Contribution of the Lymphatic System to the Replenishment of the Plasma Volume Following a Hemorrhage *

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Introduction

THE TRADITIONAL explanation of the mechanism by which the body spontaneously rebuilds its plasma volume following a hemorrhage is based on the Starling hypothesis of exchange of fluid across the capillary membrane.[18] Starling recognized that the flow of fluid out of and back into the capillary was governed by the balance between intracapillary filtration pressure and the oncotic resorptive pressure of the plasma proteins. Following a hemorrhage the intracapillary pressure falls and less fluid filters out. Plasma protein concentration is not immediately reduced by the blood loss; its resorptive power is not reduced. Thus, more fluid is drawn back into the venous end of the capillary than is lost at the arteriolar end. The result is a net gain in plasma volume tending to rebuild that volume lost by the hemorrhage. Postulated in 1896, repeatedly re-explored and confirmed, 66 years later it remains the accepted explanation.[10, 15-18]

Although the Starling concept itself appears incontrovertible, on theoretical grounds it alone is insufficient to explain all of the observed events. First, the spontaneous restoration of the plasma volume takes many hours and the Starling effect

with dilution of the plasma protein takes place promptly within minutes. Second, the intravenous administration of solutions such as physiologic saline which are freely permeable through the capillary membrane fail to restore the plasma volume. A nonpermeable colloid is needed to provide oncotic pressure. This was clearly demonstrated during World War I by Cannon, Aub, et al.[1, 3] Under Starling's concept the fluid withdrawn from the interstitial space consists only of freely permeable substances and is protein free. This permeable fluid on circulating throughout the body is held within the vascular space only so long as the intracapillary filtration pressure remains low. As the intracapillary pressure rises, it leaks out. Needed to hold it within the circulation is additional plasma protein; where could this protein come from?

The obvious immediate source of this needed plasma protein is the interstitial space and the means of recovering the protein and transmitting it to the vascular compartment are the lymphatic vessels. Drinker and others showed many years ago that the normal capillary membrane is not wholly impervious to plasma albumin and globulins.[5, 14] These proteins seep out into the interstitial space, where slowly they are gathered into the lymphatics and eventually sent back into the circulating plasma. Drinker pointed out that this recirculation of plasma protein was an essential factor in the maintenance of the body's fluid equilibrium and a principal function

of the lymphatic system. It has been estimated that in a normal animal approximately 50 per cent of the plasma protein upon which the vascular volume and blood pressure depend are at any given moment outside the vascular space in the interstitial space and lymphatic vessels.[4]

The role of the lymphatics has been extensively studied in burns, inflammation, and infectious toxic shock.[2, 7-9, 11, 14] It is curious that prior to the present study only one person has thought of examining the effect of hemorrhage on lymphatic flow. In 1948, Wessely, a Hungarian surgeon, described cannulating the thoracic duct of dogs and measuring the flow after a hemorrhage. He found a sharp, transitory increase in flow immediately after hemorrhage, and then the flow dwindled to zero. He concluded that the contribution of the lymphatic vessels to the recovery from hemorrhage was negligible. Scrutiny of his experiments, however, suggested the conclusion to have been premature. First, his experiments were conducted under anesthesia, and anesthetics affect lymph flow. Second, he bled the dogs so severely that they died promptly, within the first hours.[20] Under such severe stress any organ or system may fail well in advance of death. The capacity of the lymphatics to contribute to the spontaneous recovery of the animal might easily be overlooked under such stringent circumstances. Since there was so much logic to the hypothesis that the lymphatic vessels must be the means by which the body moves plasma protein to the blood stream and, thus, rebuilds the plasma volume after a hemorrhage, we embarked on an experimental study undiscouraged by Wessely's negative results. We took from his experiments, however, two things. First, the experimental conditions must permit observations without the need of anesthesia. Second, the hemorrhage must not be severe enough to be lethal.

The experimental observations we are reporting confirm the concept that the interstitial space is a potential source for needed plasma proteins, and the lymph vessels an effective path for recovering them to rebuild the plasma volume after a hemorrhage.

Historical Note

Starling's contributions were so fundamental and his influence so persuasive that it is historically informative to review in some detail what he did and said. In his studies published under the title, "On the Absorption of Fluids from the Connective Tissue Spaces,"[18] he considered absorption from serous cavities by means of the lymphatic vessels, but centered in large part on the transfer of fluids across the capillary membrane. The possibility of fluid reaching the blood stream via the thoracic duct after a hemorrhage he dismissed on the basis of the work of others. Regarding the effects of hemorrhage he wrote,

"2. Effects of artificial anoemia.

There are, however, certain facts which have been known to physiologists for the last fifty years and which, to my mind, prove conclusively the absorption by the blood vessels of the fluids in the connective tissue spaces. If an animal be bled to a certain amount, the remaining blood very shortly afterwards is found to be more dilute than before. It contains less haemoglobin and blood corpuscles and relatively more plasma. The plasma is also more dilute than before, showing that the increase in volume of blood chiefly consists of added water and salts, or at any rate, a fluid which contains less proteid than the plasma. In older works on physiology, we find this dilution of the blood ascribed to an increased flow of lymph from the thoracic duct into the blood. The result of bleeding, however, is to diminish the flow of lymph from the thoracic duct, and the dilution of the blood takes place just as well when the lymph is being led away by a cannula inserted in the duct. As an example of this change I may quote the following figures given by Tscherewkow.[19]

(1) Dog 11.4 kilos. Withdrawal of 220 c.c. blood reduced solids of serum from 7.72% to 7.14%.

(2) Dog 6.5 kilos. Withdrawal of 150 c.c. blood reduced solids of serum from 7.77% to 6.45%.

I have made some experiments to ascertain whether this absorption of fluid is effected only in the abdominal viscera, or whether it may take place in the connective tissues of the peripheral parts of the body.

I find that after total extirpation of the abdominal viscera, the organism reacts in the same way as in a normal animal to a considerable bleeding. We may conclude therefore that this absorption of fluid by the blood vessels, after bleeding, takes place throughout the body. This conclusion is also borne out by the experiments of Dr. Lazarus Barlow [12] on the specific gravity of the tissues."

The weight of Starling's argument regarding the resorption of fluid after a hemorrhage was, thus, thrown against a role for the lymphatics. Later, however, after presenting in detail his evidence for resorption across the capillary membrane, he said,

"The importance of these measurements lies in the fact that, although the osmotic pressure of the proteids of the plasma is so insignificant, it is of an order of magnitude comparable to that of the capillary pressures; and whereas capillary pressure determines transudation, the osmotic pressure of the proteids of the serum determines absorption. Moreover, if we leave the frictional resistance of the capillary wall to the passage of fluid through it out of account, the osmotic attraction of the serum for the extravascular fluid will be proportional to the force expended in the production of this latter, so that, at any given time, there must be a balance between the hydrostatic pressure of the blood in the capillaries and the osmotic atttraction of the blood for the surrounding fluids. With increased capillary pressure there must be increased transudation, until equilibrium is established at a somewhat higher point, when there is a more dilute fluid in the tissue-spaces and therefore a higher absorbing force to balance the increased capillary pressure. With diminished capillary pressure there will be an osmotic absorption of salt solution from the extravascular fluid, until this becomes richer in proteids; and the difference between its (proteid) osmotic pressure and that of the
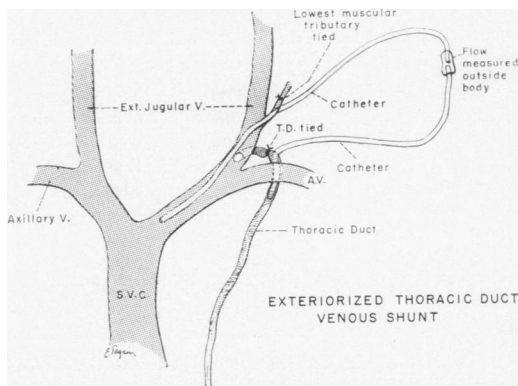

FIG. 1. Anatomic Diagram Illustrating the External Thoracic Duct Bypass. The thoracic duct is tied off just proximal to its point of entrance into the external jugular vein. A plastic catheter is inserted into the lower thoracic duct, taking all flow outside and then through a second plastic catheter back into the external jugular vein. Flow is measured outside the body at the junction of the two plastic catheters.

intravascular plasma is equal to the diminished capillary pressure.

Here then we have the balance of forces necessary to explain the accurate and speedy regulation of the quantity of circulating fluid. It is evident however that we cannot explain in this way the absorption of serum or other fluids rich in proteids from the serous cavities and connective tissues. I would point out however that we have as yet no sufficient evidence that such fluids are absorbed by the blood vessels. If we inject serum into the pleural cavity we find that it is absorbed very much more slowly than is a similar amount of salt solution. The absorption is indeed so slow that it is impossible to exclude the possibility that the whole of it has taken place through the lymphatics. In two experiments in which I made the limb oedematous with serum instead of salt solution, I could obtain no evidence of absorption of the oedema fluid by the blood vessels."

He thus laid the case for a role of the lymphatics. He did not go on to test it.

Methods and Materials

Dogs were chosen for the experiments. They were friendly mongrels in good nutritional state and were petted throughout the course of the experiments. Restless and irritable animals were excluded be-

TABLE 1. *Plasma Volumes Before, Immediately and Shortly after Hemorrhage*

Dog	Measured Plasma Volume Before Bleeding	Volume of Plasma Bled	Calculated Plasma Volume Immediately After Bleeding	Measured Plasma Volume Immediately After Bleeding	Measured Plasma Volume ± 2 Hours After Bleeding
I	480	133	347	392	420 (95 min.)
II	408	128	280	301	333 (120 min.)
IV	661	199	462	477	595 (135 min.)
V	734	212	522	490	615 (80 min.)

The determinations were made just before the bleeding, within 5 to 8 minutes and again 80 to 135 minutes after the bleeding. Volumes in ml.

cause motion stimulates lymph flow. Their weights ranged from 10 to 18 kilograms.

The flow of lymph in the thoracic duct was measured by an exteriorized thoracic duct-to-vein shunt. Under nembutal anesthesia (6.0 mg./kg.), the cervical portion of the thoracic duct was cannulated through a low left cervical incision (Fig. 1). The polyvinyl catheter was brought outside the skin and connected to a second catheter, the latter inserted through a proximal muscular tributary into the lateral aspect of the left external jugular vein at a point 2.0 to 4.0 cm. above the left axillary vein. The inner tip of the second catheter was placed at the junction of the right and left innominate veins. The tributary was ligated but the flow of blood through the external jugular was not interrupted. The system provided a continuous lymphatic return and the external junction of the catheters permitted measurement of the flow and sampling of the lymph at will without anesthesia.

While the animal was still under the anesthesia indwelling catheters were also placed in the femoral artery and vein of one hind leg for measuring blood pressure, bleeding and sampling.

On the first postoperative day the animals were alert and eating. Owing to occasional clotting of the blood at the tip of the catheter in the venous tree they were first heparinized, then maintained on warfarin sodium. As long as there was no stasis within the catheters, clotting of lymph was not a problem. Because of the several transcutaneous catheters, Bicillin (Wycillin) was administered prophylactically.

The patency of the shunt system was tested by observing the increase of lymph flow occuring after feeding a fatty meal. The plasma volumes were determined with I^{131} tagged human serum albumin. Radioactivity was measured in a well-type scintillation counter. Mixing was assumed complete in 12 minutes. The total protein and albumin concentrations were determined by the Biuret method, the latter after precipitation of the globulin fraction with sodium sulfite.

Experiments and Results

The experiments were divided into two groups. First, the sequels to hemorrhage were observed in the unoperated animal; and second, the thoracic duct flow was measured before and after a hemorrhage. The rationale, conduct of the experiment, results, and interpretations of each group are described separately.

I. Control Observations—Sequels to Hemorrhage in the Unoperated Animal

a. **Rationale.** In patients following an acute hemorrhage, it has been repeatedly observed that the fall in hematocrit takes

many hours. In 1941, Ebert, Stead and Gibson observed a comparable long, latent period in the rebuilding of the plasma volume in volunteers following a moderate blood withdrawal.[6] These observations are consonant with the concept of replenishment of the plasma volume by the lymphatic vessels because the flow of lymph is sluggish. Since the dog was to be used in our experiments, it was essential to know whether a comparable, slow sequence takes place in the dog after an acute hemorrhage.

b. **Conduct of the Experiment.** The plasma volume, hematocrit, serum total protein and albumin concentrations were followed in four dogs from 68 to 78 hours following a hemorrhage. The animals were given their last meal 24 hours prior to

FIG. 3. The Replenishment of the **Vascular** Space Following Hemorrhage in Four Animals. The courses of the plasma volumes and hematocrits were measured for 70 or more hours.
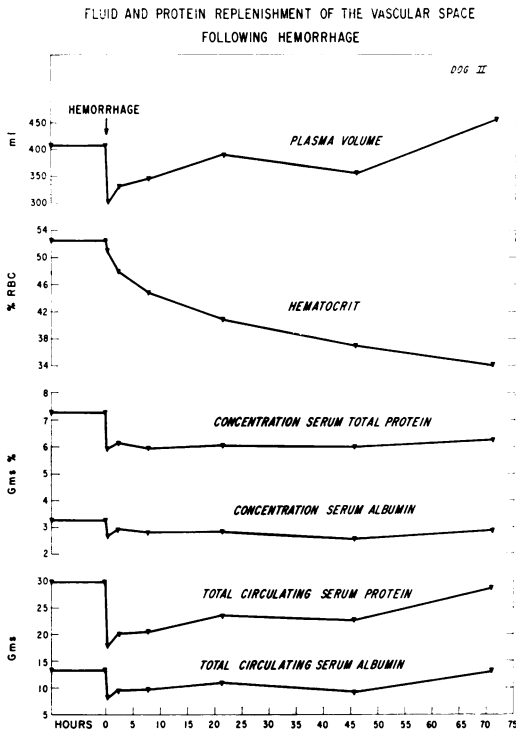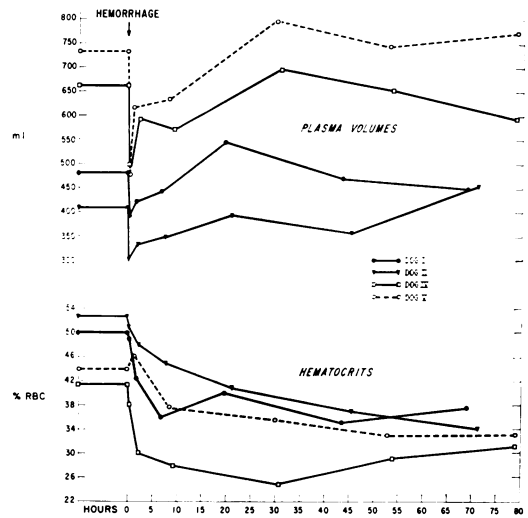
FIG. 2. Fluid and Protein Replenishment of the Vascular Space Following Hemorrhage. The courses of the plasma volume, hematocrit, serum concentrations of total protein and albumin and the amounts of these proteins accumulating in the plasma after hemorrhage are shown in a single animal (Dog 2) following a 30 per cent hemorrhage.

onset of the experiment and allowed water freely until the control measurements were made immediately before the hemorrhage. The dogs were bled 30 per cent of their calculated blood volume; repeated determinations were made thereafter. Food and water were withheld throughout the observations.

c. **Results.** 1. *Plasma Volume:* The measured plasma volume was immediately reduced by the hemorrhage. The measured initial reduction correlated closely with the amount of blood withdrawn (Table 1). Within the first two hours after the hemorrhage a prompt but slight rise in blood volume was observed (Fig. 2, 3). From then on the recovery of the volume was slower taking 20 hours to reach 80 per cent or more of the initial volume.

2. *Hematocrit:* The hematocrit fell slowly and continuously throughout the period of observation. This fall is essentially the reciprocal of the rise of the plasma volume (Fig. 2). There were two exceptions to this generalization: First, in Dog V the hemato-
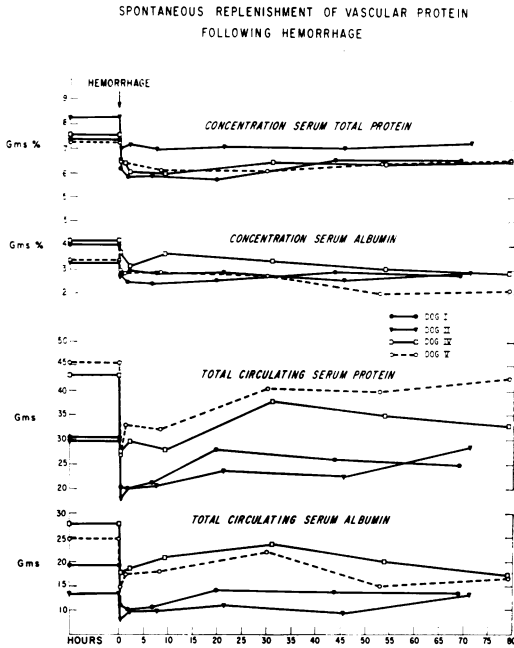
FIG. 4. The Dilution of Plasma Proteins and their Reaccumulation in the Vascular Space in Four Animals Following Hemorrhage.

crit rose transiently immediately after the hemorrhage. (This same rise was occasionally seen in other dogs repeated in later sections; it is absent in splenectomized animals.)[13] Second, in Dog IV (Fig. 3) the hematocrit rose slightly after the thirty-second hour.

3. *Serum Protein Concentrations:* The serum proteins, both the total protein and the albumin, were promptly diluted to a low level which was maintained throughout the observations in all four animals (Fig. 2, 4). The biggest part of the dilution occurred within the first five minutes.

TABLE 2. *Weight of Plasma Protein Lost by Hemorrhage and Regained Subsequently*

Dog	Measured Grams Lost by Hemorrhage	Calculated Grams Regained at 24 Hrs.	Calculated Grams Regained at 48 Hrs.
I	8.5	7.5	5.4
II	9.3	5.6	5.1
IV	13.0	8.5	9.6
V	13.3	11.5	13.5
Avg.	11.3	8.3	8.4

The maximal dilution was reached between one-half and two hours.

4. *Amount of Circulating Proteins:* The calculated amount of total protein and albumin circulating in the plasma rose slowly and continuously in all animals following the initial loss immediately after the hemorrhage (Fig. 2, 4). The measured amounts of plasma total protein withdrawn from these four dogs in the bleeding and the calculated amounts regained in 24 and 48 hours are given in Table 2.

d. **Interpretation.** The contrasts between the courses of the plasma volume, the hematocrit, and the concentrations of the proteins indicate that two processes are taking place—one rapid and the other slow. The rapid process is the dilution of the protein concentrations. Sizable within the first five minutes it is complete well within two hours after the hemorrhage. The change is consistent with the Starling hypothesis of resorption of an increased amount of water from the interstitial space as a result of the fall in blood pressure. Pappenheimer's experiments showed this change could occur within 15 minutes.[16]

While this dilution is taking place there is little or no measurable rise in the plasma volume. Presumably the dilution is accompanied by some rise. It is simply too small to be measured by the technic available. The probable reasons why the plasma volume does not go on increasing are twofold. First, the dilution of protein concentration reduces the oncotic pressure, and second, as the blood pressure rises following any increase in volume, the seepage increases again and equilibrium is promptly reached with little gain in volume.

The drop in protein concentration must represent a significant redistribution of water within the body, even though it is not accompanied by much increase in plasma volume. It is striking that the lowered concentration reached is maintained steadily throughout the period of the observations.

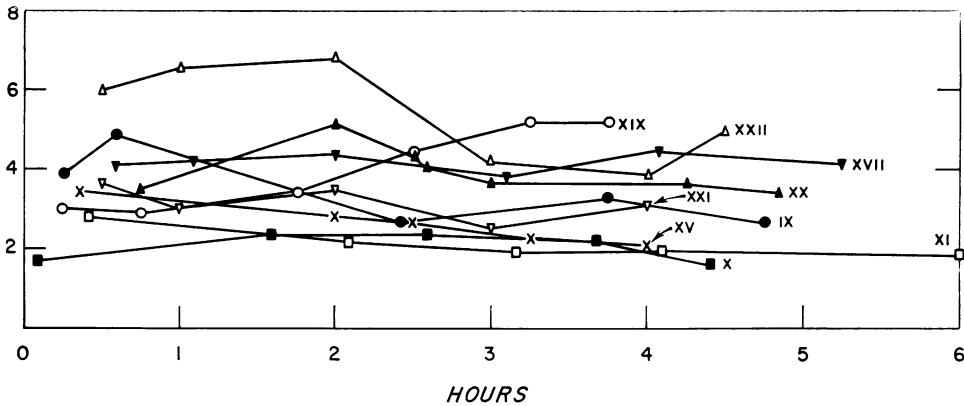CONTROL EXPERIMENTS — THORACIC DUCT FLOWS

Fig. 5. The Flow of Lymph in the Thoracic Duct of Nine Fasting, Unanesthetized Dogs. The flow was measured for four to six hours.

The slow process is the gradual accumulation of protein in the circulation. The substantial rise in plasma volume and fall in hematocrit must be related to this accumulation and presumably dependent on it. The Starling hypothesis cannot account for it since by this hypothesis protein does not pass the capillary membrane back into the blood stream. The slow course of the hematocrit in these dogs conforms to the clinical observation in the human being after a hemorrhage.

II. Thoracic Duct Observations—Effect of Hemorrhage on Flow of Fluid and Protein

a. Rationale. The observations quoted in the previous section following a hemorrhage in the normal unoperated dog strengthened the original hypothesis of the study and the need for direct measurement of lymphatic flow.

b. Conduct of the Experiments. Fourteen experiments were carried out in ten dogs with the exteriorized thoracic duct bypass. Three or more days after the bypass operation and after patency had been proven, both fasting control and posthemorrhage flows were followed and the protein concentrations of the lymph measured.

1. Control Fasting Flows: The predictability and variability of the flow of thoracic duct lymph in the fasting unanesthetized state were tested in nine of the animals. Fasted from the morning before and allowed water until the start of the observations, the flow was measured in each dog from four to six hours.

2. Effect of Hemorrhage on Flow: The effect of hemorrhage on the flow of lymph in the thoracic duct was observed in 14 experiments on ten dogs. In each experiment approximately 30 per cent of the estimated blood volume was removed. The bleeding time varied from 20 to 60 minutes. The animals were fasting, unanesthetized and supported in a Pavlov-type stand. Their blood pressure, pulse and respiratory rates, hematocrit, lymph flow, and protein concentrations of plasma and lymph were measured throughout the experiments. The blood withdrawn during the hemorrhage was reinfused toward the end of each experiment, and the effect of the transfusion observed. The reinfusion in 12 of the experiments was approximately four hours after the hemorrhage and in two, 24 hours later.

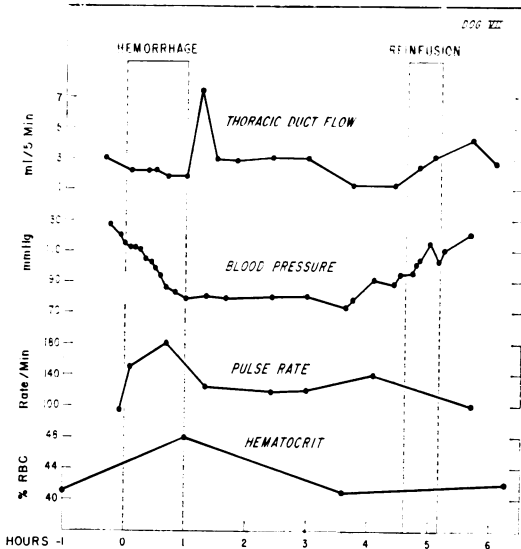c. Results. 1. Control Fasting Flows: In seven of the animals the flow was re-

FIG. 6. Effect of Hemorrhage on Thoracic Duct Flow, Blood Pressure, Pulse Rate and Hematocrit in a Single Animal (Dog 7). The effect of subsequent re-infusion of the blood withdrawn four hours previously is also shown.

markably constant throughout the period of observation (Fig. 5). The volume of flow ranged from 2.0 to 5.0 ml./5 min. For each animal whether at the lower or upper end of the range, the flow was reasonably constant. In two of the animals, No. XIX and XXII, the flow varied over a wider range. In No. XIX, it started at the average of three and rose to five. In No. XXII, the initial level was the highest of all the animals, above 6.0 ml./5 min., but fell during the third hour to a range consistent with the other animals. No unusual behavior was noted in either of these two animals.

2. *Effect of Hemorrhage on Flow:* In each of the 14 experiments the physiologic strain induced by the hemorrhage was measured by recording the blood pressure and the pulse and respiratory rates throughout the period of observation. A moderate variation in degree of response was encountered. For example, in the first experiment in one animal the blood pressure did not fall; in the second experiment a week later in the same animal, the blood pressure fell in more characteristic fashion. The pulse

rate rose in all animals (Fig. 6, 7). In the majority the respiratory rate rose. Some of the animals became transiently restless after the hemorrhage.

In many of the animals the hematocrit rose immediately following the hemorrhage, returning to the prehemorrhage level after two to three hours. (The relation of this variation to the spleen is considered in a subsequent paper.)[13]

The fasting rate of flow of thoracic duct lymph was established in each experiment before starting the hemorrhage. The level was consistent with that observed in the same animal during a previous control experiment.

With the onset of hemorrhage the first change noticed was an abrupt, transient rise in flow (Fig. 6–8). At the peak of this rise the flow had increased to two to three times the fasting level. The time of onset of the spike varied in the experiments. In some it started within a few minutes after
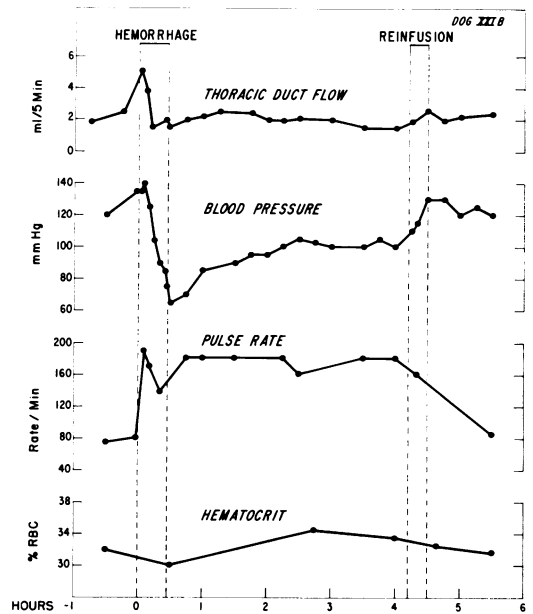

FIG. 7. Effect of Hemorrhage on Thoracic Duct Flow, Blood Pressure, Pulse Rate and Hematocrit in Dog 21 B. The abrupt rise in flow appeared immediately after start of the hemorrhage, earlier than in the experiment depicted in Figure 6. Effect of reinfusion at the fourth hour is also shown.
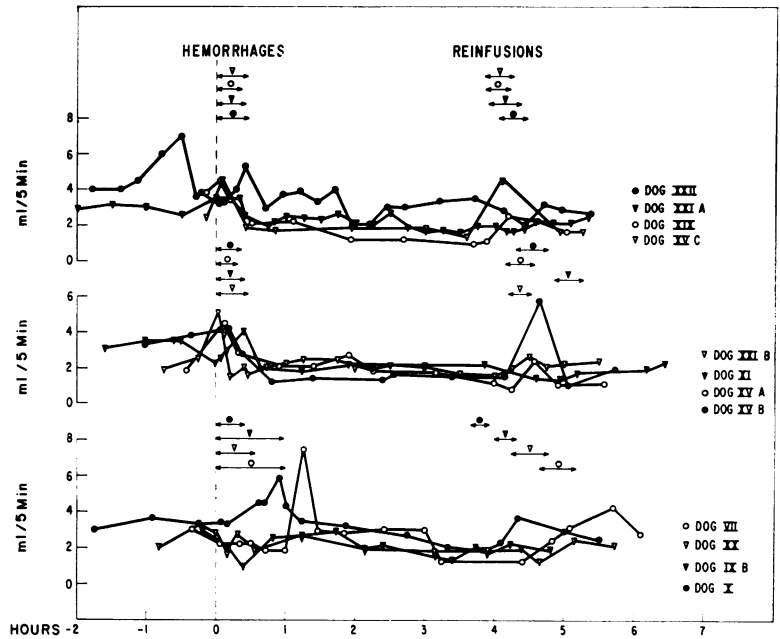
THORACIC DUCT FLOWS FOLLOWING HEMORRHAGE

FIG. 8. The Flows of Thoracic Duct Lymph in 12 Dogs Following Hemorrhage and Re-infusion of the Blood in the Fourth and Fifth Hours.

the start of the hemorrhage (Fig. 7). In others it was delayed until after the hemorrhage had been completed and the blood pressure had reached its lowest level (Fig. 6). The spike was not seen in all of the experiments—slight in one and absent in two. The duration of this increased flow varied from 20 minutes to an hour.

With cessation of the increased flow the

lymph flow settled back to approximately the prehemorrhage fasting level where it was maintained. In a few of the experiments it was a bit lower than the fasting level and decreased further slightly during the four hours following the hemorrhage (Fig. 8).

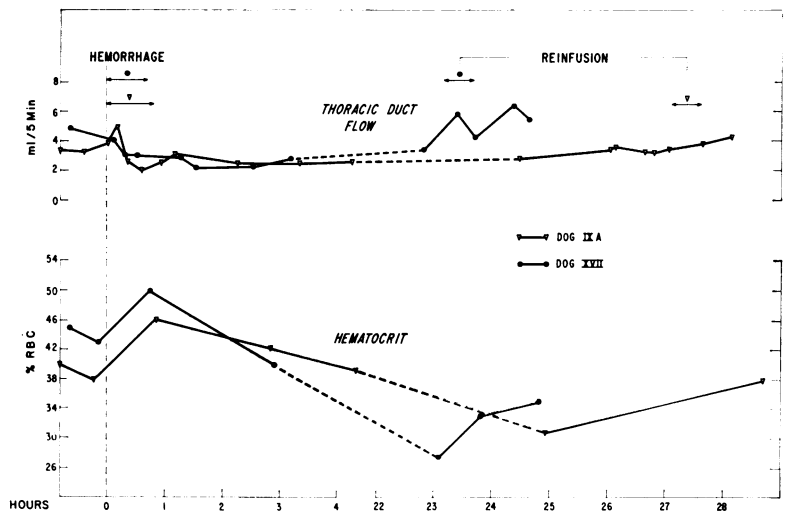In the two experiments in which the thoracic duct flow was observed for 24

FIG. 9. The Flow of Thoracic Duct Lymph and Course of Hematocrit in Two Experiments in which Re-infusion was Delayed until the 23rd and 27 Hours.

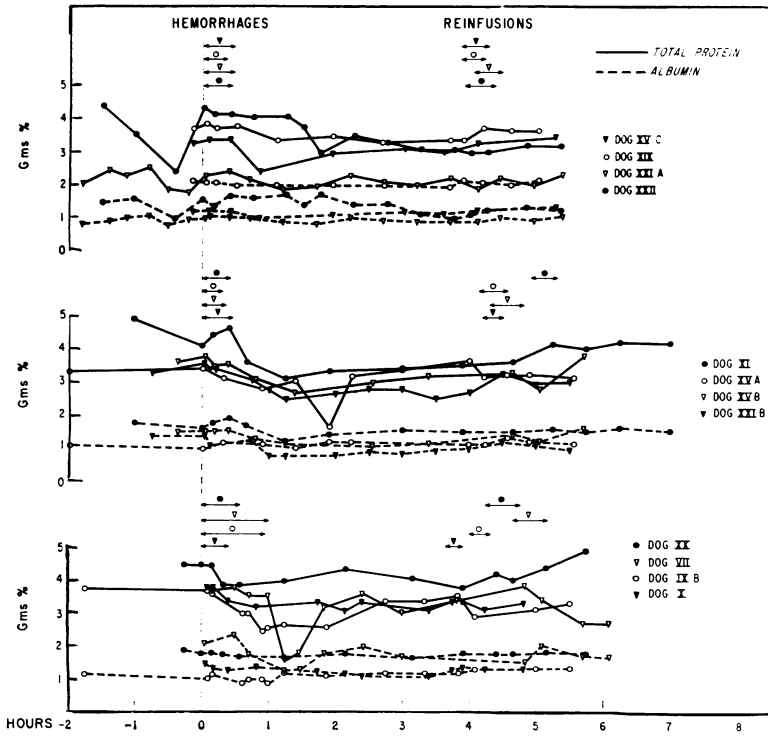LYMPH PROTEIN CONCENTRATIONS FOLLOWING HEMORRHAGE

FIG. 10. The Protein Concentrations of Thoracic Duct Lymph Following Hemorrhage. The total protein concentration (solid lines) and the albumin concentration (broken lines) encountered are shown for the 12 experiments in which the withdrawn blood was re-infused in the 4th or 5th hours.

hours following the hemorrhage, the flow was maintained throughout at the slightly lower than fasting level (Fig. 9).

Re-infusion of the blood withdrawn during the hemorrhage was associated in all experiments with an improvement in the general physiologic status of the animal. The blood pressure rose; the pulse rate dropped. In those 12 experiments in which the re-infusion was carried out within four hours after the hemorrhage, there was no consistent change in the hematocrit following the re-infusion. In some experiments the hematocrit decreased; in others it rose slightly or remained unchanged. In the two animals in which re-infusion was delayed for approximately 24 hours (Fig. 9), the hematocrit had fallen to a low level before the re-infusion and rose significantly in the first hours following the re-infusion.

The flow of lymph in the thoracic duct was increased in the majority but not in all following the re-infusion (Contrast Fig. 6, 7). In two animals there was a dramatic increase almost as great as the spike immediately following the hemorrhage (Dogs XV, VII—Fig. 8). One of the two animals in which the re-infusion was delayed for 24 hours had a moderate burst, the other virtually none (Fig. 9).

TABLE 3. *Weight of Protein Delivered per Hour by Thoracic Duct to Blood Stream*

Average Grams per Hour Before Hemorrhage	Average Grams per Hour After Hemorrhage				
	1st hr.	2nd hr.	3rd hr.	4th hr.	24th hr.
1.49	1.1	.86	.78	.67	1.25

Averages are of 14 experiments except for 2 at 24th hour.

3. *Lymph Protein Concentrations:*
Changes in concentration of the lymph proteins were variable as a result of the hemorrhage (Fig. 10). In the majority of the experiments, the fluctuations did not exceed those encountered in the fasting control experiments. In a few others, however, there were dramatic changes in the total protein and albumin concentrations. In Dogs VII and XV the total protein concentration fell to 50 per cent of its fasting value, transiently, during the period of the outburst of lymph immediately following the hemorrhage. In Dog VII there was a corresponding fall in the albumin concentration at the same time, but a comparable fall was not seen in Dog XV (Fig. 10). No significant changes in either total protein or albumin concentrations were encountered with reinfusion of the previously withdrawn blood.

4. *Amount of Protein Delivered to Vascular Tree:* The amounts of protein delivered by the thoracic duct to the vascular tree per hour are given in Table 3. The measured amounts of plasma protein withdrawn in the bleeding and the cumulative amounts regained through the thoracic duct are given in Table 4. Slowly the thoracic duct returns to the blood stream the equivalent of the protein removed. In the first two hours after the hemorrhage the thoracic duct returned only one-fourth of the protein removed, and in the second two hours a little less. Over the course of 24 hours, on the other hand, more than twice the amount lost had been returned.

d. Interpretations. The observations of this second section show that the lymphatic vessels continue to furnish fluid and protein to the blood stream only slightly abetted, and that the protein contributed is adequate to explain the slow process described in the first section, namely, the slow rise in plasma volume and fall in hematocrit.

The thoracic duct is not the sole contributor. The right lymphatic duct and the

TABLE 4. *Plasma Protein Lost by Hemorrhage and Cumulative Protein Regained Through Thoracic Duct*

Grams Lost by Hemorrhage	Grams Regained by Lymph		
	in 2 Hrs.	in 4 Hrs.	in 24 Hrs.
7.8	2.0	3.4	20.4

Amounts are averages of 14 experiments for first 4 hours. The value at 24 hours is a calculation based on this.

cervical lymph vessels were presumably continuing to contribute lymph in addition to that flowing through the thoracic duct. The quantities of these additions were not measured but a conservative estimate is that the thoracic duct furnishes but 80 per cent of the total. The amounts given in Table 4 are therefore minimal.

The apparent excess of protein furnished by the thoracic duct should occasion no surprise. While the protein rich lymph is trickling into the blood stream plasma proteins are continuing to filter out through the functioning capillaries. This slow passage of plasma protein into the interstitial space is a normal part of circulation and must be continuing in these surviving animals. To replenish the plasma volume, therefore, the lymphatic vessels must contribute not only the amount lost by the hemorrhage but also enough to maintain the amount seeping out in continuing circulation.

Comment

Hemorrhage is perhaps the commonest and certainly one of the most devastating complications of surgical and medical disease. Understanding of the immediate physiolgic consequences of hemorrhage and the efforts of the body to mobilize its defenses is of undoubted practical importance to therapy. The deleterious consequences must be offset and the compensatory efforts abetted. The continuing flow of lymph slowly moving protein from the interstitial space into the blood stream is a compensatory effort of the first magnitude.

The observations made in these experiments divide the efforts of the body to rebuild its plasma volume into an immediate, rapid process and a sluggish time consuming one. In the light of the findings the Starling phenomenon assumes a restricted role and the lymphatic system emerges as essential to the spontaneous rebuilding of the circulating plasma volume. Protein is needed to rebuild the volume and the lymphatic vessels are the only means of moving protein from the reservoir in the interstitial space into the blood stream. This takes time because lymph flows slowly.

This essentiality of the lymphatic system to recovery from hemorrhage should occasion no surprise. Indirect evidence has existed for a long time that this should be the case. Protein is needed to provide oncotic pressure; non-colloid solutions are inadequate. Protein cannot pass backward through the capillary wall from the interstitial space into the blood stream. Starling knew this in 1896. Modern experiments using proteins tagged with radioactive isotopes have confirmed this amply.[13, 21]

Clinical experience has also furnished indirect evidence that there must be another means than the Starling phenomenon to transfer protein and this means must be the lymphatic vessels. Ebert, Stead and Gibson, in 1941, documented the long period required for rebuilding of the plasma volume. Traumatic rupture of the thoracic duct has told the surgeon again and again of the massive amounts of proteins passing through the thoracic duct. It has remained to show that the flow of thoracic duct lymph continues despite a crippling hemorrhage.

These observations have a practical meaning. If a patient who has had a hemorrhage is found to have a low hematocrit it can be assumed that the patient's store of plasma protein is depleted. The patient needs protein as well as red cells. The redistribution of protein from the interstitial space to the blood stream will have placed a severe burden on the homeostatic mechanism governing the distribution of water and electrolytes. Infusion of red cells to correct the hemocrit will fail to restore this essential equilibrium.

Summary

The contribution of the lymphatic vessels to the restoration of the plasma volume following a hemorrhage has been explored in the dog. An exteriorized thoracic duct-venus shunt has been constructed with two polyvinyl catheters in such manner that the flow and content of lymph could be measured at will in the healthy, surviving, unanesthetized animal. Following a severe but non-lethal hemorrhage, the flow of thoracic duct lymph increases abruptly and transiently. Thereafter the flow settles back into a rate slightly below the pre-hemorrhage level. There it continues for 24 hours and longer. In those 24 hours more than twice as much protein is delivered to the blood stream as was removed by the hemorrhage. The rate of increase in plasma volume parallels the protein contribution of lymphatic flow.

The Starling phenomenon appears to have a restricted role in the recovery from hemorrhage. The essentiality of the lymphatic system to the recovery from shock has been defined.

Addendum

Most recently Alican and Hardy have reported experiments in endotoxic shock and shock from hemorrhage in which the flow of lymph from the liver and in the thoracic duct have been measured along with portal vein and systemic artery pressures. The flow of thoracic duct lymph was observed to increase following the I.V. injection of endotoxin and also immediately following the onset of hemorrhage. This effect of hemorrhage was abolished by curarizing the animal and ascribed by them, therefore, to muscular action. The experiments were acute with the dog under light anesthesia. The results, however, are in agreement with our own and reinforce the concept of the importance of the thoracic duct in

the compensation to shock (Alican, F. and J. D. Hardy: Mechanisms of Shock as Reflected in Studies of Lymph of Abdominal Organs. Surg., Gynec. & Obst., 113:743, 1961).

Acknowledgment

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