It has been suggested that circulatory failure in hemorrhagic shock is due in large part to a derangement of the peripheral circulation. The exact nature of this derangement is as yet obscure. It is known that arterial pressure is low and blood flow to many areas (e.g., skeletal muscle) is reduced. It is also known that one of the important compensatory mechanisms in shock is an increased sympathetic discharge. Previous studies on the peripheral circulation in shock have been restricted almost exclusively to descriptions of the changes in resistance to blood flow. This is only one function of the peripheral vascular bed. A complete analysis must also take into account the concomitant effect of shock on the other functions, e.g., capacitance, the relative size of the capillary bed open to flow, and the rate and direction of capillary filtration transfer.

Using the technique described by Mellander in which all these functions can be studied simultaneously, an investigation was carried out examining the effects of reduced regional blood flow on the several functions of the peripheral circulation. The results of that study indicated that reduction of regional blood flow to skeletal muscle in the hind part of the cat impaired and eventually abolished the reactivity of all consecutive sections of the muscle vascular bed to stimulation of lumbar sympathetic vasoconstrictor nerve fibers and to close intra-arterial infusion of l-norepinephrine. It was found, however, that the time-course of the changes in reactivity was different for the various sections of the vascular bed. Thus the section most sensitive to reduction in regional blood flow consisted of the pre-capillary sphincters, the tone of which determines the size of the capillary surface area available for flow and hence for transcapillary exchange. Next most sensitive to flow reduction were the pre-capillary resistance vessels, and least sensitive the post-capillary section (post-capillary resistance vessels and capacitance vessels). This implied that the normal response pattern of the vascular bed to constrictor fiber influence, with respect to the resistance and capacitance functions and the transcapillary filtration exchange, was considerably altered under these circumstances.

Since reduction in regional blood flow can be considered to cause an "accumulation of metabolites," that study shed light on the relative effects of local metabolic factors and extrinsic nervous factors on the various vascular sections. It could be concluded that the pre-capillary functions were more under the dominance of local metabolic factors, while the post-capillary functions were more dominated by extrinsic nervous influences. Since the manner in which the reactivity of the various vascular sections changed during the period of reduced regional blood flow...
could help to explain many of the features of peripheral circulatory function in the various stages of shock (reversible as well as irreversible), it seemed important to make additional observations on the muscle vascular bed in experiments more closely related to shock than those cited above. For this purpose, experiments were done to study the effect of hemorrhagic hypotension on the reactivity of the various vascular sections to sympathetic constrictor fiber stimulation.

Because the purpose of the present study was to elucidate the response pattern of the peripheral circulation to graded sympathetic constrictor fiber activation during hemorrhagic hypotension, the experiments were so designed that interference by other factors was eliminated as far as possible. Thus, for example, the sympathetic vasodilator nerve fiber system was blocked and a major portion of the intestines was removed to prevent possible absorption of deleterious materials from the gastrointestinal tract. The influence of such factors may be added to the present analysis as they are investigated, and experiments in the intact organism are planned as a further step in this analysis.

**Methods**

Experiments were performed on 19 cats weighing about 3 kg and anesthetized intravenously with a mixture of chloralose (not more than 50 mg/kg) and urethane (not more than 100 mg/kg). In most experiments artificial respiration was given at a level just sufficient to suppress spontaneous breathing. The experimental technique and the method of analyzing the recordings have been presented previously. The hind part of the cat was isolated from the upper part at the level of the hips, leaving intact only the abdominal aorta, the inferior caval vein, and the lumbar sympathetic nerve trunks. To permit access to the large abdominal vessels and the sympathetic nerve trunks virtually all of both the small and large intestine was removed. Tight ligatures were placed about both ankles of the hind limbs and the base of the tail so that the vascular bed that remained represented almost entirely skeletal muscle. In a few experiments the skin was removed from the hind part to provide an almost pure skeletal muscle preparation. In about half of the experiments reflex adrenal medullary secretion was prevented by ligating the right adrenal gland and denervating the left.

For measurement of blood flow a drop recorder, operating an ordinate writer was inserted in the inferior vena cava. With this recorder, the height of the ordinate is inversely related to the blood flow. To calibrate blood flow, the return from the drop recorder was temporarily diverted into a graduated cylinder. Such measurements were made immediately before each nerve stimulation and at the point of maximum response.

By enclosing the hind part of the body in a water-filled, temperature-regulated plethysmograph, it was possible to record phasic changes in both regional blood volume and in regional extravascular fluid volume. In some experiments changes in regional blood volume were also recorded using a radioactive isotope monitoring technique.

Arterial pressure was measured from the inferior mesenteric artery. The venous outflow pressure of the hind part could be set at any desired level by altering the height of the drop recorder above heart level.

The lumbar sympathetic trunks were sectioned at approximately the mid-abdominal level. The peripheral ends, immersed in paraffin oil, were stimulated with a bipolar platinum electrode at the level of the fourth lumbar ganglion. At this level the sympathetic trunks contain virtually all of the efferent fibers to the hind part. Supramaximal voltage (5 volts) was used to ensure excitation of all fibers. The duration was set at 3 msec. Various frequencies within the physiological discharge range (0-20 impulses/sec) were used. Atropine was given intravenously in all experiments in a dose sufficient to block the action of the sympathetic cholinergic vasodilator fibers.

In experiments in which the vascular responses to 1-norepinephrine were tested, this agent was administered intra-arterially to the hind part through an indwelling cannula in the tail artery. Hemorrhagic hypotension was produced by allowing the animal to bleed freely from one carotid artery into a pressure bottle. A constant arterial pressure, usually between 40 and 50 mm Hg, was maintained during the period of hypotension by minor adjustments of the pressure within the bottle. The temperature of the bottle was kept at 38°C.

With this technique phasic changes in blood flow, in blood volume, and in net transcapillary fluid exchange, induced by sympathetic vasoconstrictor nerve fiber stimulation or by 1-norepinephrine could be recorded continuously while at the same time the pressure gradient across the vascular bed could be kept constant. In each experiment, the responses of the vascular bed to nerve stimula-
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...tion (or norepinephrine) were tested first at the normal flow level, then repeatedly during the period of hemorrhagic hypotension, and again after return of the shed blood to the animal.

Results

Figure 1 shows the original recording from a representative experiment in which the animal was bled approximately 7 ml/kg to lower arterial pressure to about 50 mm Hg (zero time). This, in turn, reduced the regional blood flow to approximately one-half of the control flow. After 145 minutes at the reduced pressure level the shed blood was returned to the animal. Before bleeding, the venous pressure level was set so as to provide an isovolumetric state of the hind part at rest (no change in tissue volume). At this time a "control" stimulation of the regional lumbar sympathetic trunks (2 impulses/sec) was carried out (A in fig. 1). This caused a decrease in volume. As has been shown previously the early rapid decline in the volume curve is due to the response of the capacitance vessels and represents the amount of blood emptied from this section by constriction, while the latter more slowly declining portion of the curve is due to a net inward filtration of extravascular fluid which becomes part of the venous return from the region. The blood flow curve shows, as expected, the reduction in flow due to the response of the resistance vessels.

During the period of hemorrhagic hypotension, and after the return of the blood to the animal, the effect of nerve stimulation was repeatedly tested (B-G in fig. 1) using the same stimulation characteristics as at A. For reasons of limitation of space, the record from 36 to 98 minutes has been omitted. The responses to sympathetic stimulation obtained during this period have been included in figures 2 and 3 showing data derived from the experiment presented in figure 1. As can be seen from the values indicated in figure 1 for regional resistance (PRU) and change in resistance caused by nerve stimulation (change in PRU), there is a progressive decline in the resistance response during the period of hypotension which goes on to almost complete abolition (F). Similarly, from the calibrated volume curve, it can be seen that there is also some decline in the capacitance response.

Late in the period of hemorrhagic hypotension, when stimulation of the constrictor nerves did not significantly increase regional resistance (F), intra-arterially infused L-norepinephrine in "physiological" doses (up to 5 μg/kg/min) completely failed to evoke a constriction of the resistance vessels (not shown in fig. 1). If, however, the dose of L-norepinephrine was increased far above the physiological range it was often possible to elicit at this stage a distinct constrictor response in both the resistance and capacitance vessels. This is shown in figure 1, Q, where L-norepinephrine was infused intra-arterially in a dose of 12 μg/kg/min.

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FIGURE 1

Cat 3.1 kg, skeletal muscle preparation. Chloralose-urethane. Effect of hemorrhagic hypotension on resistance and capacitance blood vessels and net transcapillary filtration exchange to regional sympathetic vasoconstrictor nerve stimulation at 2 imp/sec (A-G). At Q, l-norepinephrine in supraphysiological dose (15 µg/kg/min) infused. Responses of resistance vessels indicated by PRU and change in PRU. Responses of capacitance vessels demonstrated by the initial rapid decrease in the volume curve, and the effects on capillary filtration by the later, slower and continuous change in the volume curve during stimulation. Hemorrhagic hypotension maintained for 145 min. After this the shed blood was returned (record from 36 to 38 min omitted). Note the declining reactivity of resistance and capacitance vessels during the period of hemorrhagic hypotension. At B-D there is declining rate of inward movement of extravascular fluid, at E there is no change in capillary filtration and at F there is outward filtration on sympathetic stimulation. The large dose of norepinephrine given at Q was able to evoke a distinct response of the resistance vessels and to produce inward filtration. With return of shed blood there was almost complete recovery of all vascular responses to nerve stimulation (G). Filtration coefficient determined at a, b, c, d, e, and f.

was the decline of both responses. Whatever the hypotensive level, however, there was always a more rapid decline, and an earlier abolition, of the resistance response than of the capacitance response. In this regard the effects of the level of arterial pressure on the rate of decline, and the time to abolition, of the responses were similar to previous experiments in which it was shown that the more severe the regional flow reduction (partial
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Reactivity of resistance and capacitance vessels to vasoconstrictor fiber stimulation (2 imp/sec). Data taken from exp. shown in figure 1. Note the much more rapid decline in the resistance response than in the capacitance response during the period of hemorrhagic shock. Both responses recovered to about normal when the shed blood was returned.

Figure 2

At normal blood flow sympathetic vasoconstrictor nerve fiber stimulation causes a greater increase of pre-capillary resistance than of post-capillary resistance. This decreases mean capillary hydrostatic pressure and, thereby, produces a net inward movement of extravascular fluid. As shown in figure 1 A this can be noted from the more slowly and continuously declining portion of the volume curve that follows the capacitance response. It can also be seen from figure 1 that during the period of hypotension there is impairment in the ability of nerve stimulation to produce an inward movement of fluid (B-D), which reaches eventually a point at which nerve stimulation causes no net transfer of fluid across the capillary wall (E). Evidence for this is found in the volume curve which becomes isovolumetric immediately following the capacitance response. In figure 1 F nerve stimulation causes an outward movement of capillary fluid as is demonstrated by the progressively upward deflection of the volume curve after the capacitance response. The fact that this was not due to a slow relaxation of the capacitance vessels during nerve stimulation was demonstrated in previous experiments, and in some of the present ones using an isotope technique for recording changes in the volume of blood present in the hind part. At the stage when stimulation of the constrictor fibers produced an outward filtration, the large dose of l-nor-epinephrine infused at Q in figure 1 produced not only a distinct response of the resistance vessels but also a net inward filtration as noted by the slowly declining volume curve after the capacitance response. After re-infusion of the shed blood, constrictor nerve stimulation again was able to elicit a net inward movement of extravascular fluid (G).

Figure 3 shows more directly the change in the rate and direction of net capillary fluid transfer induced by vasomotor nerve stimulation. The data have been taken from the experiment shown in figure 1. During the control period the net inward movement of extravascular fluid amounted to 0.16 ml/min/100 g tissue. After 102 minutes of hypoten-
sion, nerve stimulation failed to alter net capillary fluid transfer and following this, at 120 minutes, nerve stimulation caused a loss of fluid from the circulation at the rate of 0.035 ml/min/100 g tissue. Following return of the shed blood to the animal, nerve stimulation was once again able to cause a net inward movement of extravascular fluid at the rate of 0.14 ml/min/100 g tissue.

When one considers these responses seen in the vascular bed of skeletal muscle, it is apparent that inward filtration on nerve stimulation occurs at a time when there is a noticeable resistance response. After the resistance response has virtually disappeared (and a capacitance response still remains) there occurs an outward filtration.

The direction of fluid movement on nerve stimulation gives additional information on the relative development of pre-capillary and post-capillary resistance. In this preparation and under these experimental conditions, an inward movement of extravascular fluid must be due to a decrease in mean capillary hydrostatic pressure. Such a change in capillary pressure must, in turn, be due to a relatively more pronounced increase in pre-capillary resistance than in post-capillary resistance as has been shown previously. Therefore, from the results obtained, it can be said that in the control period, and early in the period of hypotension, nerve stimulation increases pre-capillary resistance relatively more than post-capillary. A point is reached at which they are both increased to such an extent that mean capillary pressure is unchanged (no net transfer). Finally, with outward movement of fluid from the circulation, nerve stimulation must cause a relatively greater increase in post-capillary resistance than in pre-capillary. With regard to this final stage, it should be noted that it occurs at a time when there is still a capacitance response present, which response must have some resistive component and which is post-capillary in location. Also it occurs at a time when there is very

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**Figure 3**

Net filtration transfer during constrictor fiber stimulation (2 imp/sec). Data from exp. in figure 1. Influx of extravascular fluid indicated by a minus sign and outward transfer of capillary fluid by a plus sign. Note that during the period of hemorrhagic shock the rate and finally also the direction of fluid movement is changed.
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Fig. 4

Effects of varying frequency of vasoconstrictor fiber stimulation on the reactivity of the resistance and capacitance vessels during control period and during hemorrhagic shock maintained for 130 min. Comparison of responses to 2 and 10 imp/sec in the same cat. Responses expressed as percentages of control values obtained at 2 imp/sec. Responses at 10/sec are greater than at 2/sec until finally the responses are abolished. For any given frequency the resistance response declines more rapidly than the capacitance response. Note that increasing the frequency, by providing greater responses, will "protect," temporarily, against declining reactivity but more so for the capacitance function than for the resistance function.

little of the total resistance response remaining. On the basis of these observations, it seems possible that, at the point of outward filtration, all or almost all of the resistance response then present resides in the post-capillary section. This slight resistance response will have little importance with respect to impeding blood flow but will be an important factor in capillary filtration transfer.

This preparation affords opportunity to determine another important parameter of the vascular bed under consideration, namely, the tone of the pre-capillary sphincters. The tone of the pre-capillary sphincters determines the number of capillaries open to flow, and, therefore, the size of the capillary surface area directly available for exchange. This parameter can be studied by determining the capillary filtration coefficient (ml fluid filtered/min/100 g tissue/mm Hg change in mean capillary pressure). Therefore, changes in the filtration coefficient reflect changes in the tone of the pre-capillary sphincters.

In the control period (fig. 1 a) the filtration coefficient was 0.016 ml/min/100 g/mm Hg, which is of the same order of magnitude as that found in cat skeletal muscle by previous workers. Two minutes after the onset of the period of hemorrhagic hypotension, the filtration coefficient was found to be 0.030 ml/min/100 g/mm Hg (fig. 1 b), and remained
at about this level through the rest of the hypotensive period (fig. 1 c, d, e). Return of the blood to the animal was associated with a decrease in the filtration coefficient to the control value (fig. 1 f). It should be emphasized that to obtain exact information on the filtration coefficient one has to take into consideration changes in the ratio of pre-capillary to post-capillary resistance which occurs during the period of hypotension, as discussed in detail by Cobbold et al. In other experiments in this study it was found that the normal ability of the sympathetic vasoconstrictors to decrease the filtration coefficient was abolished very early in the period of hemorrhagic hypotension. From this it can be concluded that the nervous control of the pre-capillary sphincters is very rapidly interfered with during hemorrhagic hypotension.

Hemorrhagic hypotension, if sufficiently prolonged, abolishes all of the responses to constrictor nerve stimulation studied here. The first response that fails is that of the pre-capillary sphincters, next after this, that of the pre-capillary resistance vessels, while the response of the post-capillary vessels (post-capillary resistance vessels and main capacitance vessels) is much longer maintained.

Figure 4 shows the effects of different nerve impulse frequencies on the resistance and capacitance responses. The lower frequency (2 impulses/sec) was taken to represent moderate activity of the sympathetic system, and the higher frequency (10 impulses/sec) near-maximal activity in the intact organism. At any given time, both in the control period and during the period of hypotension, the higher frequency produced greater responses than the lower frequency, until the point was reached at which, even at the higher frequency, the resistance response, and, later on, the capacitance response was abolished. Despite the fact that, during the control period, the resistance response was increased relatively more than the capacitance response by stimulation at the higher frequency, during the period of hypotension the response of the capacitance vessels was longer preserved. By gradually increasing the frequency of nerve stimulation during the period of hypotension it would be possible to maintain the magnitude of both responses at the level seen at 2 impulses/sec in the control period. However, the period of time during which this could be done was much longer for the capacitance response than for the resistance response. This implies that an increase in the sympathetic discharge rate can "protect" against declining vascular reactivity, but in the long run more so for the capacitance response than for the resistance response. These experiments also demonstrated that the period of time during which nerve stimulation produced an inward filtration of extravascular fluid was longer at the higher frequency than at the lower frequency. It was further demonstrated that there was a period during which the higher frequency caused an inward movement of extravascular fluid, at a time when the lower frequency caused an outward movement of capillary fluid.

The general pattern of vascular responses to nerve stimulation, as described above, represents responses to one component of the sympatho-adrenal system. The other component, i.e., the catechol amines released from the adrenal medulla, could conceivably alter the general pattern of vascular responses during hemorrhagic hypotension, where it is known that both components are acting. To investigate this possibility a number of experiments were performed in which the adrenals and their nerve supply were left intact. The presence of the adrenals did not alter the general pattern of response. There was still a more rapid decline of the resistance response than of the capacitance response. In a few experiments it was noted that early in the course of hemorrhagic hypotension, responses of both the resistance and capacitance vessels were slightly greater than those obtained in the control period. Even in such experiments this phenomenon was transient and was followed by responses which soon fell much below control level, the resistance re-
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response again declining more rapidly than the capacitance response. The observation that the presence of the adrenals affected the results little if at all is in agreement with previous studies which indicated that the hormonal component of the sympatho-adrenal system plays a subordinate role in the constrictor response of the skeletal muscle vascular bed. Furthermore, this finding seems to indicate that the dilator effect, produced by moderate doses of epinephrine in skeletal muscle, cannot have been of great importance in these experiments.

During the control period close intra-arterial infusions of norepinephrine in "physiological" doses (up to 5 μg/min/kg tissue) produced responses of the skeletal muscle vascular bed similar to nerve stimulation. Thus, there was an increase in resistance to blood flow, a constriction of the capacitance vessels and a net inward movement of extravascular fluid (as previously described by Mellander). It was further demonstrated that during the period of hemorrhagic hypotension there was a progressive decline in both the resistance and the capacitance responses. As with nerve stimulation, the resistance response declined more rapidly and was abolished earlier than the capacitance response. Also, there was a progressive decline in the ability of norepinephrine to produce an inward movement of extravascular fluid, which went on, as with nerve stimulation, to the point at which an outward movement of capillary fluid occurred. As shown above (fig. 1, Q) supra-physiological doses of L-norepinephrine, infused during the period of hypotension when the resistance response to sympathetic stimulation was abolished and net outward filtration occurred, sometimes could produce a constriction of both the resistance and capacitance vessels and a net inward movement of extravascular fluid.

Discussion

With normal nutritional blood flow, stimulation of the sympathetic vasoconstrictor fibers to skeletal muscle causes a constriction of resistance vessels, pre-capillary sphincters, and capacitance vessels. The constriction of the resistance vessels is relatively more pronounced in the pre-capillary resistance section than in the post-capillary resistance section, with the result that there is a decrease in mean capillary hydrostatic pressure and therefore a net inward movement of extravascular fluid. In the present experiments it was demonstrated that during the period of hemorrhagic hypotension, the ability of the nerves to elicit all these responses is interfered with. The rate of decline of this reactivity is different for each vascular section but for all sections can go on to complete abolition of reactivity.

Hemorrhagic hypotension is associated with a marked reduction in skeletal muscle blood flow, which occurs even with section of the sympathetics (fig. 1). Since the temperature of the region under study was kept constant, it can be concluded that a reduction in nutritional blood flow would produce a relative imbalance between the supply of blood and the metabolic demands of the tissue. This then can be considered as causing a relative "accumulation of metabolites" in the tissue. The term relative "accumulation of metabolites" neither specifies the agent (or agents) responsible nor excludes the parallel possibility of relative "lack of nutrients." Whatever the ultimately responsible factor (or factors) may be, it is known that such a situation results in relaxation of vascular smooth muscle. Therefore it seems logical to assume that there is a competition between this dilating factor and the constricting action of the sympathetics, and that this results in the decline in vascular reactivity noted in the present experiments.

It might be argued that this declining reactivity could be due to other factors, such as damage to the nerves, failure of elaboration of the neurohumoral transmitter substance at the nerve endings, or secretion of epinephrine from the adrenal medullae. The arguments against these have been presented previously. It is also possible that the declining vascular reactivity seen here could be
due to the elaboration of a dilator factor from some other tissue. This is a definite possibility. However, in an earlier investigation when nutritional blood flow to the region under study was reduced to the same degree as in these experiments, at the same time that nutritional blood flow to the rest of the animal was maintained at the normal level, the pattern of declining vascular reactivity was very similar to that seen here. Therefore, the declining reactivity seen during hemorrhagic hypotension must be due almost exclusively to locally elaborated dilator factors, and little, if at all, to those produced elsewhere. In this regard, one possible factor that merits special attention is the action of endotoxins absorbed from the intestinal tract. It should be noted that in this preparation the intestines, from the duodenum to the rectum, were removed, and such absorption thereby prevented.

Since the declining vascular reactivity during hemorrhagic hypotension therefore in all probability is due to a relative "accumulation of metabolites," the observations described here make it clear that each vascular section has a different "sensitivity" to the effect of the accumulating metabolites. This conclusion is based on the differences in the rate of decline of reactivity that were noted in the various vascular sections during hemorrhagic hypotension. Thus, it can be said, that the section most sensitive to the accumulation of metabolites is the pre-capillary sphincters, next most sensitive the pre-capillary resistance vessels, and least sensitive the post-capillary section (post-capillary resistance vessels and main capacitance vessels).

Since the observations made during hemorrhagic hypotension are on a different part of the pressure-flow curve than the control observations, it could possibly be argued that using the figures obtained at the higher pressure for "controls" introduces a "mechanical" artifact. Moreover, since the change in pressure may well be greater for the resistance section than for the capacitance section, such a mechanical factor could, at first glance, account for the more rapid decline in the resistance response. The arguments against this have been presented previously. Furthermore, as seen in figure 1 B the responses elicited immediately after the onset of hypotension were nearly as large as those in the control period both for the resistance and the capacitance vessels.

The observation that the various vascular sections show a different sensitivity to the "accumulation of metabolites" deserves further emphasis in terms of circulatory homeostasis during hemorrhagic hypotension. It has been shown that the reactivity of the pre-capillary sphincters to nerve stimulation is abolished quite early in the course of hemorrhagic hypotension. This has several effects. First, it causes the reduced volume of blood flow to be distributed over a wider area of the capillary bed. In this way, by reducing the distance for diffusion within the tissues and by reducing the mean velocity of flow, there can occur an increased oxygen extraction from the blood and a facilitated elimination of waste products from the tissues, which would act to compensate for the reduced blood flow. Second, it increases the area of the capillary bed over which fluid can be mobilized by filtration. Because the action of the pre-capillary sphincters makes up only a small fraction of the overall resistance to blood flow, the loss of tone here will not significantly affect resistance to blood flow.

In contradistinction to this, the action of metabolites on the somewhat larger pre-capillary vessels (arterioles and small arteries) will be a very important factor for determining the resistance to blood flow. In this regard, the declining reactivity of the resistance vessels, and, in particular, the pre-capillary resistance vessels has several effects. First, the early rapid interference with reactivity here limits the degree of neurogenic reduction in blood flow obtainable, and, in this way, may tend to prevent severe ischemia. It must be emphasized that early in the course of hemorrhagic hypotension, the reduced reactivity of the resistance vessels implies only that the increase in resistance on nerve stimu-
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ulation is less than in the control period. It does not signify failure of nerve stimulation to increase resistance. Such a failure does occur but is late in the course of hemorrhagic hypotension and may, during a considerable period of time, be compensated for by an increased discharge rate of the vasoconstrictor fibers.

The observation that the reactivity of the resistance vessels to sympathetic activation is related to both the severity and the duration of shock, may help to explain the contradictory findings of other investigators that the vascular resistance of skeletal muscle in shock may be increased, decreased, or normal. Also, while the reactivity of the pre-capillary resistance vessels is more rapidly interfered with than the post-capillary resistance vessels, early in the course of hemorrhagic hypotension, nerve stimulation still causes a relatively more pronounced increase in pre-capillary resistance than post-capillary. Consequently for a long period of time, vasoconstrictor stimulation causes a lowering of mean capillary hydrostatic pressure and a net inward movement of extravascular fluid. Again, it is only late in the course of the hypotensive period, when there is presumably almost complete abolition of the pre-capillary resistance response, that nerve stimulation causes a relatively more pronounced development of post-capillary resistance resulting in a net loss of fluid from the circulation. This fluid loss appears to be further enhanced by the occurrence of sludging, which is mainly a post-capillary phenomenon. Sludging is independent of nerve stimulation and can be shown not to be the sole factor in fluid loss from the circulation in these experiments by the observation that the tissue can be made to gain fluid volume during nerve stimulation where it is isovolumetric both before and after nerve stimulation.

The other function that is long maintained during hemorrhagic hypotension is the capacitance response, which is mainly post-capillary. The retention of reactivity here provides for a mobilization of the blood localized in this depot section, thereby enhancing "venous return" and cardiac output.

One of the major compensatory mechanisms of the organism in hemorrhage is the increased activity of the sympathetic nervous system. Provided that in vivo there is a generalized reflex increase of sympathetic discharge to all consecutive sections of the vascular bed in shock, which, in fact, available experimental evidence seems to indicate, the present study permits some conclusions concerning the response pattern which appears in the peripheral circulation. With regard to the vascular bed in skeletal muscle it can be seen that the increased sympathetic activity increases resistance to blood flow, but this is tempered to a great extent by the antagonistic action of the dilating metabolic factors. It also provides a capacitance response which, by decreasing the volume of blood contained in the vascular bed, makes peripheral blood available for the central circulation. Furthermore, it actually increases the circulating blood volume by causing a net inward movement of extravascular fluid. As has been pointed out, this is brought about by the relatively greater development of pre-capillary resistance than post-capillary which causes a decrease in mean capillary hydrostatic pressure. It has also been pointed out that the action of the locally produced metabolic factors interferes with the development of pre-capillary resistance, which impairs to some extent the ability of the sympathetic nerves to lower capillary pressure. While this tends to reduce the role of sympathetic impulses in mobilizing extravascular fluid, it is compensated for by the increase in filtration coefficient brought about by the concomitant relaxation of the pre-capillary sphincters.

These effects of the sympathetic system all seem to act in a compensatory manner. Depending on the severity of the hemorrhage and the extent to which these mechanisms are called into play, they may correct either completely or partially the circulatory derangement. One critical feature would seem to be whether or not these compensations can pre-
vent a progressive decline of reactivity. If reactivity is fairly well maintained, then the net direction of transcapillary fluid movement will tend to be into the circulation, and with this there will be some constriction of the resistance vessels and a maintained pronounced constriction of the capacitance vessels. These adjustments in the vascular bed of skeletal muscle favor survival of the organism.

However, if the compensations are inadequate to balance the amount of hemorrhage, then declining vascular reactivity will occur. In this situation two decompensating phenomena can be deduced from the results of these studies. First, a point will be reached at which, with loss of pre-capillary resistance response in the face of preserved post-capillary resistance response, the action of the nerves will cause fluid to leave the circulation. In the cat experiment shown in figure 1, at 120 minutes after the onset of hemorrhage, fluid was leaving the capillaries at the rate of 0.035 ml/min/100 g tissue. In a 70 kg man with 30 kg of muscle mass this could conceivably result in a decrease in circulating blood volume of more than 600 ml/hour. Note also that this would be accomplished by filtering only 2 ml of fluid into the interstitial space of every 100 g of muscle, a volume hardly detectable as gross edema. The extent to which this fluid can be returned to the circulation by the lymphatics is not known, but the observation that there is a progressive decline in thoracic duct lymph flow in hemorrhagic shock suggests that this fluid might well be permanently lost from the circulation. Furthermore, since the maximum capacitance response to nerve stimulation in the hind part of the cat (about 500 g), noted above, amounted to 5 ml, corresponding to some 300-500 ml in the adult human being, at least this volume could be pooled in the capacitance section of the skeletal muscle vascular bed, when its nervous control fails. Therefore it seems likely that in these late stages of hemorrhagic hypotension, when intravascular fluid leaves the circulation and blood is gradually pooled in the capacitance vessels, "venous return" and cardiac output would decrease. This, in turn, would further impair vascular reactivity, producing a "vicious circle" from which the organism could not survive.

The results of this investigation may also be applied as an aid in understanding some aspects of the treatment of hemorrhagic hypotension. Since the study has only concerned itself with skeletal muscle, whose responses may not be representative of other tissues, the suggestions noted here obviously need to be investigated further in other tissues. Restoration of blood volume at a time when there is a noticeable resistance response and an inward movement of extravascular fluid on nerve stimulation, will restore vascular reactivity to normal. Even at the point at which there is an outward filtration on nerve stimulation, complete recovery can be obtained (fig. 1 G), but may not be, especially after a long period during which there has been outward filtration. Also of importance is the observation that partial restoration of the circulating blood volume will increase vascular reactivity, not necessarily to normal, but will prolong the period of time to abolition of reactivity.

Most investigators agree that the administration of norepinephrine during hemorrhagic hypotension has a beneficial effect upon the myocardium.17-10 There is, however, less agreement as to whether or not its action on the vascular bed is beneficial. The results of this study suggest an explanation for this controversy. Since this agent acts similarly to, and synergistically with, the vasoconstrictor nerves, administering it in "physiological" doses early in the course of hemorrhagic hypotension can be expected to act in a compensatory manner a) by increasing the pre-capillary to post-capillary resistance ratio and thereby cause a movement of extravascular fluid into the circulation and b) by constricting the capacitance vessels thus increasing "venous return." Later on, like the nerves, it can be expected to enhance fluid loss from the circulation. However, at this point, increasing the dosage beyond the "physiological" range can be beneficial by increasing the
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capacitance response and at the same time reversing the direction of transcaponary fluid movement (fig. 1 Q).

The results of this study also offer a possible explanation for the beneficial action of sympatholytic agents in hemorrhagic hypotension. Since there is a stage at which the vasoconstrictor nerves cause fluid to leave the circulation, blocking their action at this stage should prevent this important decompensating phenomenon. Such agents will of course also block the prevailing neurogenic constriction of the capacitance vessels, leading to some "pooling" of blood. The relatively small amount of circulating blood "lost" in this way when the capacitance response is already failing should be contrasted with the much greater fluid loss that at this stage would occur if the outward filtration effect due to the action of the sympathetics was maintained for a long time. In this regard the observations of Nickerson are of some interest. He noted that the administration of a sympatholytic agent did not provide protection against hemorrhagic shock if the volume of re-infused blood was in itself inadequate to allow survival.

While this study has been concerned only with the effects of hemorrhagic hypotension, it seems clear that any factor, regardless of etiology, which has the effect of reducing tissue blood flow will impair vascular reactivity and lead to the train of events shown here.

Summary

During hemorrhagic shock there is impairment, and eventually abolition, of the responses of both the resistance and the capacitance vessels in cat skeletal muscle to regional lumbar sympathetic vasoconstrictor nerve fiber stimulation and to close intrarterial infusion of L-norepinephrine. The rate of decline of reactivity is faster, and the time to abolition shorter, for the resistance response than for the capacitance response.

Also, the pre-capillary resistance response declines faster and is abolished earlier than the post-capillary resistance response. This impairs and eventually abolishes the ability of constrictor nerve stimulation to decrease mean capillary hydrostatic pressure, and, thereby, causes a net inward movement of extravascular fluid. Preservation of the post-capillary response beyond that of the pre-capillary results eventually in a net outward movement of capillary fluid on nerve stimulation.

Replacement of the shed blood restores vascular reactivity to normal. This can occur even when nerve stimulation results in a net loss of capillary fluid, but may not, if this period of shock has been very long.

The evidence indicates that pre-capillary functions (small arteries, arterioles, and pre-capillary sphincters) are more under the influence of local metabolic factors than of extrinsic nervous influence. On the other hand, post-capillary functions (post-capillary resistance vessels, and main capacitance vessels) are more dominated by extrinsic nervous influence. However, even in this section the nervous influence may be overcome by relatively large concentrations of "metabolites" as is seen late in the period of hemorrhagic shock.

From the results obtained here, it is suggested that early in hemorrhagic shock the sympathetics, at least with respect to skeletal muscle, act in a compensatory manner by maintaining "venous return" (maintained capacitance response) and by increasing circulating blood volume (inward movement of extravascular fluid). The dominant action of local dilator factors on pre-capillary functions has the effect of limiting the magnitude of nerve-induced increased resistance to blood flow and, by impairing the reactivity of the pre-capillary sphincters, distributes the available blood flow over a greater than normal fraction of the capillary bed.

Late in the course of hemorrhagic shock, with abolition of pre-capillary responses, the action of the sympathetics would appear to be decompensatory, in that they cause a loss of fluid from the capillaries. This phenomenon may provide a partial explanation for

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the observed beneficial effect of sympatholytic agents in hemorrhagic shock.

The sequence of deteriorating vascular reactivity in skeletal muscle, while not necessarily representative of all tissues, serves to explain many of the hitherto puzzling features of the peripheral vasculature in shock. It also suggests a mechanism, common to all states with reduced tissue blood flow, that may explain lack of response to treatment.

References
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