	50
	137	137	30	30	30	45	55	63
	125	125	33	35	37	40	45	45
	130	130	30	30	25	30	30	27
means	123	123	34*	33*	35*	41*	44*	45*
standard error	±6	±6	±2	±3	±3	±3	±4	±5
Skin Small Vein Pressure (mm Hg)	9	8	5	6	6	7	7	7
	12	13	7	9	8	8	7	7
	9	9	4	4	4	4	5	5
	11	11	8	8	7	8	9	9
	10	10	6	5	6	7	7	7
	12	13	7	9	6	7	8	7
means	11	11	6*	7*	6*	7*	7*	7*
standard error	±1	±1	±1	±1	±1	±1	±1	±1
Lymph Flow Rate (ml/10 min)	.02	.02	.03	.03	.04	.05	.04	.04
	.02	.02	.02	.02	.02	.03	.06	.08
	.02	.02	.02	.01	.01	.02	.01	.02
	.02	.02	.02	.03	.03	.02	.02	.01

Table A7.--Continued.

Time (minutes)	Control		Infusion Period H400 + H64					
	-10	0	10	20	30	40	50	60
	.02	.02	.01	.01	.01	.01	.01	.01
	.02	.02	.02	.09	.09	.09	.07	.09
means	.02	.02	.02	.03	.03	.04	.04	.04
standard error	±0	±0	±.003	±.01	±.01	±.01	±.01	±.01
Lymph Total Protein (grams %)	2.6	2.6	2.8	2.4	3.1	3.4	3.7	4.0
	2.4	2.3	2.6	2.7	2.1	2.2	2.6	2.7
	0.9	0.9	0.9	0.9	1.1	0.9	0.8	1.0
	2.3	3.0	2.7	2.6	3.5	3.6	3.8	3.3
	3.8	3.8	3.7	3.1	3.1	3.0	3.2	3.2
	4.3	5.5	5.3	5.5	5.9	5.9	6.0	6.3
means	2.7	3.0	3.0	2.9	3.1	3.2	3.4	3.4
standard error	±.5	±.6	±.6	±.6	±.7	±.7	±.7	±.7
Plasma Protein (grams %)		6.4			5.7			5.7
		6.2			5.9			6.0
		5.6			5.6			5.4
		6.0			6.5			6.5
		6.6			6.1			6.0
		8.4			8.1			8.0
means		6.5			6.3			6.3
standard error		±.4			±.4			±.4

Table A7.--Continued.

Time (minutes)	Control		Infusion Period					
			H400 + H64					
	-10	0	10	20	30	40	50	60
Hematocrit		38			40			47
		44			54			56
		42			56			57
		46			54			59
		42			54			55
		33			49			55
means		41			51*			55*
standard error		±2			±2			±2

* = $p \leq 0.01$ relative to control.

† = $p \leq 0.05$ relative to control.

Table A8.--Effects of histamine base infused into the left ventricle of the heart and intra-arterially (after a 3 minute delay) into forelimbs perfused at constant inflow for 60 minutes on lymph flow, protein concentration of lymph and plasma, vascular pressures and hematocrit.

	Control		Infusion Period					
			H400 + H64					
Time (minutes)	-10	0	10	20	30	40	50	60
Systemic Arterial Blood Pressure (mm Hg)	104	104	30	30	35	37	40	45
	100	102	32	37	37	35	32	32
	110	112	40	35	42	50	52	55
	107	107	37	37	35	35	30	30
	107	105	30	27	22	17	25	22
	105	110	35	30	30	30	30	30
means	106	107	34*	33*	34*	34*	35*	36*
standard error	±1	±2	±2	±2	±3	±4	±4	±5
Perfusion Pressure (mm Hg)	99	99	105	137	133	126	120	120
	90	92	77	82	82	80	80	77
	90	95	75	80	90	95	90	100
	112	107	85	87	85	75	70	67
	110	105	100	90	80	75	65	60
	100	100	105	130	115	87	80	75
means	100	100	91	101	98	90	84	83
standard error	±4	±2	±6	±10	±9	±8	±8	±9
Skin Small Vein Pressure (mm Hg)	6	6	30	31	19	14	12	11
	10	10	21	18	16	17	16	15
	9	10	12	10	11	9	9	10
	11	9	22	19	17	15	14	13

Table A8.--Continued.

	Control		Infusion Period					
			H400 + H64					
Time (minutes)	-10	0	10	20	30	40	50	60
	11	10	23	19	18	17	18	13
	13	13	26	17	12	12	10	11
means	10	10	22*	19*	16*	14	13	12
standard error	±1	±1	±3	±3	±1	±1	±1	±1
Lymph Flow Rate	.02	.02	.10	.25	.19	.10	.05	.04
(ml/10 min)	.05	.05	.42	.53	.31	.22	.16	.14
	.01	.01	.19	.22	.18	.14	.12	.09
	.01	.01	.32	.43	.37	.23	.16	.15
	.02	.03	.47	.57	.39	.27	.18	.09
	.02	.02	.21	.11	.15	.07	.03	.03
means	.02	.02	.29*	.35*	.27*	.17*	.12†	.09
standard error	±.01	±.01	±.06	±.08	±.04	±.03	±.03	±.02
Lymph Total Protein	1.3	1.4	2.3	2.9	3.6	3.6	5.6	4.7
(grams %)	1.9	2.1	2.5	3.6	3.6	3.7	3.5	3.6
	3.1	3.0	3.8	3.7	4.1	4.3	4.4	4.2
	2.8	2.9	4.1	4.4	4.1	4.2	4.3	4.4
	2.6	2.7	3.9	3.8	3.6	3.4	3.5	3.4
	2.5	2.7	2.6	2.7	3.7	3.7	3.8	3.8
means	2.4	2.5	3.2†	3.5*	3.8*	3.8*	4.2*	4.0*
standard error	±.3	±.3	±.3	±.3	±.1	±.2	±.3	±.2

Table A8.--Continued.

Time (minutes)	Control		Infusion Period H400 + H64					
	-10	0	10	20	30	40	50	60
Plasma Proteins (grams %)		6.4			6.6			7.0
		4.5			4.9			5.0
		5.8			5.6			5.9
		5.8			6.4			5.6
		5.4			5.0			3.6
		6.1			4.9			4.0
means		5.7			5.6			5.2
standard error		±.3			±.3			±.5
Hematocrit		31			52			50
		39			60			61
		36			48			54
		34			57			54
		30			45			34
		36			41			33
means		34			51*			48*
standard error		±1			±3			±5

* = $p \leq 0.01$ relative to control.

† = $p \leq 0.05$ relative to control.

Table A9.--Effects of 4 μg histamine base/minute infused intra-arterially for 60 minutes into forelimbs perfused at constant inflow following 60 minutes of hypotension produced by acetylcholine base infused intravenously at a concentration necessary to lower and maintain aortic pressure near 60 mm Hg for the first 60 minutes.

	Control		Acetylcholine Infusion						Histamine Infusion					
Time (minutes)	-10	0	10	20	30	40	50	60	70	80	90	100	110	120
Systemic Arterial	120	120	47	50	55	62	65	65	65	67	70	70	67	70
Blood Pressure	125	125	47	50	60	60	60	63	63	67	70	75	75	75
(mm Hg)	100	100	50	70	55	60	63	55	57	60	60	63	63	60
	125	130	75	77	60	55	57	57	57	57	60	57	60	67
	110	110	57	55	61	65	55	54	54	55	53	55	55	48
	125	125	65	65	55	50	50	50	50	50	45	50	53	50
means	118	118	57*	61*	58*	59*	58*	57*	58*	59*	60*	62*	62*	62*
standard error	±4	±5	±5	±5	±1	±2	±2	±2	±2	±3	±4	±4	±3	±5
Perfusion Pressure	90	90	50	60	60	67	72	80	62	67	70	70	67	70
(mm Hg)	120	120	53	60	75	75	75	70	65	63	68	72	73	73
	95	95	100	100	100	100	100	95	65	65	65	60	60	60
	115	115	125	130	100	90	85	85	57	60	65	62	67	72
	100	110	100	140	103	107	110	105	73	73	73	75	75	68
	120	120	130	125	130	120	115	115	65	70	60	60	75	75
means	107	108	93	103	95	93	93	92	65*ω	66*ω	67*ω	67*ω	68*ω	68*ω
standard error	±5	±5	±14	±15	±10	±8	±7	±7	±2	±2	±2	±3	±2	±2
Skin Small Vein	18	18	17	18	18	18	18	18	17	17	17	18	19	19
Pressure	10	10	9	10	10	10	9	6	6	7	7	8	7	7
(mm Hg)	10	10	10	10	10	9	10	9	9	9	9	9	9	9
	11	11	8	7	8	8	9	9	10	11	13	12	12	13
	17	16	15	18	16	17	17	18	18	18	18	18	18	17
	10	10	12	11	12	12	11	11	14	15	14	14	14	14
means	13	13	12	12	12	12	12	12	12	13	13	13	13	13
standard error	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2

Table A9.--Continued.

Time (minutes)	Control		Acetylcholine Infusion						Histamine Infusion					
	-10	0	10	20	30	40	50	60	70	80	90	100	110	120
Lymph Flow Rate (ml/10 min)	.03	.03	.02	.02	.02	.03	.02	.03	.04	.02	.02	.02	.02	.02
	.01	.01	.01	.01	.01	.01	.01	.01	.03	.02	.02	.02	.01	.02
	.02	.02	.01	.01	.01	.01	.01	.01	.01	.02	.01	.02	.02	.02
	.01	.01	.01	.01	.01	.01	.01	.01	.03	.09	.09	.09	.08	.08
	.02	.02	.04	.07	.04	.06	.04	.06	.07	.11	.15	.18	.18	.15
	.01	.01	.01	.01	.01	.01	.01	.01	.01	.02	.02	.02	.02	.02
means	.02	.02	.02	.02	.02	.02	.02	.02	.03	.05†Ω	.05†Ω	.06*ω	.06*ω	.05†Ω
standard error	±.003	±.003	±.01	±.01	±.01	±.01	±.01	±.01	±.01	±.02	±.02	±.03	±.03	±.02
Lymph Total Protein (grams %)	2.8	2.6	3.1	2.5	2.6	2.4	2.5	2.8	2.5	2.5	2.3	2.7	2.3	2.6
	2.0	2.0	2.0	2.0	2.2	2.6	2.2	2.2	2.0	2.0	2.1	2.2	2.2	2.3
	1.5	1.6	1.4	1.6	1.5	1.8	1.6	1.5	1.6	1.5	1.7	1.8	2.2	2.4
	2.2	2.2	2.9	2.7	2.6	2.5	2.4	2.4	2.3	2.5	2.9	3.3	3.5	3.4
	2.5	2.4	2.2	2.1	2.2	2.2	2.1	2.1	2.3	2.2	1.8	2.3	2.7	3.0
	2.6	2.7	2.6	2.7	2.9	2.7	2.6	2.6	2.6	2.6	2.8	2.8	3.0	3.0
means	2.3	2.3	2.4	2.3	2.3	2.4	2.2	2.3	2.2	2.2	2.3	2.5	2.7*ω	2.8*ω
standard error	±.2	±.2	±.3	±.2	±.2	±.1	±.2	±.2	±.2	±.2	±.2	±.2	±.2	±.2
Plasma Protein (grams %)		5.1			5.4			5.3			5.3			5.3
		6.2			6.1			6.0			6.2			6.8
		4.7			5.2			4.9			5.2			5.2
		4.7			4.7			4.9			4.6			4.8
		5.7			5.0			4.8			4.9			5.0
		5.4			5.3			5.4			5.5			5.5
means		5.3			5.3			5.2			5.3			5.4
standard error		±.2			±.2			±.2			±.2			±.3
Hematocrit		31			35			37			37			38
		36			41			46			46			49
		37			35			38			40			41
		37			38			38			38			39
		36			38			35			34			34
		35			40			42			44			44
means		35			38†			39*			40*			41*
standard error		±1			±1			±2			±2			±2

* = $p \leq 0.01$ relative to control.

† = $p \leq 0.05$ relative to control.

ω = $p \leq 0.01$ relative to minute 60.

Ω = $p \leq 0.05$ relative to minute 60.

Table A10.--Effects of 4 μg histamine base/minute infused intra-arterially for 60 minutes into forelimbs perfused at constant inflow following 60 minutes of hemorrhagic hypotension with aortic pressure maintained near 40 mm Hg.

	Control		Hemorrhage						Histamine Infusion					
Time (minutes)	-10	0	10	20	30	40	50	60	70	80	90	100	110	120
Systemic Arterial	105	105	45	40	45	55	50	40	67	70	75	70	75	75
Blood Pressure	130	130	45	45	45	50	45	35	35	37	30	30	30	30
(mm Hg)	115	120	45	45	35	35	33	35	35	35	35	35	35	35
	90	90	40	40	45	43	35	35	43	43	35	33	34	33
	120	125	45	40	35	42	32	45	45	35	35	25	20	20
	130	130	50	52	50	57	50	50	50	50	50	50	50	40
means	115	117	45*	44*	43*	47*	41*	40*	46*	45*	43*	41*	41*	39*
standard error	±6	±7	±1	±2	±3	±4	±4	±3	±5	±6	±7	±7	±8	±8
Perfusion Pressure	95	95	170	140	155	175	165	175	150	150	150	140	140	140
(mm Hg)	125	125	185	180	153	175	175	185	180	165	155	135	125	110
	110	115	200	190	175	165	165	150	120	95	100	95	95	95
	75	75	120	145	150	170	170	165	135	130	135	145	140	135
	115	120	160	155	95	105	85	95	82	95	95	85	75	75
	110	110	205	195	200	170	200	165	160	160	165	169	169	160
means	105	107	173*	168*	155*	160*	160*	156*	138†	133†	133†	128 Ω	124 Ω	119 ω
standard error	±7	±8	±13	±10	±14	±11	±16	±13	±14	±13	±12	±13	±14	±13
Skin Small Vein	13	13	8	7	6	6	6	6	8	10	10	9	9	9
Pressure	15	15	5	6	7	6	6	7	10	10	10	10	11	10
(mm Hg)	13	12	10	10	11	11	12	11	12	10	10	10	12	13
	13	12	15	10	9	8	9	8	8	9	8	9	9	8
	11	9	8	10	8	10	8	8	9	9	11	11	11	10
	16	14	10	10	9	8	8	9	8	9	9	8	9	10
means	14	13	9*	9*	8*	8*	8*	8*	9*	10*Ω	10*Ω	10*Ω	10*Ω	10*Ω
standard error	±1	±1	±1	±1	±1	±1	±1	±1	±1	±.2	±.4	±.4	±1	±1

Table A10.--Continued.

Time (minutes)	Control		Hemorrhage						Histamine Infusion					
	-10	0	10	20	30	40	50	60	70	80	90	100	110	120
Lymph Flow Rate (ml/10 min)	.03	.03	.09	.09	.07	.06	.04	.04	.03	.03	.02	.02	.01	.01
	.01	.01	.03	.02	.03	.02	.02	.02	.03	.01	.01	.01	.02	.01
	.01	.01	.02	.01	.01	.01	.02	.01	.01	.02	.02	.01	.01	.01
	.02	.02	.01	.01	.02	.05	.06	.10	.13	.16	.15	.11	.09	.11
	.02	.02	.01	.02	.02	.02	.02	.01	.01	.02	.02	.02	.01	.02
	.01	.01	.03	.06	.08	.01	.05	.04	.04	.03	.03	.03	.02	.02
means	.02	.02	.03	.04	.04	.03	.04	.04	.04	.05	.04	.03	.03	.03
standard error	±.003	±.003	±.01	±.01	±.01	±.01	±.01	±.01	±.02	±.02	±.02	±.02	±.01	±.02
Lymph Total Protein (grams %)	1.7	1.5	1.5	1.5	1.6	1.8	1.8	2.6	1.9	1.9	2.0	2.0	2.0	2.0
	2.1	2.2	2.5	2.7	2.7	2.3	2.2	2.1	2.2	2.1	2.1	2.1	2.0	1.9
	2.2	2.6	2.7	2.7	2.8	3.0	2.8	3.0	3.0	3.1	3.1	2.8	2.8	2.9
	1.8	1.7	1.8	1.9	1.6	1.5	1.4	1.4	1.5	1.3	1.4	1.3	1.3	1.4
	2.2	1.9	1.9	2.0	2.1	2.3	2.2	2.7	2.1	2.4	1.7	1.5	1.5	1.3
	2.7	2.7	2.5	2.5	2.5	2.5	2.4	2.4	2.2	2.3	2.2	2.2	2.1	2.1
means	2.1	2.1	2.2	2.2	2.2	2.2	2.1	2.4	2.2	2.2	2.1	2.0	2.0	1.9
standard error	±.2	±.2	±.2	±.2	±.2	±.2	±.2	±.2	±.2	±.2	±.2	±.2	±.2	±.2
Plasma Protein (grams %)		4.5			4.3			3.8			3.9			3.9
		5.7			4.7			4.3			4.5			3.3
		3.8			3.5			3.2			3.0			3.3
		4.5			3.9			3.6			3.6			3.6
		4.2			3.5			3.2			3.3			3.2
		6.1			5.5			5.3			5.2			5.2
means		4.8			4.2*			3.9*			3.9*			3.8*
standard error		±.4			±.3			±.3			±.3			±.3
Hematocrit		43			43			48			51			50
		34			40			41			35			32
		25			29			33			30			33
		28			28			30			32			30
		30			35			35			35			37
		41			45			47			47			47
means		34			37†			39*			38*			38*
standard error		±3			±3			±3			±4			±3

* = $p \leq 0.01$ relative to control.

† = $p \leq 0.05$ relative to control.

ω = $p \leq 0.01$ relative to minute 60.

Ω = $p \leq 0.05$ relative to minute 60.

Table A11.--Effects of 64 µg histamine base/minute infused intra-arterially for 60 minutes into forelimbs perfused at constant inflow following 60 minutes of hemorrhagic hypotension with aortic pressure maintained near 40 mm Hg.

	Control		Hemorrhage						Histamine Infusion					
Time (minutes)	-10	0	10	20	30	40	50	60	70	80	90	100	110	120
Systemic Arterial	105	105	45	45	40	45	45	65	45	50	45	43	43	43
Blood Pressure	130	130	45	45	45	45	45	50	35	35	35	35	35	30
(mm Hg)	120	120	45	45	45	45	45	55	45	40	45	43	40	40
	125	125	45	45	45	45	45	55	30	25	25	25	25	20
	110	110	45	43	43	45	50	50	35	30	30	25	25	20
	130	135	30	35	40	35	37	45	45	50	60	65	70	67
means	120	121	43*	43*	43*	43*	45*	53*	39*Ω	38*ω	40*Ω	39*Ω	40*Ω	37*ω
standard error	±4	±5	±3	±2	±1	±2	±2	±3	±3	±4	±5	±6	±7	±7
Perfusion Pressure	95	95	145	185	175	140	130	135	100	105	100	100	95	95
(mm Hg)	120	120	150	210	220	125	240	255	135	180	165	150	150	150
	110	110	195	210	220	175	170	170	65	70	75	70	65	60
	115	115	200	185	185	165	175	175	105	110	105	105	105	100
	100	95	160	165	165	170	175	175	65	95	105	100	100	105
	125	130	175	185	200	200	225	205	85	85	85	85	85	87
means	111	111	171*	190*	194*	179*	186*	186*	93 ω	108 ω	106 ω	102 ω	100 ω	100 ω
standard error	±5	±6	±9	±7	±9	±12	±16	±17	±11	±16	±13	±11	±12	±12
Skin Small Vein	10	9	10	11	11	9	9	8	10	11	11	11	10	10
Pressure	15	15	14	10	10	10	12	20	35	40	35	25	28	32
(mm Hg)	12	12	7	9	10	10	10	10	15	17	17	15	14	13
	14	13	14	18	20	20	23	25	33	25	20	20	21	20
	16	16	13	15	18	17	15	14	17	20	23	23	24	24
	11	11	8	7	7	8	7	7	16	15	17	18	16	17
means	13	13	11	12	13	12	13	14	21*ω	21*ω	21*ω	19†Ω	19†Ω	19†Ω
standard error	±1	±1	±1	±2	±2	±2	±2	±3	±4	±4	±3	±2	±3	±3

Table A11.--Continued.

Time (minutes)	Control		Hemorrhage						Histamine Infusion					
	-10	0	10	20	30	40	50	60	70	80	90	100	110	120
Lymph Flow Rate (ml/10 min)	.01	.01	.01	.02	.04	.04	.04	.05	.20	.25	.21	.15	.11	.11
	.02	.02	.02	.05	.07	.07	.07	.09	.15	.32	.27	.19	.16	.14
	.01	.01	.01	.01	.01	.02	.02	.02	.07	.12	.10	.08	.04	.03
	.03	.02	.03	.08	.08	.07	.08	.09	.20	.36	.28	.16	.12	.13
	.01	.01	.01	.01	.01	.02	.03	.03	.03	.15	.26	.22	.18	.14
	.02	.02	.02	.02	.03	.06	.10	.06	.11	.26	.58	.47	.38	.31
means	.02	.02	.02	.03	.04	.05	.06	.06	.13*	.24*ω	.28*ω	.21*ω	.17*ω	.14*Ω
standard error	±.003	±.002	±.003	±.01	±.01	±.01	±.01	±.01	±.03	±.04	±.07	±.06	±.05	±.04
Lymph Total Protein (grams %)	1.6	1.6	1.7	2.1	2.7	1.9	1.9	1.7	2.3	2.2	3.0	2.9	3.4	2.3
	1.6	1.6	1.6	2.5	1.9	2.1	2.1	2.7	2.9	2.2	2.2	2.1	2.0	1.9
	1.7	1.8	1.6	1.8	2.6	2.6	2.8	2.9	3.9	3.9	2.6	2.7	2.7	2.5
	1.6	1.8	1.9	2.2	2.2	2.1	2.2	2.2	1.9	2.5	2.4	2.3	2.3	2.3
	2.9	3.2	3.4	3.0	3.5	3.0	2.8	3.2	2.7	4.3	4.2	3.9	3.6	3.7
	3.0	3.0	3.2	3.2	3.3	3.3	3.4	3.4	3.0	3.0	3.1	2.9	2.9	2.9
means	2.1	2.2	2.2	2.5	2.7†	2.5	2.5	2.7†	2.8†	3.0*	2.9*	2.8†	2.8†	2.6
standard error	±.3	±.3	±.3	±.2	±.3	±.2	±.2	±.3	±.3	±.4	±.3	±.3	±.3	±.3
Plasma Protein (grams %)		5.0			5.0			4.9			4.5			3.9
		4.9			4.2			4.1			4.2			4.2
		3.8			3.5			3.1			3.3			3.1
		4.5			4.4			4.4			4.1			4.3
		4.6			4.5			4.8			5.0			4.6
		5.8			5.8			5.7			5.7			5.7
means		4.8			4.6			4.5			4.5			4.3
standard error		±.3			±.3			±.4			±.3			±.4
Hematocrit		35			35			44			42			41
		39			41			48			52			54
		31			40			40			41			41
		34			34			35			35			35
		44			46			46			47			47
		38			37			36			38			38
means		37			39			42*			43*			43*
standard error		±2			±2			±2			±3			±3

* = $p \leq 0.01$ relative to control.

† = $p \leq 0.05$ relative to control.

ω = $p \leq 0.01$ relative to minute 60.

Ω = $p \leq 0.05$ relative to minute 60.

Table A12.--Effects of 4 μg histamine base/minute infused intra-arterially into naturally perfused forelimbs on weight, vascular pressures, blood flows and vascular resistances.

Time (minutes)	Control		Infusion Period				
	-5	0	5	15	30	45	60
Change in Weight (grams)	0	1	20	30	38	48	54
	0	-1	18	28	34	37	37
	0	1	14	24	28	32	32
	0	0	20	30	40	51	63
	0	0	17	27	32	37	40
	0	0	16	24	29	34	36
means	0	.2	18*	27*	34*	40*	44*
standard error	±0	±.3	±1	±1	±2	±3	±5
Systemic Arterial Blood Pressure (mm Hg)	130	130	130	130	130	130	130
	130	130	130	130	130	130	130
	120	120	120	125	120	120	120
	115	115	115	115	120	117	115
	127	125	127	130	120	120	127
	140	145	145	140	140	140	140
means	127	128	128	128	127	126	127
standard error	±4	±4	±4	±3	±3	±4	±4
Skin Small Vein Pressure (mm Hg)	7	7	25	25	18	22	25
	13	13	16	17	17	14	13
	7	7	18	15	15	17	11
	8	8	17	17	17	17	19

Table A12.--Continued.

Time (minutes)		Control		Infusion Period				
		-5	0	5	15	30	45	60
		12	10	19	17	16	14	13
		12	12	27	25	23	23	23
	means	10	10	20*	19*	18*	18*	17*
	standard error	±1	±1	±2	±2	±1	±2	±2
Cephalic Vein Pressure (mm Hg)		6	7	9	9	10	8	7
		6	6	15	15	10	14	16
		3	3	5	5	5	6	4
		5	5	12	12	11	11	11
		5	5	8	9	8	8	8
		7	7	14	13	13	12	12
	means	5	6	11*	11*	10*	10*	10*
	standard error	±1	±1	±2	±2	±1	±1	±2
Brachial Vein Pressure (mm Hg)		6	6	15	15	11	14	14
		5	5	8	8	8	5	3
		4	4	3	5	5	5	3
		6	6	9	9	9	8	7
		5	5	11	11	10	11	10
		6	6	12	12	10	10	11
	means	5	5	10*	10*	9*	9*	8*
	standard error	±.3	±.3	±2	±1	±1	±2	±2

Table A12.--Continued.

Time (minutes)	Control		Infusion Period				
	-5	0	5	15	30	45	60
Cephalic Flow	8	8	26	31	26	31	30
(ml/min/100 grams)	17	17	26	27	27	27	26
	13	13	21	26	28	29	21
	17	17	24	24	24	23	22
	19	19	23	23	24	24	23
	14	14	21	21	21	21	21
means	15	15	24*	25*	25*	26*	24*
standard error	±2	±2	±1	±1	±1	±2	±2
Brachial Flow	14	14	17	17	18	31	30
(ml/min/100 grams)	8	8	17	18	15	27	26
	10	10	9	15	16	29	21
	8	8	17	18	15	23	22
	12	12	19	19	17	24	23
	10	10	15	15	15	21	21
means	10	10	16*	17*	16*	26*	24*
standard error	±1	±1	±1	±1	±1	±2	±2
Total Skin Resistance	16	15	5	4	5	4	4
(mm Hg x min x ml^{-1} x 100 g^{-1})	7	7	4	4	4	4	4
	9	9	6	5	4	4	6
	7	7	4	4	5	5	5
	6	6	5	5	5	5	5
	10	10	6	6	6	6	6
means	9	9	5*	5*	5*	5*	5*
standard error	±2	±2	±.4	±.3	±.3	±.3	±.4

Table A12.--Continued.

Time (minutes)	Control		Infusion Period				
	-5	0	5	15	30	45	60
Total Muscle Resistance	9	9	7	7	7	4	4
(mm Hg x min x ml^{-1} x 100 g^{-1})	16	16	7	7	8	5	5
	12	12	13	8	7	4	6
	14	14	6	6	7	5	5
	10	10	6	6	7	5	5
	13	14	9	9	9	6	6
means	12	13	8*	7*	8*	5*	5*
standard error	±1	±1	±1	±1	±.3	±.3	±.3

* = $p \leq 0.01$ relative to control.

† = $p \leq 0.05$ relative to control.

Table A13.--Effects of histamine plus norepinephrine (4 μg base/minute, of each) infused simultaneously intra-arterially into naturally perfused forelimbs on weight, vascular pressures, blood flows and vascular resistances.

Time (minutes)	Control		Infusion Period				
	-5	0	5	15	30	45	60
Change in Weight (grams)	0	0	-10	-4	0	4	8
	0	1	-8	-2	4	8	10
	0	0	-8	-4	-2	3	4
	0	0	-10	-5	-5	-2	4
	0	1	-9	-8	-7	-1	1
	0	0	-12	-6	-3	-1	0
means	0	.3	-10*	-5*	-2	2	5*
standard error	±0	±.2	±1	±1	±2	±2	±2
Systemic Arterial Blood Pressure (mm Hg)	135	135	145	145	140	140	140
	130	135	135	150	130	165	155
	135	135	140	140	140	140	140
	110	110	110	110	110	110	110
	130	130	130	130	130	130	130
	120	120	115	115	115	110	110
means	127	128	129	132	128	132	131
standard error	±4	±4	±6	±7	±5	±9	±7
Skin Small Vein Pressure (mm Hg)	7	7	30	32	27	33	35
	5	5	23	18	23	23	18
	9	9	15	20	30	16	10
	11	10	37	25	19	25	25

Table A13.--Continued.

Time (minutes)	Control		Infusion Period				
	-5	0	5	15	30	45	60
	12	12	14	20	25	27	32
	13	13	22	25	25	25	23
means	10	9	24*	23*	25*	25*	24*
standard error	±1	±1	±4	±2	±2	±2	±4
Cephalic Vein Pressure (mm Hg)	1	1	1	2	2	1	1
	5	5	0	0	0	0	0
	4	4	2	0	0	2	4
	9	9	5	5	5	5	5
	7	7	0	4	1	2	0
	7	7	2	2	2	2	2
means	6	6	2*	2*	2*	2*	2*
standard error	±1	±1	±1	±1	±1	±1	±1
Brachial Vein Pressure (mm Hg)	12	12	21	24	20	20	23
	10	10	20	20	20	22	25
	4	4	10	9	10	12	15
	3	3	12	10	10	15	17
	11	11	15	13	5	5	5
	5	5	10	10	10	10	9
means	8	8	15*	14*	13*	14*	16*
standard error	±2	±2	±2	±3	±3	±3	±3

Table A13.--Continued.

Time (minutes)	Control		Infusion Period				
	-5	0	5	15	30	45	60
Cephalic Flow	11	11	2	7	11	8	3
(ml/min/100 grams)	9	9	8	7	4	2	2
	23	23	2	2	2	2	2
	12	12	2	2	2	2	2
	25	25	6	17	8	5	2
	12	12	4	4	4	3	3
means	15	15	4*	7*	5*	4*	2*
standard error	±3	±3	±1	±2	±2	±1	±.2
Brachial Flow	4	4	3	4	4	4	5
(ml/min/100 grams)	5	5	4	3	3	2	2
	5	5	1	2	3	2	2
	5	5	2	2	1	1	2
	16	16	3	15	5	6	3
	9	9	4	6	4	4	4
means	7	7	3*	5	3*	3*	3*
standard error	±2	±2	±1	±2	±1	±1	±1
Total Skin Resistance	12	12	72	20	13	17	46
(mm Hg x min x ml^{-1} x 100 g^{-1})	14	14	17	21	33	83	78
	6	6	69	70	70	69	68
	8	8	53	53	53	53	53
	5	5	22	7	16	26	65
	9	9	28	28	28	36	36
means	9	9	44*	33†	36*	47*	58*
standard error	±1	±1	±10	±10	±9	±11	±6

Table A13.--Continued.

Time (minutes)	Control		Infusion Period				
	-5	0	5	15	30	45	60
Total Muscle Resistance ($mm\ Hg \times min \times ml^{-1} \times 100\ g^{-1}$)	31	31	41	30	30	30	23
	24	24	29	43	37	72	65
	26	26	130	66	43	64	63
	21	21	49	50	100	95	47
	7	7	38	8	25	21	42
	13	13	26	18	26	25	25
means	20	20	52*	36	44†	51*	44†
standard error	±4	±4	±16	±9	±12	±12	±7

* = $p \leq 0.01$ relative to control.

† = $p \leq 0.05$ relative to control.

Table A14.--Effects of histamine plus norepinephrine (4 μg base/minute, of each) infused simultaneously intra-arterially into forelimbs perfused at constant inflow on weight, vascular pressures, blood flows, and vascular resistances.

Time (minutes)	Control		Infusion Period				
	-5	0	5	15	30	45	60
Change in Weight (grams)	0	0	0	8	12	17	18
	0	1	0	2	5	7	9
	0	1	4	9	14	16	17
	0	0	4	9	15	17	19
	0	0	0	8	11	14	17
	0	0	0	6	9	11	12
means	0	.3	1	7*	11*	14*	15*
standard error	±0	±.2	±1	±1	±2	±2	±2
Systemic Arterial Blood Pressure (mm Hg)	145	145	170	155	160	155	155
	110	109	145	165	150	150	153
	100	98	150	150	130	100	100
	139	140	175	135	130	112	112
	140	140	150	150	150	150	155
	106	105	125	125	115	110	120
means	123	123	153*	147*	139†	130	133
standard error	±8	±9	±7	±6	±7	±10	±10
Perfusion Pressure (mm Hg)	125	127	110	200	215	225	225
	120	123	200	175	210	200	150
	82	80	185	150	175	185	198
	122	120	200	150	160	175	175

Table A14.--Continued.

Time (minutes)	Control		Infusion Period				
	-5	0	5	15	30	45	60
	126	125	195	155	150	150	155
	75	75	175	125	150	155	155
means	109	108	194*	159*	177*	182*	176*
standard error	±10	±10	±5	±10	±12	±12	±12
Skin Small Vein Pressure	14	13	35	27	27	21	17
(mm Hg)	16	17	28	27	29	27	27
	15	17	42	24	24	23	23
	11	10	40	35	37	30	15
	11	11	20	20	22	20	25
	11	11	40	25	25	22	19
means	13	13	34*	26*	27*	24*	21*
standard error	±1	±1	±4	±2	±2	±2	±2
Cephalic Vein Pressure	11	12	26	17	15	17	17
(mm Hg)	0	0	5	5	4	4	4
	4	5	9	7	7	5	5
	7	6	35	30	27	18	9
	5	5	4	5	7	4	5
	5	5	3	6	6	4	3
means	5	6	14*	12†	11	9	7
standard error	±2	±2	±6	±4	±4	±3	±2

Table A14.--Continued.

Time (minutes)	Control		Infusion Period				
	-5	0	5	15	30	45	60
Brachial Vein Pressure (mm Hg)	7	7	25	12	10	11	11
	7	7	20	17	15	14	15
	7	7	15	12	15	17	12
	7	6	9	5	9	12	15
	7	7	10	8	7	7	7
	5	5	9	5	3	3	3
means	7	7	15*	10	10	11†	11†
standard error	±.3	±.3	±3	±2	±2	±2	±2
Cephalic Flow (ml/min/100 grams)	18	18	13	18	20	20	20
	9	19	5	6	5	5	5
	17	16	13	17	17	12	12
	7	7	6	7	7	6	7
	19	19	16	18	18	18	18
	15	15	12	15	15	14	12
means	14	14	11*	14	14	13	12*
standard error	±2	±2	±2	±3	±3	±3	±2
Brachial Flow (ml/min/100 grams)	17	17	16	17	16	16	15
	9	10	10	10	10	14	15
	8	8	12	10	12	13	13
	9	9	13	9	7	7	7
	6	6	8	6	6	6	6
	5	5	8	5	5	10	10
means	9	9	11	10	9	11	11
standard error	±2	±2	±1	±2	±2	±2	±2

Table A14.--Continued.

Time (minutes)	Control		Infusion Period				
	-5	0	5	15	30	45	60
Total Skin Resistance (mm Hg x min x ml^{-1} x 100 g^{-1})	6	6	14	10	10	10	10
	14	14	39	28	41	39	29
	5	5	14	8	10	15	16
	16	16	28	17	19	26	24
	6	6	12	8	8	8	8
	5	5	14	8	10	11	13
means	9	9	20*	13	16*	18*	17*
standard error	±2	±2	±5	±3	±5	±5	±3
Total Muscle Resistance (mm Hg x min x ml^{-1} x 100 g^{-1})	7	7	12	11	13	13	14
	13	12	18	16	20	13	9
	9	9	14	14	13	13	14
	13	13	15	16	22	23	23
	20	20	23	25	24	24	25
	14	14	21	24	29	25	15
means	13	13	17†	18*	20*	19*	17†
standard error	±2	±2	±2	±2	±3	±3	±3

* = $p \leq 0.01$ relative to control.

† = $p \leq 0.05$ relative to control.

Table A15.--Effects of 4 μg histamine base/minute infused intra-arterially into naturally perfused forelimbs for 60 minutes on lymph flow, protein concentration of lymph and plasma, vascular pressures and hematocrit.

Time (minutes)	Control		Infusion Period					
	-10	0	10	20	30	40	50	60
Systemic Arterial Blood Pressure (mm Hg)	105	105	95	90	85	85	82	81
	125	119	110	107	105	108	105	108
	120	120	125	125	125	125	130	130
	135	135	130	130	132	135	135	133
	120	120	115	115	115	115	115	115
	115	115	116	123	121	116	117	113
means	120	119	115	115	114	114	114	113
standard error	±4	±4	±5	±6	±7	±7	±8	±8
Skin Small Vein Pressure (mm Hg)	19	19	24	22	18	21	21	20
	12	12	27	27	27	27	27	27
	12	12	25	25	25	25	27	28
	9	8	29	23	29	30	25	22
	14	18	30	30	31	32	32	31
	18	18	23	23	23	23	22	22
means	14	15	26*	25*	26*	26*	26*	25*
standard error	±2	±2	±1	±1	±2	±2	±2	±2
Lymph Flow Rate (ml/10 min)	.01	.01	.05	.29	.23	.13	.18	.23
	.01	.01	.09	.09	.40	.37	.32	.37
	.01	.01	.26	.27	.23	.15	.11	.08
	.02	.02	.07	.17	.45	.48	.59	.66

Table A15.--Continued.

Time (minutes)	Control		Infusion Period					
	-10	0	10	20	30	40	50	60
	.01	.01	.30	.37	.30	.16	.12	.11
	.02	.02	.51	.54	.64	.51	.52	.47
means	.01	.01	.21†	.29*	.38*	.30*	.31*	.32*
standard error	±.01	±.01	±.07	±.06	±.06	±.07	±.08	±.09
Lymph Total Protein (grams %)	1.9	2.1	3.0	2.8	3.8	2.8	3.3	3.3
	2.4	2.3	5.0	6.4	6.4	5.7	4.9	4.9
	3.3	3.3	4.1	5.8	5.2	5.2	5.2	5.2
	3.5	3.5	5.2	5.2	5.0	5.1	4.9	4.0
	1.9	2.2	2.3	2.3	2.3	2.3	2.3	2.3
	3.4	3.6	5.6	5.3	4.9	4.1	3.6	3.6
means	2.7	2.8	4.2*	4.6*	4.6*	4.2*	4.0*	3.9*
standard error	±.3	±.3	±.5	±.7	±.6	±.6	±.5	±.4
Plasma Protein (grams %)		6.4						
		5.5						
		5.5						
		6.8						
		5.3						
		6.0						
means		5.9						
standard error		±.2						

* = $p \leq 0.01$ relative to control.

† = $p \leq 0.05$ relative to control.

Table A16.--Effects of simultaneous intra-arterial infusions of histamine and norepinephrine, 4 µg base/minute of each, into naturally perfused forelimbs for 60 minutes on lymph flow, protein concentration of lymph and plasma, vascular pressures and hematocrit.

Time (minutes)	Control		Infusion Period					
	-10	0	10	20	30	40	50	60
Systemic Arterial Blood Pressure (mm Hg)	97	93	105	105	110	105	110	120
	100	100	120	120	125	120	120	130
	115	120	123	123	120	120	120	125
	120	110	128	125	115	100	80	80
	115	110	130	125	125	125	125	125
	115	115	135	130	130	130	130	135
means	110	108	124	121	121	117	114	119
standard error	±4	±4	±4	±4	±3	±5	±7	±8
Skin Small Vein Pressure (mm Hg)	8	8	23	20	22	18	17	20
	12	11	43	40	38	35	35	36
	12	12	27	33	32	30	30	30
	10	9	30	25	17	17	14	9
	11	9	31	30	30	28	29	28
	12	12	41	42	43	44	46	46
means	11	10	33*	32*	30*	29*	29*	28*
standard error	±1	±1	±3	±4	±4	±4	±5	±5
Lymph Flow Rate (ml/10 min)	.01	.01	.02	.02	.01	.03	.01	.01
	.01	.01	.01	.01	.01	.01	.01	.01
	.02	.01	.07	.12	.16	.16	.13	.14
	.02	.02	.02	.01	.01	.01	.01	.02

Table A16.--Continued.

Time (minutes)	Control		Infusion Period					
	-10	9	10	20	30	40	50	60
	.01	.01	.01	.02	.02	.03	.01	.01
	.02	.02	.03	.01	.01	.02	.01	.01
means	.02	.01	.03	.03	.04	.04	.03	.03
standard error	±.002	±.002	±.01	±.02	±.02	±.02	±.02	±.02
Lymph Total Protein	4.2	4.7	4.5	4.4	4.2	4.7	4.6	4.6
(grams %)	2.8	3.5	3.6	3.6	2.8	2.9	3.2	3.2
	2.0	2.1	2.2	2.8	3.2	3.2	3.2	3.0
	2.1	2.3	2.3	2.3	2.4	2.4	2.4	2.4
	3.6	3.8	4.3	4.3	3.6	3.7	3.1	2.8
means	2.9	3.3	3.4	3.5	3.2	3.4	3.3	3.2
standard error	±.4	±.5	±.5	±.4	±.3	±.4	±.4	±.4
Plasma Protein		6.9			6.9			7.1
(grams %)		6.4			6.3			6.0
		5.3			5.3			5.4
		6.0			5.6			5.6
		6.6			6.5			6.5
means		6.2			6.1			6.1
standard error		±.3			±.3			±.3
Hematocrit		33			33			34
		39			41			41
		28			27			28

Table A16.--Continued.

Time (minutes)	Control		Infusion Period					
	-10	0	10	20	30	40	50	60
		42			47			48
		37			41			40
		38			39			40
means		36			38†			39*
standard error		±2			±3			±3

* = $p \leq 0.01$ relative to control.

† = $p \leq 0.05$ relative to control.

Table A17.--Effects of 4 μg histamine base/minute infused intra-arterially into forelimbs perfused at constant inflow for 60 minutes on lymph flow, protein concentration of lymph and plasma, vascular pressures and hematocrit.

Time (minutes)	Control		Infusion Period					
	-10	0	10	20	30	40	50	60
Systemic Arterial Blood Pressure (mm Hg)	137	140	135	135	135	136	133	133
	127	130	125	125	125	130	130	133
	115	112	115	117	115	113	115	115
	113	113	101	115	117	115	115	112
	100	105	101	105	105	110	110	112
	115	115	120	125	125	127	130	120
means	118	119	116	120	120	122	122	121
standard error	±5	±5	±6	±4	±4	±4	±4	±4
Perfusion Pressure (mm Hg)	127	135	65	65	65	65	63	63
	120	130	63	63	60	63	63	60
	100	97	90	87	90	90	87	87
	113	120	68	70	70	70	70	70
	100	105	52	62	70	70	73	65
	112	112	50	55	60	62	64	70
means	112	117	65*	67*	69*	70*	70*	69*
standard error	±4	±6	±6	±5	±5	±4	±4	±4
Skin Small Vein Pressure (mm Hg)	10	10	13	13	13	13	12	11
	13	12	10	11	12	12	12	12
	11	11	11	11	11	11	12	12
	7	7	6	8	8	8	8	8

Table A17.--Continued.

Time (minutes)	Control		Infusion Period					
	-10	0	10	20	30	40	50	60
	14	13	12	12	13	14	14	15
	7	7	8	10	10	10	10	9
means	10	10	10	11	11	11	11	11
standard error	±1	±1	±1	±1	±1	±1	±1	±1
Lymph Flow Rate	.02	.02	.02	.06	.06	.11	.19	.18
(ml/10 min)	.02	.02	.10	.23	.23	.22	.21	.20
	.02	.02	.02	.03	.03	.04	.05	.07
	.01	.01	.01	.03	.16	.14	.13	.12
	.03	.03	.24	.33	.30	.32	.32	.30
	.02	.02	.18	.31	.29	.25	.25	.25
means	.02	.02	.10†	.17*	.18*	.18*	.19*	.19*
standard error	±.003	±.003	±.04	±.06	±.05	±.04	±.04	±.03
Lymph Total Protein	3.4	3.6	3.6	4.1	4.6	5.0	5.6	6.7
(grams %)	2.3	2.2	3.3	4.0	4.5	5.0	4.3	5.1
	2.7	2.7	2.8	3.0	2.9	2.9	3.3	3.7
	2.3	2.3	2.3	2.6	3.8	4.0	4.3	4.0
	1.5	1.5	2.9	3.4	3.4	3.9	4.4	4.1
	2.3	2.5	3.7	4.0	3.9	4.2	4.1	4.3
means	2.4	2.5	3.1*	3.5*	3.9*	4.2*	4.3*	4.7*
standard error	±.3	±.3	±.2	±.3	±.3	±.3	±.3	±.5

Table A17.--Continued.

Time (minutes)	Control		Infusion Period					
	-10	0	10	20	30	40	50	60
Plasma Protein (grams %)		6.5			6.0			6.1
		6.0			6.1			5.6
		5.9			6.0			6.0
		5.1			5.2			5.3
		4.8			4.9			5.2
		5.0			4.5			4.7
means		5.6			5.5			5.5
standard error		±.3			±.3			±.2
Hematocrit		36			37			36
		32			33			33
		30			29			29
		35			36			36
		24			25			26
		37			39			40
means		32			33			33
standard error		±2			±2			±2

* = $p \leq 0.01$ relative to control.

† = $p \leq 0.05$ relative to control.

Table A18.--Effects of simultaneous intra-arterial infusions of histamine and norepinephrine, 4 μg base/minute of each, into forelimbs perfused at constant inflow for 60 minutes on lymph flow, protein concentration of lymph and plasma, vascular pressures and hematocrit.

	Control		Infusion Period					
Time (minutes)	-10	0	10	20	30	40	50	60
Systemic Arterial Blood Pressure (mm Hg)	100	105	145	130	130	125	120	120
	110	117	133	135	140	140	140	135
	140	137	177	175	172	170	165	162
	110	110	130	125	122	120	120	120
	107	107	122	122	122	115	112	112
	120	120	132	125	127	137	132	130
means	115	116	140*	135*	136*	135*	132*	130*
standard error	±6	±5	±8	±8	±8	±8	±8	±7
Perfusion Pressure (mm Hg)	90	90	150	150	170	175	185	185
	110	115	205	205	205	215	215	215
	130	135	165	165	172	175	175	175
	112	115	137	132	130	155	167	167
	100	100	170	165	170	165	165	170
	115	115	180	170	175	180	190	190
means	110	112	168*	165*	170*	178*	183*	184*
standard error	±6	±6	±10	±10	±10	±8	±8	±7
Skin Small Vein Pressure (mm Hg)	11	10	27	26	27	27	27	26
	11	11	35	37	40	42	40	37
	16	14	33	35	34	34	33	33
	8	8	31	32	29	30	28	26

Table A18.--Continued.

Time (minutes)	Control		Infusion Period					
	-10	0	10	20	30	40	50	60
	6	5	29	26	27	26	26	25
	7	8	38	28	30	33	32	35
means	10	9	32*	31*	31*	32*	31*	30*
standard error	±2	±1	±2	±2	±2	±2	±2	±2
Lymph Flow Rate	.02	.03	.03	.01	.01	.01	.01	.01
(ml/10 min)	.01	.02	.03	.01	.01	.01	.01	.01
	.01	.01	.07	.11	.11	.08	.06	.05
	.01	.01	.03	.05	.04	.03	.03	.02
	.03	.03	.15	.23	.15	.09	.06	.06
	.02	.01	.02	.01	.01	.01	.01	.01
means	.02	.02	.06†	.07*	.06†	.04	.03	.03
standard error	±.003	±.004	±.02	±.04	±.02	±.02	±.01	±.01
Lymph Total Protein	3.6	4.1	4.0	4.3	4.0	4.2	4.1	4.3
(grams %)	3.7	4.0	4.0	3.6	3.8	3.6	3.7	3.5
	4.3	4.2	3.7	4.1	4.1	3.3	3.5	3.2
	3.4	3.1	2.9	3.2	3.2	3.2	3.3	3.2
	4.5	4.7	5.5	5.7	5.8	5.6	5.6	5.6
	4.0	3.9	4.0	4.0	4.4	4.4	4.5	4.2
means	3.9	4.0	4.0	4.2	4.2	4.1	4.1	4.0
standard error	±.2	±.2	±.3	±.3	±.4	±.4	±.3	±.4

Table A18.--Continued.

Time (minutes)	Control		Infusion Period					
	-10	0	10	20	30	40	50	60
Plasma Protein (grams %)		6.1			6.2			6.4
		6.4			6.7			6.9
		5.7			6.3			6.0
		5.3			5.5			5.6
		6.9			6.8			6.7
		6.9			7.2			6.5
means		6.2			6.5			6.4
standard error		±.3			±.2			±.2
Hematocrit		35			39			40
		40			45			45
		32			38			39
		29			34			34
		31			36			36
		33			37			39
means		33			38*			39*
standard error		±2			±2			±2

* = $p \leq 0.01$ relative to control.

† = $p \leq 0.05$ relative to control.

Table A19.--Effects of 4 μg norepinephrine base/minute infused intra-arterially into forelimbs perfused at constant inflow for 60 minutes on lymph flow, protein concentration of lymph and plasma, vascular pressures and hematocrit.

Time (minutes)	Control		Infusion Period					
	-10	0	10	20	30	40	50	60
Systemic Arterial Blood Pressure (mm Hg)	125	125	175	180	170	175	170	165
	110	117	157	150	145	142	142	140
	125	120	140	140	140	140	143	140
	115	115	157	140	127	120	120	124
	122	125	150	150	155	155	160	160
	115	115	140	135	132	135	130	130
means	119	120	153*	149*	145*	145*	144*	143*
standard error	±3	±2	±5	±7	±6	±8	±8	±7
Perfusion Pressure (mm Hg)	115	117	215	215	215	230	240	240
	105	105	200	190	200	215	210	215
	120	115	200	200	200	203	207	207
	107	110	250	215	210	210	220	220
	112	120	195	205	210	225	225	230
	120	110	190	190	215	215	215	215
means	113	113	208*	203*	208*	216*	220*	221*
standard error	±3	±2	±9	±5	±3	±4	±5	±5
Skin Small Vein Pressure (mm Hg)	15	16	23	22	22	23	17	17
	14	14	25	23	22	22	23	25
	10	9	28	26	26	26	26	26
	11	10	29	25	27	32	35	26

Table A19.--Continued.

Time (minutes)	Control		Infusion Period					
	-10	0	10	20	30	40	50	60
	12	11	12	13	13	13	14	15
	9	8	20	18	18	18	19	19
means	12	11	23*	21*	21*	22*	22*	21*
standard error	±1	±1	±3	±2	±2	±3	±3	±2
Lymph Flow Rate	.01	.01	.02	.01	.01	.01	.03	.03
(ml/10 min)	.01	.01	.02	.01	.01	.01	.03	.01
	.01	.01	.01	.01	.01	.02	.02	.03
	.02	.02	.04	.01	.03	.05	.03	.02
	.02	.02	.01	.02	.01	.01	.01	.01
	.04	.05	.05	.03	.07	.04	.05	.03
means	.02	.02	.03	.02	.02	.02	.03	.02
standard error	±.01	±.01	±.01	±.003	±.01	±.01	±.01	±.004
Lymph Total Protein	1.9	2.0	2.4	2.3	1.9	1.8	1.8	1.6
(grams %)	2.2	2.2	2.0	2.0	2.0	1.9	2.0	1.9
	1.8	2.1	2.4	1.9	1.7	1.5	1.6	1.4
	2.4	2.7	3.3	3.6	2.6	2.3	2.2	2.1
	2.8	2.6	2.2	2.2	2.4	2.0	2.1	2.0
means	2.2	2.3	2.5	2.4	2.1	1.9†	1.9†	1.8*
standard error	±.1	±.1	±.2	±.3	±.2	±.1	±.1	±.1
Plasma Protein		5.0			5.5			5.6
(grams %)		4.9			5.3			5.3
		5.7			5.3			5.7

Table A19.--Continued.

Time (minutes)	Control		Infusion Period					
	-10	0	10	20	30	40	50	60
		5.3			5.0			5.7
		4.7			5.5			5.6
		5.7			6.1			5.5
means		5.2			5.5			5.6
standard error		±.2			±.2			±.1
Hematocrit		41			48			50
		40			44			45
		35			37			48
		34			38			38
		41			43			43
		40			43			45
means		39			42†			45*
standard error		±1			±2			±2

* = $p \leq 0.01$ relative to control.

† = $p \leq 0.05$ relative to control.

Table A20.--Effects of 64 µg histamine base/minute infused intra-arterially into naturally perfused forelimbs for 60 minutes on lymph flow, protein concentration of lymph and plasma, vascular pressures and hematocrit.

Time (minutes)	Control		Infusion Period					
	-10	0	10	20	30	40	50	60
Systemic Arterial Blood Pressure (mm Hg)	115	115	75	67	65	70	75	75
	120	120	97	83	75	73	73	80
	127	127	47	50	55	60	60	63
	120	123	85	85	90	90	95	93
	113	113	87	80	70	71	71	74
	125	123	107	107	103	105	103	101
	107	107	75	75	70	75	75	70
means	118	118	82*	78*	75*	78*	79*	79*
standard error	±3	±3	±7	±7	±6	±6	±6	±5
Skin Small Vein Pressure (mm Hg)	12	12	21	19	18	17	17	18
	15	15	45	53	47	41	36	34
	11	10	11	12	12	11	11	12
	14	13	17	21	20	20	20	20
	11	11	20	19	18	19	19	19
	15	14	49	34	32	32	31	31
	13	13	14	15	14	18	17	18
means	13	13	25*	25*	23*	23*	22*	22*
standard error	±1	±1	±6	±5	±5	±4	±3	±3
Lymph Flow Rate (ml/10 min)	.02	.02	.90	1.04	.82	.73	.56	.50
	.02	.02	1.31	2.79	1.92	.83	.36	.22
	.02	.02	.59	.62	.43	.39	.31	.29
	.04	.04	.41	.50	.42	.28	.22	.16

Table A20.--Continued.

Time (minutes)	Control		Infusion Period					
	-10	0	10	20	30	40	50	60
	.02	.02	.60	.64	.46	.49	.46	.42
	.02	.02	.04	.13	.12	.07	.14	.13
	.02	.02	.59	.59	.40	.28	.27	.22
means	.02	.02	.63*	.90*	.65*	.44*	.33*	.28*
standard error	±.003	±.003	±.15	±.33	±.23	±.10	±.05	±.05
Lymph Total Protein (grams %)	2.8	3.0	4.1	4.1	3.9	3.9	3.7	4.0
	2.9	3.3	4.5	4.7	4.6	4.7	4.7	4.8
	2.9	3.1	3.5	3.6	3.9	3.7	3.8	3.4
	2.3	2.1	3.3	3.9	4.5	4.5	4.5	4.0
	1.7	2.4	4.6	4.6	4.8	4.7	4.4	4.5
	4.0	4.0	5.5	5.9	5.4	5.4	5.5	5.5
	2.8	3.0	5.2	5.5	5.3	5.2	5.3	4.7
means	2.8	3.0	4.4*	4.6*	4.6*	4.6*	4.6*	4.4*
standard error	±.3	±.2	±.3	±.3	±.2	±.2	±.3	±.3
Plasma Protein (grams %)		4.2						
		4.2						
		5.8						
		4.1						
		4.2						
		4.4						
		6.4						
means		4.8						
standard error		±.4						

* = $p \leq 0.01$ relative to control.

† = $p \leq 0.05$ relative to control.

Table A21.--Effects of 64 µg histamine base/minute and 4 µg norepinephrine base/minute infused simultaneously intra-arterially into naturally perfused forelimbs for 60 minutes on lymph flow, protein concentration of lymph and plasma, vascular pressures and hematocrit.

	Control		Infusion Period					
Time (minutes)	-10	0	10	20	30	40	50	60
Systemic Arterial Pressure	120	120	60	55	50	55	55	55
(mm Hg)	107	107	105	110	120	120	120	115
	115	110	45	30	40	40	45	45
	120	120	35	30	40	35	45	45
	115	115	85	110	105	100	100	95
	100	100	57	45	47	50	55	57
	110	105	50	35	35	30	30	35
means	112	111	62*	59*	62*	61*	64*	64*
standard error	±3	±3	±9	±14	±13	±13	±12	±11
Skin Small Vein Pressure	8	8	20	13	8	14	14	14
(mm Hg)	10	10	18	13	21	21	19	15
	9	9	17	9	6	8	10	7
	8	8	15	12	11	9	10	12
	12	11	22	13	16	15	19	20
	7	7	19	14	18	19	22	22
	8	7	24	13	10	9	9	10
means	9	9	19*	12	13†	14*	15*	14*
standard error	±1	±1	±1	±1	±2	±2	±2	±2
Lymph Flow Rate	.01	.01	.03	.04	.02	.02	.02	.01
(ml/10 min)	.02	.02	.08	.01	.09	.09	.08	.07
	.02	.02	.01	.02	.01	.09	.03	.03

Table A21.--Continued.

Time (minutes)	Control		Infusion Period					
	-10	0	10	20	30	40	50	60
	.01	.01	.10	.13	.06	.02	.02	.03
	.02	.02	.27	.24	.07	.06	.09	.08
	.01	.01	.02	.01	.01	.01	.03	.04
	.01	.01	.05	.01	.01	.01	.02	.01
means	.01	.01	.08	.07	.04	.04	.04	.04
standard error	±.002	±.002	±.03	±.03	±.01	±.01	±.01	±.01
Lymph Total Protein	3.8	4.5	5.0	5.4	4.8	5.2	5.1	4.9
(grams %)	3.3	3.0	3.3	3.3	3.5	3.4	3.4	3.2
	4.7	5.0	5.2	5.5	5.6	5.7	5.8	5.8
	4.6	4.7	5.3	6.0	6.5	6.8	6.9	6.8
	1.9	2.3	3.1	2.5	2.1	2.4	2.7	3.1
	3.0	2.8	3.3	3.7	3.7	3.7	3.7	3.7
	4.0	4.0	3.9	3.8	3.7	4.1	4.4	4.2
means	3.6	3.8	4.2†	4.3†	4.3†	4.5*	4.6*	4.5*
standard error	±.4	±.4	±.4	±.5	±.6	±.6	±.6	±.5
Plasma Protein		7.3			7.3			7.1
(grams %)		5.4			5.4			4.7
		7.8			7.7			7.5
		9.3			9.5			9.5
		6.0			6.0			6.1
		6.1			6.4			6.4
		5.5			5.2			5.3
means		6.8			6.8			6.7
standard error		±.5			±.6			±.6

Table A21.--Continued.

Time (minutes)	Control		Infusion Period					
	-10	0	10	20	30	40	50	60
Hematocrit		38			43			45
		27			30			31
		39			49			55
		40			50			58
		32			42			45
		37			42			46
		35			40			47
means		35			42*			47*
standard error		±2			±3			±3

* = $p \leq 0.01$ relative to control.

† = $p \leq 0.05$ relative to control.

Table A22.--Effects of 64 μg histamine base/minute infused intra-arterially into forelimbs perfused at constant inflow for 60 minutes on lymph flow, protein concentration of lymph and plasma, vascular pressures and hematocrit.

Time (minutes)	Control		Infusion Period					
	-10	0	10	20	30	40	50	60
Systemic Arterial Blood Pressure (mm Hg)	120	122	75	87	105	130	140	140
	103	105	77	55	57	65	65	65
	115	110	75	60	55	55	60	55
	110	115	100	97	83	86	90	95
	125	125	102	95	100	95	85	95
	137	137	125	122	105	90	83	85
means	118	119	92*	86*	84*	87*	87*	89*
standard error	±5	±5	±8	±10	±10	±11	±12	±12
Perfusion Pressure (mm Hg)	115	110	65	100	100	100	105	100
	97	95	70	70	72	82	90	85
	100	102	70	75	70	65	67	62
	105	110	92	110	99	107	107	110
	117	120	120	125	115	95	87	83
	115	115	50	60	60	57	55	55
means	108	109	78*	90†	86*	84*	85*	83*
standard error	±4	±4	±10	±10	±9	±8	±8	±9
Skin Small Vein Pressure (mm Hg)	12	12	10	10	12	14	13	14
	11	11	13	12	12	11	10	10
	11	10	11	8	8	9	9	10
	10	10	11	12	10	9	8	8

Table A22.--Continued.

Time (minutes)	Control		Infusion Period					
	-10	0	10	20	30	40	50	60
	12	11	17	15	15	11	11	11
	7	7	8	8	7	7	8	7
means	11	10	12	11	11	10	10	10
standard error	±1	±1	±1	±1	±1	±1	±1	±1
Lymph Flow Rate	.01	.01	.04	.22	.21	.20	.17	.15
(ml/10 min)	.01	.01	.28	.54	.43	.37	.32	.29
	.02	.02	.22	.42	.36	.29	.32	.25
	.01	.01	.17	.38	.23	.20	.11	.08
	.01	.01	.31	.55	.44	.27	.22	.22
	.02	.02	.09	.38	.36	.31	.25	.21
means	.01	.01	.19*	.42*	.34*	.27*	.23*	.20*
standard error	±.002	±.002	±.04	±.05	±.04	±.03	±.03	±.03
Lymph Total Protein	1.8	2.1	2.4	3.8	4.6	5.1	5.0	4.5
(grams %)	2.9	2.9	4.9	5.1	5.4	5.0	5.2	5.2
	1.0	1.1	2.5	4.5	3.8	3.8	3.7	3.8
	2.0	2.1	4.1	5.3	5.2	4.4	4.9	5.1
	1.6	1.8	3.5	4.8	4.8	4.6	4.8	4.9
	2.5	2.5	2.9	5.2	5.5	4.8	4.7	5.0
means	2.0	2.1	3.4*	4.8*	4.9*	4.6*	4.7*	4.8*
standard error	±.3	±.3	±.4	±.2	±.3	±.2	±.2	±.2

Table A22.--Continued.

Time (minutes)	Control		Infusion Period					
	-10	0	10	20	30	40	50	60
Plasma Protein (grams %)		5.7			5.5			5.4
		5.5			5.4			5.1
		4.7			4.4			4.4
		5.4			5.5			5.3
		5.3			5.6			5.3
		5.5			5.9			5.2
means		5.4			5.4			5.1*
standard error		±.1			±.2			±.2
Hematocrit		38			43			47
		38			45			47
		28			33			34
		40			42			45
		32			36			36
		38			47			47
means		36			41*			43*
standard error		±2			±2			±3

* = $p \leq 0.01$ relative to control.

† = $p \leq 0.05$ relative to control.

Table A23.--Effects of 64 μg histamine base/minute and 4 μg norepinephrine base/minute infused simultaneously intra-arterially into forelimbs perfused at constant inflow for 60 minutes on lymph flow, protein concentration of lymph and plasma, vascular pressures and hematocrits.

Time (minutes)	Control		Infusion Period					
	-10	0	10	20	30	40	50	60
Systemic Arterial Blood Pressure (mm Hg)	105	105	105	100	95	97	95	90
	105	105	85	75	72	70	75	72
	85	85	70	67	77	82	85	85
	130	130	100	95	80	67	55	52
	100	100	72	85	95	102	102	102
	95	97	82	97	95	92	95	95
means	103	104	86†	87†	86†	85†	85†	83†
standard error	±6	±6	±6	±5	±4	±6	±7	±7
Perfusion Pressure (mm Hg)	95	95	115	125	140	135	140	137
	92	92	90	92	100	107	115	112
	80	80	112	135	150	155	160	165
	120	120	105	130	140	150	145	115
	90	90	80	80	102	112	115	115
	85	87	105	120	137	150	167	165
means	94	94	101	114†	128*	135*	140*	135*
standard error	±6	±6	±6	±9	±9	±9	±9	±10
Skin Small Vein Pressure (mm Hg)	14	13	50	39	37	36	36	36
	8	8	35	24	21	20	20	20
	7	7	41	34	26	26	23	25
	7	7	37	23	23	23	22	18

Table A23.--Continued.

Time (minutes)	Control		Infusion Period					
	-10	0	10	20	30	40	50	60
	11	11	46	40	41	41	40	39
	9	9	49	40	44	47	50	50
means	9	9	43*	33*	32*	32*	32*	31*
standard error	±1	±1	±3	±3	±4	±4	±5	±5
Lymph Flow Rate	.06	.04	.69	.87	.48	.47	.26	.24
(ml/10 min)	.04	.04	.57	.98	.71	.53	.39	.29
	.04	.04	.82	.92	.59	.46	.43	.39
	.02	.02	.30	.25	.13	.16	.11	.10
	.03	.03	1.36	1.24	.88	.70	.69	.51
	.03	.04	.28	.38	.26	.25	.23	.21
means	.04	.04	.67*	.77*	.51*	.43*	.35*	.29*
standard error	±.01	±.01	±.16	±.16	±.11	±.08	±.08	±.06
Lymph Total Protein	3.9	3.8	4.2	4.9	4.8	4.8	4.5	4.3
(grams %)	4.3	4.4	5.0	6.2	6.0	5.8	5.6	5.5
	2.2	2.5	3.7	4.5	4.4	4.1	3.3	3.3
	2.4	2.4	3.9	4.1	3.9	4.0	3.8	3.6
	2.7	2.7	4.0	4.5	3.7	3.4	3.1	2.7
	3.7	3.7	4.6	4.6	4.0	4.2	3.6	3.4
means	3.2	3 3	4.2*	4.8*	4.5*	4.4*	4.0*	3.8†
standard error	±.4	±.3	±.2	±.3	±.3	±.3	±.4	±.4

Table A23.--Continued.

Time (minutes)	Control		Infusion Period					
	-10	0	10	20	30	40	50	60
Plasma Protein (grams %)		6.6			6.9			6.7
		6.9			7.0			6.9
		5.2			5.4			4.6
		5.2			5.4			4.8
		5.3			5.2			6.3
		6.0			6.3			5.9
means		5.9			6.0			5.9
standard error		±.3			±.3			±.4
Hematocrit		31			39			40
		23			29			30
		31			41			43
		40			46			45
		37			46			49
		38			49			52
means		33			42*			43*
standard error		±3			±3			±3

* = $p \leq 0.01$ relative to control.

† = $p \leq 0.05$ relative to control.

Table A24.--Effects of 64 µg histamine base/minute and 16 µg norepinephrine base/minute infused simultaneously intra-arterially into forelimbs perfused at constant inflow for 60 minutes on lymph flow, protein concentration of lymph and plasma, vascular pressures and hematocrit.

Time (minutes)	Control		Infusion Period					
	-10	0	10	20	30	40	50	60
Systemic Arterial Blood Pressure (mm Hg)	125	127	130	105	110	115	117	120
	97	100	135	105	115	125	130	130
	130	135	150	115	130	127	127	127
	135	137	145	150	150	150	155	152
	130	122	160	130	132	140	140	140
	100	100	102	110	115	112	110	110
	127	127	170	145	155	155	140	135
means	121	121	142*	123	130	132†	131†	131†
standard error	±6	±6	±8	±7	±7	±6	±6	±5
Perfusion Pressure (mm Hg)	115	117	165	175	205	230	240	245
	90	90	150	165	200	235	250	300
	105	100	120	117	135	152	170	180
	125	125	250	275	335	350	400	425
	125	120	210	215	240	260	265	270
	85	85	205	240	265	275	280	285
	125	130	230	270	305	310	310	320
means	110	110	190*	208*	241*	259*	274*	289*
standard error	±7	±7	±18	±22	±26	±24	±27	±28
Skin Small Vein Pressure (mm Hg)	6	6	64	43	42	43	44	46
	13	12	51	52	54	58	58	58
	12	11	48	49	53	52	54	53

Table A24.--Continued.

Time (minutes)	Control		Infusion Period					
	-10	0	10	20	30	40	50	60
	17	18	75	65	66	66	68	73
	11	12	40	37	36	37	38	39
	13	14	49	49	48	50	50	49
	11	11	55	52	50	50	48	52
means	12	12	55*	50*	50*	51*	51*	53*
standard error	±1	±1	±4	±3	±4	±4	±4	±4
Lymph Flow Rate (ml/10 min)	.02	.02	.12	.18	.10	.09	.07	.29
	.01	.01	.25	.25	.20	.21	.21	.19
	.02	.03	.14	.41	.30	.24	.21	.17
	.02	.02	.21	.11	.04	.03	.03	.03
	.08	.10	.94	.89	.70	.62	.55	.52
	.01	.01	.98	.93	.73	.63	.58	.57
	.02	.01	.14	.11	.06	.06	.06	.06
means	.03	.03	.40*	.41*	.30*	.27*	.24*	.26*
standard error	±.01	±.01	±.15	±.14	±.11	±.10	±.09	±.08
Lymph Total Protein (grams %)	2.5	2.8	2.8	3.1	3.3	3.0	3.0	3.0
	1.4	1.9	2.2	2.0	1.7	1.6	1.8	1.5
	3.4	3.5	5.2	5.1	5.2	4.1	3.9	3.3
	3.3	3.4	3.3	4.0	4.2	4.0	3.9	3.5
	2.5	2.6	3.4	4.1	4.0	3.7	3.4	3.1
	2.5	2.7	4.7	4.4	4.2	3.9	3.4	3.0
	3.2	2.8	3.9	3.5	3.1	3.0	3.9	2.6
means	2.7	2.8	3.6*	3.7*	3.7*	3.3†	3.3†	2.9
standard error	±.3	±.2	±.4	±.4	±.4	±.3	±.3	±.3

Table A24.--Continued.

Time (minutes)	Control		Infusion Period					
	-10	0	10	20	30	40	50	60
Plasma Protein (grams %)		4.4			4.2			4.5
		4.8			5.1			5.9
		5.8			6.1			6.1
		6.1			7.2			6.6
		5.8			6.0			6.4
		5.8			6.5			6.3
		5.7			5.3			5.6
means		5.5			5.8			5.9
standard error		±.2			±.4			±.3
Hematocrit		33			42			45
		27			36			37
		39			45			45
		44			59			60
		37			48			49
		29			39			39
		37			52			52
means		35			46*			47*
standard error		±2			±3			±3

* = $p \leq 0.01$ relative to control. † = $p \leq 0.05$ relative to control.

BIBLIOGRAPHY

BIBLIOGRAPHY

1. Appelgren, L. and D. H. Lewis. Capillary permeability-surface area product (PS) of Renkin in human skeletal muscle. Acta. Med. Scand. 184:281-282, 1968.

2. Baker, C. H. Epinephrine-induced vascular volume changes in dog forelimbs with controlled flow. Am. J. Physiol. 216: 368-372, 1969.

3. Bartholinus, T. Vasalymphatica nuper in animantibus inventa. Hafniae, 1653. Cited by E. Starling. In: Schafer Textbook of Physiology, Vol. I, Pentland, London, p. 286, 1898.

4. Best, C. H., H. H. Dale, H. W. Dudley, and W. V. Thorpe. The nature of the vasodilator constituents of certain tissue extracts. J. Physiol. (London) 62:397-417, 1927.

5. Burton, A. C. Physiology and Biophysics of the Circulation. Yearbook Medical Publishers, Chicago, 1965.

6. Carter, R. D., W. L. Joyner, and E. M. Renkin. Effects of histamine and some other substances on molecular selectivity of the capillary wall to plasma proteins and dextran. Microvas. Res. 7:31-48, 1974.

7. Clough, G., P. A. Fraser, and L. H. Smoje. Compliance measurement in single capillaries of the cat mesentery. J. Physiol. 240:9P, 1974.

8. Dale, H. H. and P. P. Laidlaw. The physiological action of β-imidazolylethylene. J. Physiol. (London) 41:318-344, 1910.

9. Daugherty, R. M., J. B. Scott, T. E. Emerson, and F. J. Haddy. Comparison of i.v. and i.a. infusion of vasoactive agents on dog forelimb blood flow. Am. J. Physiol. 214:611-619, 1968.

10. Dekanski, J. The effect of cutaneous burns on histamine in mice. J. Physiol. 104:151-160, 1945.

11. Deyrup, I. J. Circulatory changes following the subcutaneous injection of histamine in dogs. Am. J. Physiol. 142: 158-172, 1944.

12. Dobbins, D. E., G. J. Grega, J. B. Scott, and F. J. Haddy. The effect of mechanically increasing venous pressure in the canine forelimb on protein transport during the local administration of histamine and acetycholine. Microvas. Res. (In Press.)

13. Egdahl, R. H. The differential response of the adrenal cortex and medulla to bacterial endotoxin. J. Clin. Invest. 38: 1120-1125, 1959.

14. Estensen, R. D. and R. P. Gilbert. Responses of ileal segment weight to prolonged levarterenol infusion. Am. J. Physiol. 201:628-630, 1961.

15. Fung, Y. C., B. W. Zweifach, and M. Intaglietta. Elastic environment of the capillary bed. Circ. Res. 19:441-461, 1966.

16. Gabel, L. P., M. M. Winbury, H. Rowe, and R. P. Grandy. The effect of several pharmacological agents upon ^{86}Rb uptake by the perfused dog hindlimb. J. Pharmacol. Exptl. Therap. 146:117-122, 1964.

17. Garlick, D. G. and E. M. Renkin. Transport of large molecules from plasma to interstitial fluid and lymph in dogs. Am. J. Physiol. 219:1595-1605, 1970.

18. Goodman and Gilman. The Pharmacological Basis of Therapeutics. Macmillan, New York, 5th edition, 1975.

19. Grega, G. J., D. E. Dobbins, P. E. Parker, and F. J. Haddy. Effects of intravenous histamine on forelimb weight and vascular resistances. Am. J. Physiol. 223:353-360, 1972.

20. Grega, G. J., R. L. Kline, D. E. Dobbins, and F. J. Haddy. Mechanism of edema formation by histamine administered locally into canine forelimbs. Am. J. Physiol. 223: 1165-1171, 1972.

21. Guyton, A. C., H. J. Granger, and A. E. Taylor. Interstitial fluid pressure. Physiol. Rev. 51(3):527-563, 1971.

22. Haddy, F. J. Effect of histamine on small and large vessel pressures in the dog foreleg. Am. J. Physiol. 198:161-168, 1969.

23. Haddy, F. J., J. B. Scott, and G. J. Grega. Effects of histamine on lymph protein concentration and flow in the dog forelimb. Am. J. Physiol. 223:1172-1177, 1972.

24. Haddy, F. J., J. I. Molnar, and R. W. Campbell. Effects of denervation and vasoactive agents on vascular pressures and weight of dog forelimb. Am. J. Physiol. 201:631-638, 1961.

25. Hales, S. Statical Essays: Containing Haemastaticks; or An Account of Some Hydraulick and Hydrostatical Experiments Made on Blood and Blood Vessels of Animals, Vol. 2, Innys and Manby, London, 1733.

26. Halpern, B. N. Comparison of the antitoxic action of synthetic antihistamine to histamine in suprarenalectomized mice. Compt. Redn. Acad. Sc. 230:138-140, 1950.

27. Halpern, B. N., B. Benacerraf, and M. Briot. Potentiation by adrenaline of protective effect of cortisone on histamine toxicity in adrenalectomized mice. Proc. Soc. Exp. Biol. Med. 79:37-39, 1952.

28. Hinsaw, L. B., M. M. Jordan, and J. A. Vick. Mechanism of histamine release in endotoxin shock. Am. J. Physiol. 200:987-989, 1961.

29. Hinshaw, L. B., M. M. Jordan, and J. A. Vick. Histamine release and endotoxin shock in the primate. J. Clin. Invest. 40:1631-1637, 1961.

30. Hökfelt, B. The influence of hypophysectomy and of administration of adrenocorticotropin and growth hormones. Effect of histamine. Acta. Physiol. Scand. 25:Suppl. 92, p. 94, 1951.

31. Järhult, J. Comparative effects of angiotensin and noradrenaline on resistance, capacitance and precapillary sphincter vessels in cat skeletal muscle. Acta. Physiol. Scand. 81:315-324, 1971.

32. Joyner, W. L., R. D. Carter, G. S. Raizes, and E. M. Renkin. Influence of histamine and some other substances on blood-lymph transport of plasma protein and dextran in the dog paw. Microvas. Res. 7:19-30, 1974.

33. Kahlson, G. and E. Rosengren. New approaches to the physiology of histamine. Physiol. Rev. 48:155-196, 1968.

34. Kaiser, R. S. and J. N. Diana. Effect of angiotensin and norepinephrine on capillary pressure and filtration coefficient in isolated dog hindlimb. Microvas. Res. 7:207-228, 1974.

35. Kjellmer, I. and H. Odelram. The effects of some physiological vasodilators on the vascular bed of skeletal muscle. Acta. Physiol. Scand. 63:94-102, 1965.

36. Landis, E. M., L. Jonas, M. Angevine, and W. Erb. The passage of fluid and protein through the human capillaries during venous congestion. J. Clin. Invest. 11:717, 1932.

37. Lewis, T. The Blood Vessels of the Human Skin and Their Responses. Shaw and Sons, Ltd., London, 1927.

38. Ludwig, C. F. W. Lehrbuch der physiologie des mensche 2. Aufl., Vol. 2, Winter, Leipzig, p. 562, 1858-1861.

39. Majno, G., V. Gilmore, and M. Leventhal. On the mechanism of vascular leakage caused by histamine-type mediators. Circ. Res. 21:833-847, 1967.

40. Majno, G. and G. E. Palade. Studies on inflammation I. The effect of histamine and serotonin on vascular permeability: An electron microscopic study. J. Biophys. Biochem. Cytol. 11:571-605, 1961.

41. Majno, G., G. E. Palade, and G. I. Schoefl. Studies on inflammation II. The site of action of histamine and serotonin along the vascular tree: A topographic study. J. Biophys. Biochem. Cytol. 11:607-626, 1961.

42. Majno, G. and S. M. Shea. Endothelial contraction induced by histamine-type mediators. An electron microscopic study. J. Cell Biol. 42:647-672, 1969.

43. Marten, C. R., R. R. Sackler, A. M. Sackler, and M. D. Sackler. Propylthiouracil induced changes in histamine tolerance of intact and adrenalectomized rats. Fed. Proc. 12:349, 1953.

44. Mayerson, H. S. The physiologic importance of lymph. Handbook of Physiology, Circulation, Section 2, Vol. 2, American Physiological Society, Washington, D.C., p. 1035, 1963.

45. Mayerson, H. S., R. M. Patterson, A. Mckee, S. J. LeBrie, and P. Mayerson. Permeability of lymphatic vessels. Am. J. Physiol. 203:98-1062, 1962.

46. Mellander, S. and I. Nordenfelt. Comparative effects of dihydro-ergotamine and noradrenaline on resistance, exchange and capacitance functions in the peripheral circulation. Clin. Sci. 39:183-201, 1970.

47. Miller, M. E., G. C. Christensen, and H. E. Evans. Anatomy of the Dog. Saunders, Philadelphia: London, p. 432, 1964.

48. Nykiel, F. and V. Glaviano. Adrenal catecholamines in E. coli endotoxin shock. J. Appl. Physiol. 16:348-350, 1961.

49. Patterson, R. M., C. L. Ballard, K. Wasserman, and H. S. Mayerson. Lymphatic permeability to albumin. Am. J. Physiol. 194: 120-124, 1958.

50. Remington, J. W. and C. H. Baker. Blood and plasma specific gravity changes during acute alterations in hemodynamics in splenectomized dogs. Circ. Res. 6:146-154, 1958.

51. Renkin, E. M. and R. D. Carter. Influence of histamine on transport of fluid and plasma proteins in lymph. In: Advances in Experimental Medicine and Biology - Neurohumoral and Metabolic Aspects of Injury, edited by A. G. B. Kovach, H. B. Stoner, and J. J. Spitzer., Vol. 33, Plenum Press, New York, p. 119, 1973.

52. Renkin, E. M., R. D. Carter, and W. L. Joyner. Mechanism of the sustained action of histamine and bradykinin on transport of large molecules across capillary walls in the dog paw. Microvas. Res. 7:49-60, 1974.

53. Renkin, E. M. and D. G. Garlick. Blood-lymph transport of macromolecules. Microvas. Res. 2:392-398, 1970.

54. Robinson, R. L. and K. E. Jochim. The effect of histamine and anaphylactic shock on the secretion of adrenal medullary hormones. Fed. Proc. 18:129, 1959.

55. Rosenberg, J. G., R. C. Lillehei, J. Longerbeam, and B. Zimmermann. Studies on hemorrhagic and endotoxin shock in relation to vasomotor changes and endogenous circulating epinephrine, norepinephrine and serotonin. Ann. Surg. 154:611-627, 1961.

56. Roth, G. M. and W. F. Kvale. A tentative test for pheochromocytoma. Am. J. Med. Sci. 210:653-660, 1945.

57. Schayer, R. W. Relationship of stress-induced histidine decarboxylase to circulatory homeostasis and shock. Science. 131:226-227, 1960.

58. Schayer, R. W. Relationship of induced histidine decarboxylase activity and histamine synthesis to shock from stress and from endotoxin. Am. J. Physiol. 198:1187-1192, 1960.

59. Schayer, R. W. and O. H. Ganley. Adaptive increase in mammalian histidine decarboxylase activity in response to nonspecific stress. Am. J. Physiol. 197:721-724, 1959.

60. Shirley, H. H., C. G. Wolfram, K. Wasserman, and H. S. Mayerson. Capillary permeability to macromolecules: Stretched pore phenomenon. Am. J. Physiol. 190:189-193, 1957.

61. Sokal, R. R. and F. J. Rohlf. Biometry. Freeman, San Francisco, 1969.

62. Starling, E. H. On the absorption of fluid from the connective spaces. J. Physiol. (London) 19:312-326, 1896.

63. Szwed, J. J. and J. J. Friedman. Comparative effects of norepinephrine, epinephrine, angiotensin on pre- and postcapillary resistance vessels in dog skeletal muscle. Microvas. Res. 9:206-221, 1975.

64. Waddell, W. J. A simple ultraviolet spectrophotometric method for the determination of protein. J. Lab. Clin. Med. 48:311-314, 1956.

65. Weiss, S., G. P. Robb, and L. B. Ellis. The systemic effects of histamine in man. Arch. Int. Med. 49:360-396, 1932.

66. Wiederheilm, C. A. The interstitial space and lymphatic pressures in the bat wing. In: Pulmonary Circulation and Interstitial Space, edited by A. P. Fishman and H. H. Hecht, University of Chicago Press, Chicago, 1969.

67. Zweifach, B. W. P. Microscopic aspects of tissue injury. Ann. N.Y. Acad. Sci. 116:831-838, 1964.