

## CONTROL OF RESISTANCE, EXCHANGE, AND CAPACITANCE FUNCTIONS IN THE PERIPHERAL CIRCULATION<sup>1</sup>

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### I. INTRODUCTION

Circulatory research carried out over the last few decades has greatly deepened our knowledge of the nature of the regulation of blood flow in different regions of the body, many aspects of which have been described in recent reviews (20, 46, 112, 113, 157, 159, 163, 164, 216, 298). Besides studies of the resistance function of the vessels, determined from measurements of pressure and flow, recent circulatory research has also been devoted to problems concerning other peripheral vascular functions, such as **capillary flow distribution**, **transcapillary exchange of fluid and solutes**, and regional blood volume capacity. These functions are controlled by variation of smooth muscle tone in different sections of the vascular bed, and much experimental evidence has accumulated to show that such control is of utmost importance for cardiovascular homeostasis and local tissue nutrition.

<sup>1</sup> Original work discussed in this review was supported by: the Swedish Medical Research Council, research grants K68-14x-2210-02 (S. M.) and B68-14x-28-04 (B. J.); Air Force School of Aerospace Medicine under contract AF 61(052)-732 through the European Office of Aerospace Research (OAR), United States Air Force; U. S. Public Health Service, research grant HE-05675-06 from the National Heart Institute; AB Hässle, Göteborg.

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Furthermore, interesting differentiated patterns of response within various sections of the vascular bed have been revealed. Recent information about the individual characteristics of vascular smooth muscle with regard to its contractile machinery and responsiveness has contributed further understanding of how such differentiated reactions can occur.

In the present review some recent advances concerning the dimensions and the control of vascular functions in the systemic circulation will be considered. Special attention will be paid to quantitative studies in which several functions have been followed simultaneously, since such detailed analysis permits the prevailing vascular state to be defined most clearly. Skeletal muscle, skin, and intestine are the vascular circuits on which more detailed studies of this type have been performed, and the following presentation of the influence of various vascular control mechanisms is thus limited largely to these tissues. Yet, these vascular beds are important targets for the control systems concerned with the regulation of general hemodynamics and they show in addition pronounced reactions to other factors determining vascular tone. In comparison to one another, they display interesting differences in vascular design and patterns of response, and these circuits may serve as models for discussing vascular control in tissues with different functions.

The fundamental principles for transcapillary exchange (228) and various aspects of resistance and capacitance phenomena (8, 68, 131, 146, 158) have been reviewed previously.

## II. FUNCTIONAL DIFFERENTIATION OF THE VASCULAR BED

Coordination and integration of cardiac activity and peripheral vascular functions are essential for the maintenance of homeostasis in the organism. The role of the peripheral circulation in this interplay may be more easily appreciated by considering in detail its functional organization.

### A. Definitions

The vascular beds of the various tissues constitute a set of parallel-coupled circuits in the systemic circulation, each of which contains a number of series-coupled sections of different design and function (fig. 1).

1. *Windkessel vessels* (large and medium-sized arteries) transforming the pulsatile cardiac outflow into a fairly steady flow through the small blood vessels.
2. *Resistance vessels*, determining the overall resistance function and, hence, regional blood flow. There are two adjustable resistance sections:
  - a. Precapillary resistance vessels (mainly small arteries and arterioles), responsible for by far the largest fraction of regional resistance.
  - b. Postcapillary resistance vessels (venules and veins). The ratio of precapillary to postcapillary resistance determines capillary hydrostatic pressure and, hence, the fluid filtration exchange.
3. *Precapillary sphincter vessels*, the smallest precapillary resistance vessels, in which smooth muscle contraction can lead to closure of capillary entrance and thus affect capillary flow distribution. Changes in activity of these sphincters

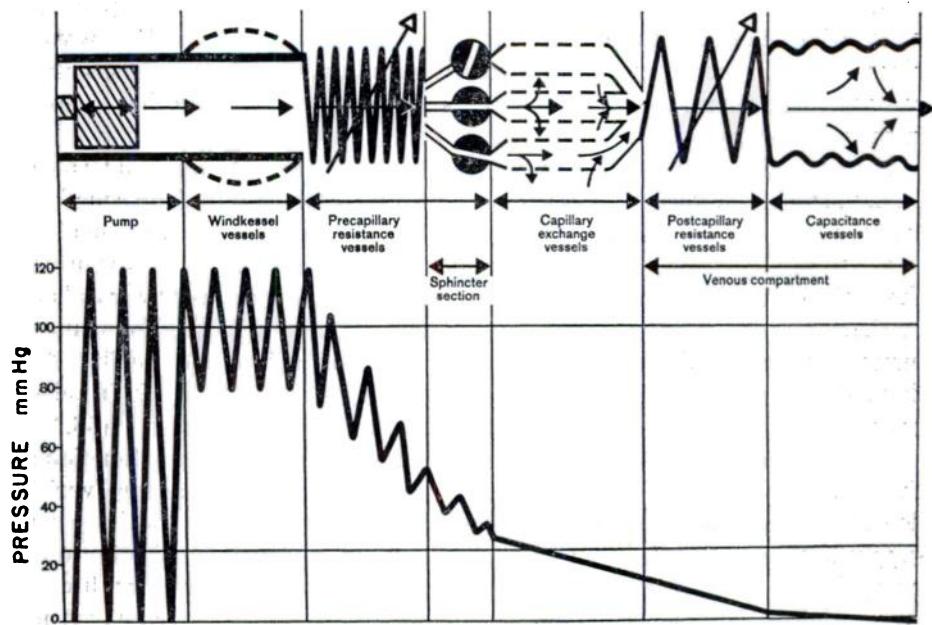


FIG. 1. Schematic illustration of the functionally differentiated consecutive sections of the vascular bed and the pressure profile along the circuit.

determine the number of patent capillaries and hence the size of the capillary surface available for normal exchange.

4. *Exchange vessels* (the true capillaries) which constitute the key section of the cardiovascular system in the sense that here the contact between external and internal environment is established by transcapillary diffusion and filtration exchange.

5. *Capacitance vessels* (mainly the voluminous venous section) containing some 80% of regional blood volume (e.g., 345). Changes of smooth muscle tone in these vessels can produce hemodynamically important shifts in regional blood content and thus influence venous return and cardiac output.

6. *Shunt vessels* (wide-bore arteriovenous channels) permitting a bypass of the exchange vessels to subserve specialized functions. They are present in some tissues only and are not illustrated in figure 1.

#### B. Vascular functions and methods of measurement

Smooth muscle elements are present in the walls of all the vascular sections listed above with the exception of the true capillaries. The all-important capillary exchange function is therefore controlled to a great extent by adjustments of smooth muscle tone in the other vessels and of the activity of the cardiac pump. The foregoing concept of a functional differentiation in the peripheral circulation can greatly facilitate the understanding of complex vascular reactions and these functional terms have been adopted in a steadily increasing number of recent

investigations. It should be emphasized that there are no strict morphological boundaries delimiting the various peripheral vascular functions. For example, blood expelled from the precapillary vessels contributes to the overall capacitance response, but, quantitatively, this effect is small in comparison to that occurring in the venous section.

In this section, there will be a brief discussion of the functional significance of adjustments in the various series-coupled vascular sections and of some methodological principles used to study the different functions in quantitative terms.

*Resistance function.* Changes in the radius of the resistance vessels are normally the main determinant of tissue blood supply, since cardiovascular regulatory mechanisms tend to keep the pressure head fairly constant. The dominance of luminal changes in this connection is obvious from the law of Poiseuille. For a discussion of the involvement of physical factors, such as changes in blood viscosity, in the resistance function the reader is referred to other reviews (158, 247).

The two main principles used in studying total regional resistance function are the constant flow/variable pressure method and the constant pressure/variable flow method. The former is to be preferred if major interference with tissue blood supply is to be avoided, but a great disadvantage is that it implies the use of pump devices in the arterial circuit, which can significantly interfere with vascular reactivity (110). Further, this method is unphysiological in the sense that pressure alterations are usually not the normal type of resistance response *in vivo*. Although small to moderate resistance changes may be recorded adequately, strong vasoconstrictor effects lead to abnormally high transmural pressures in parts of the vascular bed and, conversely, pronounced vasodilatation to such low pressures that "critical closure" may result. This method therefore may not permit correct quantitative evaluation of the whole range of resistance control. These drawbacks are not inherent in the constant pressure method, but some local interference with vascular response may result from the variation in flow *per se*. Calculation of the resistance response in terms of peripheral resistance units ( $\text{mm Hg}/\text{ml} \times \text{min} \times 100 \text{ g tissue}$ ) provides convenient processing of data, and can be physiologically meaningful if the basic pressure/flow characteristics of the vascular bed are taken into consideration (158).

Information about segmental resistances in the vascular bed can be obtained by recording central arterial and venous pressures and pressures in small arteries and veins at known flow rates (168). Measurement of capillary pressure by inserting micropipettes into the capillary lumen (227, 348) provides the possibility of separating the functionally important segmental resistances of the precapillary and postcapillary vessels. This difficult technique has hardly been applied at all to studies of mammalian vasomotor response patterns, but the ratio of pre- to postcapillary resistance and its functional significance for capillary fluid filtration can be assessed by other means (see below).

*Exchange function.* The functional properties of the capillary membrane and the kinetics of transcapillary exchange have been reviewed recently by Landis and Pappenheimer (228).

Capillary exchange will be influenced by adjustments of vascular tone and

preferentially by the reactions occurring within the pre- and postcapillary resistance vessels and the precapillary sphincters. The importance of total vascular resistance in the region of the exchange function is obvious, since it determines volume flow of blood. During precapillary sphincter closure, the very small stagnant blood volume in the corresponding capillary quickly approaches a diffusion and filtration equilibrium with the extravascular space. This capillary is then soon excluded from participating in the exchange between blood and tissue. Therefore, most of the factors determining capillary transfer, such as capillary flow distribution, size of capillary exchange surface, capillary flow velocity, *i.e.*, time available for exchange, and diffusion distances to tissue cells will be influenced, directly or indirectly, by the level of activity in the precapillary sphincters. Finally, vasomotor adjustments of the ratio of pre- to postcapillary resistance will affect capillary hydrostatic pressure and, hence, the fluid filtration exchange.

Two main methods have been used for estimation of relative changes in the functional capillary surface area as influenced by alterations in precapillary sphincter activity. One was developed by Renkin *et al.* (275, 276), who studied the capillary diffusion capacity for radioactive potassium or rubidium. They calculated the capillary "permeability-surface area product," or PS, from the arteriovenous extraction fraction for these tracers at known blood flow rates. At constant flow and constant arterial concentration of the tracer, variations in venous concentration reflect the changes in PS. Since these tracers are rapidly taken up by the tissue cells, backflux into the blood from the extravascular space is generally negligible but can be corrected for, if necessary. PS has the dimension of  $\text{ml}/\text{min} \times 100 \text{ g tissue}$ . This method alone does not permit separation of the two factors, permeability and surface area.

The other method is based upon determination of the hydrodynamic conductivity, or capillary filtration capacity, of the functioning exchange vessels in terms of the capillary filtration coefficient, or CFC (69, 130). CFC is determined by volumetric or gravimetric recording of the rate of net fluid filtration produced by a known rise in mean capillary hydrostatic pressure and it has the dimension of  $\text{ml fluid filtered}/\text{min} \times 100 \text{ g tissue} \times \text{mm Hg transcapillary pressure gradient}$ . CFC is largely independent of blood flow, whereas PS varies with flow rate. CFC, like PS, reflects the product of capillary surface and permeability and this product *per se* is an important physiological variable related to the exchange function.

It appears that the properties of the capillary membrane itself, *i.e.*, capillary permeability, are largely unaltered in most physiological circumstances. For example, the lymph/plasma ratio of dextran fractions of molecular weights varying between 10,000 and 75,000 was found to be unaltered during exercise hyperemia, and this strongly suggests that capillary permeability to large molecules is not affected by the exercise vasodilatation (13). Severe hypoxemia has been reported not to affect capillary fluid permeability in dog forelimb (296). Since capillary permeability seems to remain constant, observed changes in PS and CFC during adjustments of vascular tone would reflect alterations in functional capillary surface area, as induced by changed precapillary sphincter activity. On the other

hand, differences in PS or CFC between various vascular beds do not necessarily reflect the relative dimensions of their capillary surface areas, since capillary permeability is likely to vary in different tissues. It is worth noticing that these two independent methods have shown largely similar results with regard to the extent to which capillary surface can vary in states of vasoconstriction and metabolic vasodilatation (see below).

The Starling concept of capillary fluid filtration exchange has received wide experimental support (228). The Starling formulation concerning the rate of net transcapillary fluid movement, F, can be written:

$$F = CFC \times (P_c - \Pi_{p1} - P_{if} + \Pi_{if})$$

where CFC denotes the capillary filtration coefficient,  $P_c$  the hydrostatic capillary pressure,  $\Pi_{p1}$  plasma colloid osmotic pressure,  $P_{if}$  hydrostatic pressure in interstitial fluid, and  $\Pi_{if}$  colloid osmotic pressure in interstitial fluid. A positive value for F would indicate capillary filtration, and a negative one absorption. Deviations from the normally existing Starling equilibrium would thus lead to an increase or decrease of plasma volume.

Vasomotor adjustments might influence all variables in the above formulation (228, 250), but the most direct effects are on CFC and  $P_c$ , which are affected by smooth muscle activity in precapillary sphincters and by the ratio of pre- to postcapillary resistance, respectively.  $P_c$  is determined by the following relation (267):

$$P_c = \frac{\left(\frac{r_v}{r_a} \times P_a\right) + P_v}{1 + \frac{r_v}{r_a}}$$

where  $P_a$  is arterial inflow pressure,  $P_v$  venous outflow pressure,  $r_v$  postcapillary resistance, and  $r_a$  precapillary resistance. When discussing  $r_v/r_a$  the reverse relation, *i.e.*, pre- to postcapillary resistance ratio, has been commonly used, and this convention is adopted in the present paper. At constant arterial and venous pressures, a decrease of the ratio of pre- to postcapillary resistance leads to a rise, and an increase of the ratio to a fall in mean capillary pressure. Evidence will be presented below that vasomotor adjustments can change this ratio and, hence, lead to net filtration or absorption. The rate of such transcapillary fluid movements produced in a tissue can be measured by recording changes of tissue volume (219, 248) or weight (167, 299) and these effects can be separated from concomitant alterations in regional blood volume (3, 222, 248). The resulting changes in plasma volume are the hemodynamically important effects of such vasomotor adjustments. However, these data permit, in addition, quantification of the regional microcirculatory events, in that approximate calculation of the induced changes of  $P_c$  and  $r_v/r_a$  can be made, if CFC is determined simultaneously (*e.g.*, 248, 255, 262).

The establishment of a Starling equilibrium must not necessarily be conceived of as a balance between filtration in the arterial end of the capillary and absorp-

tion in its venous end. Periods of predominating filtration may alternate with periods of absorption in a capillary loop because of spontaneous variations in vascular tone (*cf.* 352). Further differences in  $P_c$  may prevail in various exchange vessels because of varying capillary bore and length and precapillary sphincter activity, leading to filtration and absorption between adjacent channels. There is evidence to suggest a high wall permeability in the smallest venous vessels (347), which would permit them to participate in the exchange and assist in the absorption process. These details do not seem to invalidate the basic theory advanced by Starling or the foregoing principles for adjustment of plasma volume.

It has been suggested that the process of filtration and absorption, besides its importance for fluid redistribution between the intravascular and extravascular compartments, can aid in the transport of solutes from tissue to blood (240).

*Shunt function.* The functional importance of arteriovenous shunt vessels is that they permit a large fraction of the regional blood flow to bypass the nutritive exchange vessels. True arteriovenous anastomoses have been demonstrated most clearly in the skin, where these vessels of low resistance are engaged in thermo-regulation. If the large volumes of blood required to transport heat from the core of the body to the skin should pass through the capillaries, the necessary dilatation of the arteriolar resistance vessels might lead to such increase of capillary hydrostatic pressure that oedema might ensue.

Besides the use of morphological techniques for the demonstration of arterio-venous anastomoses, dynamic studies of these vessels can be performed *in vivo* by determining the recovery in the venous effluent of intra-arterially injected microspheres of graded sizes (*e.g.*, 41, 286). In experiments in which blood flow and capillary exchange are measured simultaneously, a redistribution to non-nutritional shunts would manifest itself as a clear-cut dissociation between flow and exchange. Yet, such results must be interpreted with some caution, since a nonuniform distribution of flow in capillaries might lead to decreased exchange. This phenomenon is termed "functional shunting" and should be clearly distinguished from true shunting through nonnutritional pathways (see section IV).

*Capacitance function.* As mentioned above, the major portion of the blood volume in a region resides in venules and veins, a circumstance that justifies their designation as capacitance vessels. Contraction of venous smooth muscle is of hemodynamic significance either by its ability to mobilize blood and thus promote venous return to the heart, or by its ability to stiffen the walls of the veins and so enable them to resist a greater hydrostatic pressure. The latter type of contraction also helps to maintain venous return by preventing or reducing pooling of blood.

Besides the active venomotor responses, variations in venous transmural pressure can result in passive translocation of blood, the extent of which is greatly dependent on the prevailing venous pressure level (263). At high venous transmural pressures, as in dependent parts of the body, the veins contain a large blood volume and are distended so that their cross section is entirely circular. When a region is at heart level, the transmural pressure of the veins is about 5 to 10 mm Hg, which is still sufficient to keep their circumference almost rounded. Above

heart level, the veins tend to collapse and become elliptical or even flat. It is clear that the blood volume of well distended veins will be little affected by moderate changes in transmural pressure, whereas in the low venous pressure range considerable passive expulsion of blood will occur even for small decreases of pressure because of the concomitant change in vessel configuration. Venous transmural pressure can of course be affected from the arterial side as well. One important aspect of the above considerations is that vasomotor adjustments involving pre-capillary constriction or dilatation can lead to changes in venous pressure and hence to "passive" capacitance responses, which will be particularly pronounced in the lowest transmural pressure range (263).

The extent of active shortening or tension development that the venous smooth muscle can accomplish in response to a given stimulus depends clearly on the load and on the fibre length prevailing, just as in other types of muscle. It should be emphasized at this point that the load against which vascular muscle contracts is determined not only by the transmural pressure but also by the prevailing radius of the vessel according to the Laplace relationship. Increasing smooth muscle activity in a collapsed vein gives only little change in wall tension and it might not lead to any expulsion of blood; a paradoxical increase in blood volume may even occur, due to the fact that the vein assumes a more rounded circumference (263). As the vein is gradually filled, smooth muscle contraction becomes increasingly effective in developing force, but a point is reached at which the active component of wall tension begins to decline when the vessel is greatly distended by high transmural pressures. Similarly, a given stimulation of venous smooth muscle that leads to considerable expulsion of blood at moderate venous pressures will have little or no effect if the transmural pressure is greatly augmented, for instance by exposing the vascular bed to large hydrostatic loads.

It is thus clear that the magnitude of the venous response to a given stimulus, no matter how it is measured, is greatly influenced by the prevailing venous pressure level and by concomitant adjustments of precapillary resistance. Therefore, meaningful information about capacitance function can be obtained only by presenting sets of data for a whole spectrum of pressures and volumes or by standardizing the experiments at a defined venous pressure or volume within the physiological range. Otherwise quantitative comparison of results may not be possible.

Some aspects of the capacitance vessels have been revealed from recordings of venous pressure-volume diagrams (*e.g.*, 8, 298), but these are complicated by the presence of hysteresis phenomena. Rapid and transient venomotor adjustments can hardly be revealed by this method, since it does not permit continuous recording of the capacitance function.

Much of the available information about the control of the capacitance vessels has been obtained with methods that measure directly the shift in regional blood volume under standardized conditions. This has been done with plethysmographic or gravimetric techniques that permit continuous recording of changes in the volume or the weight of the region studied (*e.g.*, 248, 299). In such recordings the capacitance response can be distinguished from shifts in tissue volume or

weight resulting from net transcapillary fluid movements. There are several means by which these two phenomena can be separated (248). They can be distinguished most readily by their markedly different time courses, but the separation is greatly aided by combining the volumetric method with an isotope technique ( $^{51}\text{Cr}$  tagged red cells) that records the capacitance response selectively (3, 222).

Mention should also be made of the possibility of calculating regional blood volume from determinations of blood flow and of mean transit time for the passage of an intravascular indicator (e.g., 350). Capacitance responses of the whole circulatory system have been studied by observing translocations of blood between the vascular system and an extracorporeal blood reservoir (287).

The total capacitance response associated with vasomotor adjustments is of obvious hemodynamic importance because of its influence on venous return, but with some of the above methods it is possible to distinguish between its passive component, secondary to concomitant changes in precapillary resistance, and its active component, related to alterations of venous tone (219, 248). A quantitative analysis of the relative importance of these components in the capacitance response to a given stimulus at different levels of venous pressure has been carried out by means of the plethysmographic technique mentioned above (263).

The method of studying "isovolumetric" venomotor reactions by pressure recordings in occluded veins or venous beds (e.g., 51, 57, 302) is not complicated by any passive component in the response and it can be used to demonstrate separately, for instance, neurogenic influences on the venous vessels. However, the situation of arrested flow is unphysiological and other vascular functions cannot be studied simultaneously in the same region. Comparable and reproducible data can be obtained only if the actual venous compartment is properly defined and its blood volume standardized for sequential experimental runs to avoid variations in the responses due to different degrees of initial venous distension. These prerequisites have been neglected in many investigations. The isovolumetric responses may give information about the pressure load the veins could carry without deviating from the prevailing state of filling. However, this is not the common mode of operation for venous smooth muscle, and the isovolumetric data cannot be interpreted in terms of regional blood volume translocations, which is the most important aspect of venous function. This difficulty is also encountered when studying segmental resistance on the venous side by recording pressure in small and large veins at known flow rates (168).

*Simultaneous analyses of several vascular functions.* To get a detailed picture of a vasomotor response pattern in a region, quantitative information about the changes in all the vascular functions is required. Since there is much interaction between the various functions it is desirable that they be studied simultaneously. Experimental approaches aiming at such detailed analysis have been developed in a few laboratories by combining several of the techniques discussed above. The methods applied bear some relation to the principles advanced by Pappenheimer and Soto-Rivera in their studies of capillary function (267). For example, it is possible to study simultaneously and quantitatively the reactions in pre- and postcapillary resistance vessels, precapillary sphincters, and capacitance vessels

as well as changes in net transcapillary fluid movement by combining the constant pressure/variable flow method for resistance recording with the plethysmographic and radioactive chromium techniques for recording of capacitance responses, capillary fluid transfer, and CFC (*e.g.*, 3, 69, 129, 222, 248, 254, 255, 262). In these studies, several or all of these methods were applied to the study of a variety of vasomotor reactions in cat skeletal muscle, skin, or intestine and in human foot or forearm. Another group of investigators has used a gravimetric technique for detailed studies of local control mechanisms in the intestinal circulation (*e.g.*, 204, 299). A different experimental approach has been to study simultaneously segmental resistances and changes of tissue weight, investigations performed mainly on the dog forelimb (*e.g.*, 167, 296). The resistance function and capillary diffusion capacity have been studied simultaneously in dog skeletal muscle (275, 276).

### III. THE VASCULAR SMOOTH MUSCLE EFFECTOR

#### A. *Nature of vascular tone*

Peripheral vascular functions are actively controlled by adjustments of the level of "tone" in the different vessels. Vascular tone (or tonus) is due to smooth muscle activity, and the term is used here to signify the average level of contractile state in the musculature within a region or section of the peripheral circulation. We should try, however, also to understand the meaning of the term tone at the cellular level by considering some functional characteristics of vascular smooth muscle.

Tone in skeletal muscle, engaged in the maintenance of body posture, is due to asynchronous or tetanic contractions of the individual motor units. Also vascular smooth muscle tone can be conceived of as the integrated result of phasic twitches initiated by action potentials. Experimental evidence for such a system has been obtained with muscle from some different types of vessel during recent years (see below), but in a review published as late as 1963 it was stated that "vascular smooth muscle shows no conducted electrical activity and no spikes" (138). There is now much evidence that vascular smooth muscles from different sites show great individual variations in their functional characteristics, and this invalidates many earlier generalized conclusions drawn from studies of preparations of large arteries.

*Correlation between electrical and mechanical activity.* Since Funaki's report on action potentials recorded by intracellular microelectrodes from smooth muscle cells in the small vessels of the frog tongue (141), there have been descriptions of electrical activity in vessels from several sites and species. Action potentials of the plateau type were found in turtle aorta (280) whereas spike-like potentials have been recorded from mammalian veins (15, 71, 142, 257, 307), from small arterial vessels (315, 319), and occasionally from large mammalian arteries (212, 213). The resting membrane potential is generally low, 30 to 65 mV, in vascular smooth muscle cells (15, 141, 142, 257, 280, 319). The action potentials may appear single or in short bursts giving rise to well defined phasic contractions, or spike discharge may be more continuous, resulting in a maintained "tonus," which is then of

tetanic nature (15, 71, 142, 194). The relation found between electrical and mechanical activity indicates that the action potential reflects some process in the normal mechanism of activation of the contractile apparatus in these vascular smooth muscle cells. Membrane excitation is therefore one of the phenomena occurring in the normal sequence of events that leads to contraction (15, 35, 307).

The functional characteristics of the muscle will depend to a great extent on how the action potential is triggered in the individual cell and on the possibilities for electrotonic spread of excitation to the neighbouring cells. Smooth muscle in many types of vessel shows rhythmic contractions either *in situ* or when studied *in vitro* as isolated strips. Such rhythmicity is seen by vital microscopy in the hemodynamically important, small precapillary vessels, where it has been termed "vasomotion" (e.g., 260, 346), and it is also observed in some parts of the venous tree (343). Adjustments of tone in precapillary vessels, observed in circulatory experiments as changes in flow resistance, may to a great extent reflect variations in the frequency, duration, and amplitude of such phasic constrictions in the numerous arterioles of the vascular bed.

The coordinated contractions are, by themselves, strongly suggestive of conducted electrical activity, since propagated action potentials are the most likely means of communication by which the different cells are made to operate in synchrony. Electrophysiological studies of recent years have shown that the phasic contractions are indeed associated with propagated electrical activity (15, 71, 142, 280). The action potential may be preceded by slow depolarizations (15, 142) resembling the diastolic depolarization seen in recordings from the cardiac sinus node. Accordingly the frequency of activation of the smooth muscle will depend on the slope of their "pacemaker potentials." Activity of the nervous elements in the vascular wall is not essential for impulse generation and propagation of the muscle rhythmicity can therefore be considered a result of myogenic mechanisms (197). Vascular smooth muscle with these functional characteristics belongs to the single-unit type in Bozler's classification of smooth muscle (44). It should be noted that in this work he did not place the musculature of the vessels in this category, since at that time information was available mainly for large arteries, which as a rule do not show propagation.

Smooth muscle in several regions or sections of the vascular system shows little or no tendency to automaticity and synchronized contractions. Its mechanical activity may still be correlated with action potentials, triggered for instance by impulses in the vasomotor nerve fibres, but the action potentials may not be conducted from one muscle cell to another. The musculature of these vessels thus conforms to the multi-unit type of smooth muscle (44). Tone in vessels dominated by such nonpropagating muscle may represent the integrated result of asynchronous, twitch-like contractions.

Mention should also be made of the possible existence of vascular muscle in which activation of the contractile apparatus is not dependent on action potentials. It is known that certain types of striated muscle fibres operate with graded changes in membrane potential and slow, graded contractures instead of spikes and twitches (225). Nature may have supplied some sections of the vascular tree

with smooth muscle of such "contracture type." Recent studies on rabbit pulmonary artery are of interest in this connection (321). Experiments with intracellular microelectrodes showed graded depolarization but no spike discharge when contraction occurred in response to an increased extracellular potassium ion concentration. Noradrenaline and sympathetic nerve activity evoked tension development without triggering spikes and also without giving any measurable changes in the resting membrane potential. The adrenergic contractile responses of rabbit pulmonary artery thus appeared to be entirely independent of electrical events at the cell membranes. Negative results of this kind must be judged with caution in view of the technical difficulties associated with microelectrode work on vascular smooth muscle, but they should make us consider the possible role of contracture muscles in some parts of the circulatory system. Various degrees of dissociation between electrical and mechanical activity are produced in propagating vascular smooth muscle by drugs and by shifts in ionic environment (15, 71, 194, 195, 307).

Tone may thus be established by somewhat different mechanisms in different parts of the vascular system. In some vessels myogenic automaticity and myogenic propagation maintain rhythmic, phasic contractions or tetani, creating a "basal tone" which is then modulated by vasomotor nerves, by circulating vasoactive agents, or by local control factors. Other vessels develop tone in response to asynchronous spike discharge, which depends to a great extent on impulse activity in the vasomotor nerves, and little tone remains after such vessels are acutely denervated. Finally, vascular tone may be of nontetanic nature but depend on graded contractures in slow muscle fibres. It has even been suggested that these would be able to support tension by a passive "catch process" once it has been developed by active contraction (305). The different mechanisms of vascular tone, delineated above, may not be distinctly separated *in vivo*; they may operate simultaneously in one and the same vessel and the smooth muscle might shift from one type of behaviour to another depending, for instance, on the ionic or metabolic milieu. This may manifest itself as a change in the normal relation between spike activity and contraction (15, 71, 194, 307).

*The contractile process.* So far an attempt has been made to categorize vascular smooth muscle on the basis of the electrical characteristics of the cell membrane. Other components of the cellular machinery may account for additional individualities of vascular smooth muscle with regard to contractile activity and responsiveness (35).

A widely accepted molecular model of the contractile process involves a reaction between a system of fibrous proteins (actomyosin-tropomyosin), an energy-delivering substance (ATP), and ionic "activators" ( $\text{Ca}^{++}$  and  $\text{Mg}^{++}$ ) (for ref. see 270). This scheme can be applied to vascular smooth muscle as to other contractile tissues (107). Recent studies indicate that tropomyosin or a closely related protein may play a role in skeletal muscle as an inhibitor of ATPase activity and that release of calcium ions into the sarcoplasm may trigger contraction by disinhibiting this system (86, 270). Such a mechanism has not been investigated for vascular smooth muscle, but the fact that actomyosin shows quantitatively the

same  $\text{Ca}^{++}$  dependence whether extracted from vessels or from striated muscle (107) suggests a similar molecular organization of the contractile apparatus in the two tissues.

The design of the actomyosin system in mammalian smooth muscle is far from clear. In contrast to the disciplined order of thick and thin myofilaments in striated muscle there appear to be in mammalian smooth muscle filaments of a single size arranged with no obvious regularity except that they are oriented longitudinally or perhaps in an oblique fashion (289). There is some evidence that these filaments may consist of actin (94). Myosin is certainly present in mammalian smooth muscle but its exact state and localization within the cell have not been revealed so far. In contrast to skeletal muscle actomyosin, the contractile protein of both arterial and uterine smooth muscle can be extracted at low ionic strength (108, 231, 258). Laszt and Hamoir (231) suggested the name of tonoactomyosin for this protein, which they considered to be responsible for arterial tonus and for tonic contractions of vascular smooth muscle as induced for instance by potassium (230, 231; see also 9). There is evidence, however, that tonoactomyosin is not a special kind of protein but is in fact a form of actomyosin, and possible explanations for its particular solubility characteristics have been discussed (108).

The state and arrangement of the actomyosin system in the smooth muscle cells of different vessels must be one important determinant of their mechanical behaviour.

Probably of even greater importance for the differentiation of smooth muscle are the energy-delivering metabolic processes. These are not known in great detail for vascular smooth muscle but the following references may be given as examples of recent studies concerned with oxygen and substrate dependence, lactate formation, ATP and creatinin phosphate metabolism, etc., in this tissue (30, 70, 76, 241). The enzymatic equipment of the cells that determines the aerobic and anaerobic pathways available for resynthesis of the limited stores of ATP and creatinin phosphate may differ among vascular muscles as it does for instance between "red" and "white" skeletal muscle. The vascular response to a vasoactive substance may be expected to vary widely if the agent exerts its action through some specific enzyme function, being important in some vessels and negligible in others.

The ionic "activators" as indispensable participants in the basic contractile process offer additional target mechanisms for vascular control systems and drugs. Particular attention has been directed towards the role of calcium as a mediator in excitation-contraction coupling (34, 185, 194). Different pools of membrane-bound calcium have been proposed as the sites of attack of different smooth muscle stimulants and inhibitors (72). The beauty of these models should not prevent us from challenging their validity by further experimental work.

#### *B. Modes of adjustment of vascular tone*

The complexity of the contractile machinery of smooth muscle and its variable dependence on electrical membrane activity make it highly probable that any change in the cell environment may influence several components of the

system, sometimes in opposite directions with regard to the final mechanical response. Particular conditions for multiple and variable actions exist in propagating muscle with spontaneous automaticity. In such muscle, effects can occur with respect not only to the contractile response of the individual cells but also to the contraction frequency, as determined by pacemaker activity, and to the coordination of the response, as determined by mechanisms for intercellular conduction. The integrated tone of a vascular section with such smooth muscle may thus be influenced by agents with different combinations of "inotropic," "chronotropic," and "dromotropic" actions (191). The point may be illustrated by reference to recent studies on isolated smooth muscle from portal vein, which shows spontaneous rhythmicity. Increased extracellular osmolarity inhibited the contractile activity of this vascular preparation by a combination of negative chronotropic, inotropic, and dromotropic actions (192, 252). Isoproterenol, on the other hand, evoked a more complex pattern of response consisting of a negative inotropic but a positive chronotropic effect, the integrated result being inhibition of tension (194). The simplicity and regularity of dose-response curves, based on smooth muscle contractions, are impressive in the face of the possibilities for multiple and variable drug actions in this tissue.

Adjustments of vascular tone occur *in vivo* through the influence of numerous factors on smooth muscle activity. Changes in the chemical and physical environment with regard to electrolyte concentrations, pH, oxygen tension, osmolarity, temperature, passive stretch, etc., are important modulators of vascular tone. These factors affect vascular smooth muscle activity because they are more or less directly involved in the basic machinery of the muscle cell itself. By their action on the smooth muscle of resistance vessels and precapillary sphincters these factors may play important roles in local feedback mechanisms controlling tissue blood supply (see further below).

Other vascular control systems, particularly those which mediate central nervous or other remote influences on peripheral vessels, operate by means of more specific transmitters or circulating amines and polypeptides. These substances themselves are not involved as necessary constituents of the cellular machinery of the smooth muscle but they can affect this machinery, apparently after reacting with specific "receptor sites" on the effector. Differences in receptor distribution between vessels may contribute to differentiation of the circulatory control with regard to parallel-coupled and series-coupled vascular circuits.

Finally, vascular tone can be influenced by exogenous agents, *i.e.*, vasoactive drugs, which act either directly on the smooth muscle or indirectly through the normal vascular control systems.

#### IV. CIRCULATORY DIMENSIONS

Tissues in which the circulation is primarily concerned with the local supply of nutrients and removal of metabolic waste products should be expected to have vascular beds that, at maximal dilatation, are large enough, with regard to blood supply and capillary exchange surface area, to meet maximal metabolic demands.

This vascular design seems to exist in the myocardium and the central nervous system. In some tissues the vascular beds are too small for states of maximal metabolic activity, the most typical example of this being skeletal muscle. During strenuous exercise the acute high-energy demands are supplied, to a great extent, *via* anaerobic metabolic pathways, and the consequent "oxygen debt" of the organism must be "repaid" in subsequent periods of rest. In a third group of tissues the maximal vascular dimensions are far in excess of the local nutritional demands, and this can be attributed to other aspects of the regional circulation than transportation of true nutritive factors. In the kidney this refers to excretion of waste products, in the skin to dissipation of heat, in glandular tissues to delivery of raw material for secretion, and in adipose tissue to mobilization of energy stores.

Quantitative aspects of vascular design with regard to resistance function can be revealed from flow data pertaining to a state of maximal vasodilatation. To permit direct comparison between tissues, the flow values should be expressed per unit tissue weight ( $\text{ml}/\text{min} \times 100 \text{ g}$ ) at a given perfusion pressure (100 mm Hg). Such data are shown for different organs in the body in figure 2, which includes, in addition, approximate flow values "at rest." It should be emphasized that several of these organs contain different tissues, and an uneven flow distribution between the "parallel-coupled" vascular circuits within such an organ is commonly present. In the brain, for example, gray matter is reported to have vascular dimensions yielding maximal flows in the range of 300 to 400  $\text{ml}/\text{min} \times 100 \text{ g}$  tissue, whereas white matter receives flows only 15 to 20% of this figure (171). The situation is similar in intestine and, to some extent, in skin and skeletal muscle, as will be discussed in some detail below. The kidney with its highly specialized vascular design seems to exhibit particularly complex compartmental flow patterns (325).

The data presented by the columns of figure 2 are used for a rough deduction of flow values "at rest" and at maximal dilatation in the various organs of man (bottom of fig. 2) taking into consideration the weights of the respective organs in an adult person. It is evident that the cardiac pump is not capable of delivering, at unchanged pressure, an output equal to the sum of the regional blood flows pertaining to a state of maximal dilatation. Maintenance of vascular tone in resistance vessels above a given minimal level is therefore essential for adequate cardiovascular function.

This raises the important question of the mechanism responsible for vascular tone at rest. Neurogenic vasoconstrictor fibre discharge under resting conditions contributes to the limitation of peripheral flow but its influence varies in different organs. It is negligible in the coronary and cerebral circulation and moderate in skeletal muscle but can be quite pronounced in the cutaneous vascular bed (112). There is evidence that the role of known specific circulating vasoconstrictor agents for the establishment of resting vascular tone is quite insignificant (114) although unidentified "plasma factors" may be of some importance (37). A high level of vascular tone remains in most tissues after complete elimination of known extrinsic excitatory influences (114). This "basal tone," which may be

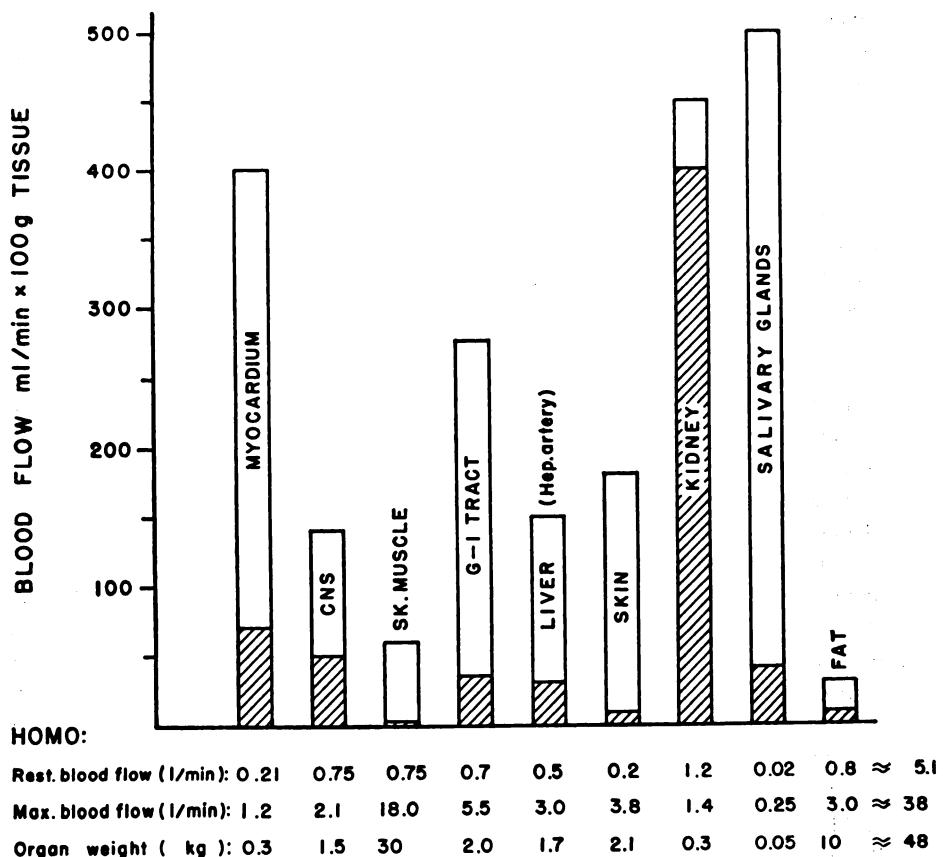


FIG. 2. Diagram illustrating approximate blood flows of different organs at maximal vasodilatation (*total areas*) and "at rest" (*hatched areas*) expressed in ml/min × 100 g tissue at perfusion pressure 100 mm Hg (ref.: 20, 46, 129, 159, 163, 264, 274, 298, 322).

*Below:* Approximate figures for regional blood flows in a 70-kg man "at rest" and at maximal dilatation are deduced on the basis of organ weights. (The organs included comprise some 70% of total body weight.)

ascribed to inherent automaticity of the vascular smooth muscle cells (section III), is particularly pronounced in the resistance vessels of myocardium, brain, skeletal muscle, and splanchnic organs, but is virtually absent in such specialized vascular structures as the arteriovenous anastomoses of the skin (114). By inhibition of the resting tone a tissue can use its "flow reserve," the extent of which is roughly indicated by the unshaded areas of the columns in figure 2.

The peripheral vascular bed seems to exhibit a differentiation with regard to the localization of basal tone within its consecutive sections. Thus, pre-capillary resistance vessels and precapillary sphincters have a high level of basal tone, but this is less evident in the capacitance vessels (133, 255).

In comparison with the available information about total resistance function in the various vascular circuits, relatively little is known about the circulatory

dimensions of the exchange and capacitance functions, and quantitative data on such aspects are largely limited to skeletal muscle, skin, and intestine. The vascular design of these circuits will be considered in some detail below.

*Skeletal muscle.* Striated muscle may be considered a more homogeneous tissue than most other organs and is by far the largest one in the organism. Its blood supply primarily subserves tissue nutrition and the flow is distributed through a vascular bed of relatively uniform design. Skeletal muscle exhibits a greater variation in metabolic rate than most other tissues, and the rate is graded in relation to somatomotor nerve activity. This requires great flexibility in regional vascular control and prompt adjustments of the cardiac pump to meet the variable flow demands of muscle, which during strenuous exercise can correspond to more than 80% of maximal cardiac output. Therefore, the vascular bed of skeletal muscle is hemodynamically one of the most important circuits in the systemic circulation. On account of its structural and functional organization it has served as a circulatory model for study of the principles of vascular smooth muscle control, of factors involved in functional hyperemia, and of kinetics in capillary filtration and diffusion exchange.

Resting skeletal muscle blood flow is about 2 to 5 ml/min  $\times$  100 g tissue at normal perfusion pressure. Acute elimination of resting vasoconstrictor fibre influence roughly doubles flow and, during complete smooth muscle relaxation in the resistance vessels, flow can increase to 40 to 60 ml/min  $\times$  100 g (*e.g.*, 20).

Morphological studies have shown that capillary density in skeletal muscle varies in different species and, to some extent, also in different muscles of the same animal (294). From capillary counts, Pappenheimer calculated the total capillary surface in 100 g of cat skeletal muscle to be around 7000 cm<sup>2</sup> (266). In resting skeletal muscle, only a fraction of the total number of capillaries is open to flow because of precapillary sphincter activity, and hence the size of the functional capillary surface area is correspondingly smaller. Changes in functional capillary surface area associated with adjustments of vascular tone have been assessed by measurement of capillary filtration and diffusion capacities in terms of CFC and PS (section II). At rest, CFC in cat skeletal muscle is about 0.010 to 0.015 ml/min  $\times$  100 g  $\times$  mm Hg and approximately half this value in the human forearm (69, 228, 254). It increases to 0.04 to 0.05 at maximal vasodilatation (69, 219). Corresponding figures for PS, measured in the dog, are 3 to 5 ml/min  $\times$  100 g and 8 to 10, respectively (276). This indicates that the functional capillary surface area at rest in the experimental animals is about a third of maximum, *i.e.*, about 2500 cm<sup>2</sup>/100 g muscle, if calculated from Pappenheimer's figure above. Lipid soluble substances, such as O<sub>2</sub> and CO<sub>2</sub>, seem to be exchanged across the entire capillary surface, whereas transfer of lipid insoluble agents is believed to occur only through an intercellular pore system, the total area of which is calculated to be less than 0.2% of the entire capillary surface area (228).

In the vascular bed of resting muscle at least 80% of total resistance resides in precapillary and somewhat less than 20% in postcapillary vessels, *i.e.*, the pre- to postcapillary resistance ratio is around 4/1 (267). Under these circum-

stances an approximate Starling equilibrium prevails. Maximal vasodilatation is associated with a decrease in the resistance ratio, leading to a rise of capillary pressure of some 15 mm Hg and to a net transcapillary fluid filtration at a rate of about  $0.8 \text{ ml/min} \times 100 \text{ g tissue}$  (219).

The regional blood content in a skeletal muscle at heart level is about 2.5 to 3 ml/100 g tissue at rest, and it was shown to increase by about 30% upon maximal relaxation of vascular smooth muscle under circumstances in which arterial and venous pressures were kept constant at 110 and 10 mm Hg, respectively (248). This capacitance response was elicited by a supramaximal dose of acetylcholine given intra-arterially.

Hilton recently called the attention to some interesting characteristics of the circulation in "red" (tonic) skeletal muscle (180, 183). He observed flows both at rest and at maximal dilatation greatly exceeding those given above, which referred to muscles containing mainly "white" (phasic) fibres. He further presented evidence to show that regulation of flow in red muscle differs in several respects from that in white muscle.

Comparative studies have shown resting blood flows of about 20 to 30 ml/min  $\times 100 \text{ g}$  in red muscle (soleus), which was more than twice the flow in acutely denervated white muscle (gastrocnemius) (121, 273). During maximal vasodilatation soleus flow increased to about 115 ml/min  $\times 100 \text{ g}$  and CFC increased from the range of 0.020 to 0.025 ml/min  $\times 100 \text{ g} \times \text{mm Hg}$  at rest to about 0.075 (121). It thus appears that the circulatory dimensions related to the resistance vessels and to the capillary exchange surface of red muscles are at least twice as large as those of white muscles both at rest and maximal dilatation. This seems to provide for an oxygen delivery and exchange in red muscle sufficient for maintaining a predominantly aerobic metabolism even in situations of high work loads, whereas in white muscle quite low rates of contraction can lead to "oxygen debt" (121). Since most skeletal muscles seem to contain red fibre elements to some extent, the muscle vascular bed may not be as homogeneous as commonly believed.

The existence of true arteriovenous shunts in skeletal muscle has been suggested, but there is little direct evidence for this hypothesis. Dynamic studies based on transit of microspheres of different sizes have demonstrated that only a few percent of total flow passed through vessels wider than  $20 \mu$ , even at maximal vasodilatation (78, 271). Vascular adjustments associated with a changed relation between total flow and extraction of substances have often been taken to support the presence of true shunts, but alternative explanations have also been given. As mentioned, skeletal muscle may not be entirely homogeneous because of mixture of red and white fibres and the presence of connective tissue. Differences in metabolism, vascular dimensions, vasomotor control, etc., between these tissues may lead to changed capillary flow distribution during adjustments of skeletal muscle vascular tone and, hence, to possibilities for varying solute extraction. This might occur even in a homogeneous tissue, for example, by redistribution of flow within a capillary network consisting of capillaries with varying exchange capacities (276). Changed extraction may thus

often be explained by "dual circulation" or by "functional shunting," which, from the physiological point of view, is quite different from passage of blood through wide-bore arteriovenous shunts with no exchange function.

*Skin.* The homeostatic thermoregulatory function of the skin, rather than the metabolic demands of the tissue itself, is reflected in the design and control of its vascular system. Great variations in the circulation through a skin region will thus be observed in association with shifts in ambient and body temperature and also in local tissue temperature. It must be emphasized that the skin is a complex tissue with accessory organs, of which the sweat glands may be especially important from the circulatory point of view. Also, there is a varying number of arteriovenous anastomoses in different skin areas, and they seem distributed mainly to apical regions (159). We are thus dealing with a vascular bed less uniform than that of skeletal muscle, and quantitative circulatory data of general applicability are more difficult to give. Most of the information about the cutaneous circulation has been obtained in studies on particular regions, such as the rabbit ear, the paws of the cat and dog, and the human hand and foot.

Blood flows in the range of 3 to 10 ml/min  $\times$  100 g have been reported for the human hand at local temperatures of 25 to 35°C in comfortably warm subjects (61, 313). At a local temperature of 44°C hand blood flow increased to 40 ml/min  $\times$  100 g or more (268, 282) and this appears to represent nearly maximal cutaneous vasodilatation. Considering the proportion of other tissues in the hand, the maximal flow rate of skin proper has been estimated to be about 180 ml/min  $\times$  100 g (159). Values approaching this figure were obtained also for forearm skin (89). Direct recordings of venous outflow from the cat paw at normal local temperature and during maximal dilatation gave flow figures comparable to those reported for the human hand (14, 262).

The large range of variation in the total resistance function of the cutaneous circulation depends to a significant extent on the opening and closing of the wide-bore arteriovenous shunts. These vessels, which are about 40  $\mu$  in internal diameter at maximal dilatation, have a thick muscle coat and are present abundantly in the human hand and foot, the rabbit ear, and the pads of the paws in the cat and dog (159). The fraction of the total regional flow passing shunts has been studied by determining the recovery of graded microspheres in the venous effluent. In the rabbit ear, this fraction varied between 5 and 70% (286). For the whole hind leg of the dog a mean value of 21% was found with wax spheres 40  $\mu$  in diameter. Shunting was reduced to less than 1% by ligation of the paw, a finding that shows that the arteriovenous anastomoses are mainly localized in this region (41). Denervation of the leg and local warming were often associated with marked increases of shunt flow.

As to the dimensions of the capillary network in the cutaneous vascular bed the available information is scanty. Measurements of CFC have been carried out in the cat paw and values about 0.030 to 0.040 were found under conditions in which the regional blood flow was about 7 ml/min  $\times$  100 g (14, 262). These data may indicate a somewhat greater vascularization in skin than in skeletal

muscle (see also 338). CFC has not been determined in skin at maximal physiological vasodilatation, but values three times resting control have been reported for the cat paw in acute second degree burn, which is associated with maximal resistance-vessel dilatation (14). However, some effect on CFC of increased capillary membrane permeability cannot be ruled out in this condition.

The blood volume per unit tissue weight contained in the cutaneous capacitance vessels at rest seems to exceed that in skeletal muscle (248). It appears that the superficial veins and the subpapillary venular plexus, which are of great importance for heat dissipation, can accumulate large volumes of blood during dilatation. A 40% increase of regional blood volume was observed upon acute sympathectomy in cat paw at 37°C (251).

*Intestine.* The gut is a composite organ containing three main tissue layers, the mucosa, submucosa, and muscularis. Accordingly, it has quite a complex circulatory arrangement. The vascular beds of these different tissues are coupled in parallel and each of them consists of functionally differentiated consecutive sections. Furthermore, the major part of the intestinal circulation is coupled in series with the portal system of the liver.

Under normal circumstances the intestine is seldom at complete "rest," but shows some activity in terms of motility and mucosal absorption, secretion, enzyme production, etc. Therefore a resting state is difficult to define. The term may be used for a state of reduced secretion and motility, as after fasting and atropinization. Intestinal blood supply varies between different sections of the gut and under different levels of activity, and these variations may explain the fairly wide range of flows reported in the literature (see 153, 164).

The circulatory dimensions in cat small intestine have been studied in some detail under standardized experimental conditions and will be reported below, first for whole intestinal segments and then with regard to flows in the various compartments of the gut wall. At rest total blood flow is usually about 30 to 40 ml/min × 100 g tissue at normal perfusion pressure, and after elimination of resting vasoconstrictor fibre activity about 40 to 60 ml. During maximal relaxation of vascular smooth muscle, intestinal flow may increase up to 250 to 275 ml/min × 100 g (126, 129, 238).

The capillary bed of intestine also shows remarkably great dimensions. CFC in resting intestine is about 0.1 ml/min × 100 g tissue × mm Hg and can increase to 0.3 to 0.5 during maximal vasodilatation (129). These values are about 10 times larger than the corresponding ones in skeletal muscle. Similarly, the PS value in resting intestine is about 10 times larger than in muscle, or about 30 ml/min × 100 g (83). These far greater dimensions of the intestinal exchange surface are probably related to both greater intestinal capillary density and capillary permeability.

The blood content of the intestinal capacitance vessels is, at normal venous pressure, about 7 to 9 ml/100 g tissue, which is about three times that in skeletal muscle, and it increases during maximal vasodilatation by about 30 to 40% (129).

The presence of shunt vessels in the intestinal circulation is a matter of debate. Spanner described a specialized vascular structure in the intestinal submucosa consisting of arterioles with longitudinal smooth muscle, which arborized into a dense meshwork of thin-walled veins (310). In later studies abundant arteriovenous anastomoses have been reported to exist in the stomach, whereas they seem to be less frequent in the intestine, if present at all (17, 42). Dynamic studies with microspheres in the dog jejunum showed only a few percent recovery of spheres larger than  $20 \mu$  in diameter, whereas about 25% of size 12 to  $20 \mu$  were recovered (235). It thus appears that some fairly wide-bore arteriovenous channels exist in the intestine, but from these studies it cannot be decided whether they are nutritive or nonnutritive vessels.

The distribution of flow between the various intestinal tissue layers has been estimated by isotope methods with both lipid soluble and lipid insoluble tracers. The lipid insoluble substances often show diffusion limitation, especially at high flow rates, and such methods may therefore not give reliable information about flow (215, 229). The data given below refer to studies in which direct measurement of total intestinal flow was performed simultaneously with recording of the clearance curve ( $\gamma$ -activity) for the lipid soluble  $^{85}\text{Kr}$  after intra-arterial administration. These curves could be resolved into four components, and corresponding tissue compartments were identified by autoradiography and by recording  $\beta$ -activity after local krypton injection into different tissue layers (238). Flow distribution was studied at rest and during maximal vasodilatation and estimates of flow were obtained for mucosa, submucosa, muscularis, and mesenteric fat. The following flow data, expressed in  $\text{ml}/\text{min} \times 100 \text{ g}$  tissue, were reported for the intestinal compartments. At rest the mucosa received 40 to 60 ml, the muscularis 10 to 15 ml, and a small tissue fraction located in the submucosa and around the intestinal crypts 400 to 600 ml. During maximal vasodilatation the mucosal flow was 150 to 200 ml, muscularis flow 35 to 40 ml, and submucosal flow 800 to 1000 ml. The extremely high blood flow rates in the submucosa, calculated from a fast initial component of the clearance curve, might indicate some kind of shunting. Circumstantial evidence, obtained by a number of independent methods, strongly suggested the possibility of an extra-vascular "shunt" mechanism, created by countercurrent exchange of material between the ascending and descending limbs of the vascular loops located in the intestinal villi. Experimental data were taken to indicate that such exchange, occurring at the base of the villi, would preferentially involve easily exchangeable agents, such as the lipid soluble krypton, oxygen, and antipyrine, whereas a relatively larger fraction of less diffusible, lipid insoluble agents, such as rubidium, passed the vascular hairpin loops of the villi. These investigations were recently summarized by Lundgren (238). The proposed countercurrent mechanism was most efficient at low flow rates and was postulated to create a barrier hindering too rapid an absorption of solutes from the intestinal lumen to blood and, conversely, to limit oxygen diffusion in the reverse direction.

Compartmental intestinal flows in dog ileum have been studied by determining the distribution of labelled microspheres retained in the smallest precapil-

lary vessels (235). The deduced blood flows were: mucosa 42, submucosa 34, and muscularis 48 ml/min  $\times$  100 g. Flow distribution in dog ileum has further been studied by measuring the content of deuterium oxide in the various tissue layers after intra-arterial administration of the tracer. The deduced flow values were: mucosa 38, submucosa 56, and muscularis 66 ml/min  $\times$  100 g (272). The mucosal flow observed with these methods is thus comparable to that estimated from the Kr washout curve, whereas the muscularis flow is much greater and deviates remarkably from smooth muscle flow in other regions, such as stomach (75). If a shunt phenomenon occurs in the submucosa, as suggested by the Kr method, this would not be manifest as a high submucosal tissue blood flow with the two other techniques.

#### V. VASCULAR CONTROL SYSTEMS

In normal life the cardiovascular system is exposed to the problem of satisfying the highly variable circulatory demands of the different tissues without exceeding the limits of the cardiac pump. The economy of the cardiovascular system is maintained and its purpose properly fulfilled by regulation of vascular tone and cardiac activity. By graded adjustments of inhibitory and excitatory influences on vascular tone in the various circuits, suitable redistributions of the prevailing cardiac output will occur, assuring regional blood supplies in relation to the functional priorities and metabolic states of the different organs. This often implies a "rationing system" with flow reductions affecting preferentially the tissues that can easily tolerate flow limitation.

Peripheral circulatory control implies adjustments of smooth muscle tone in the vascular bed by influences originating from sites within and outside the tissue itself. This permits distinction between local and remote control systems, both of which can operate *via* feedback mechanisms. Synergistic action of local and remote influences on the vascular smooth muscle effector may be observed, but their interaction is more commonly characterized by antagonism. Both the local and the remote control systems encompass mechanisms capable of inducing discrete as well as profound adjustments of peripheral vascular functions, resulting, as a rule, in precise and well adapted changes in cardiovascular dynamics.

Although details of integrated remote control remain to be elucidated, several of the specific mediators, the transmitters, and the circulating hormones, have been identified unequivocally. Definite knowledge about the corresponding final links of the local control systems is still lacking. For such reasons, the picture of the remote control seems clearer at present and in the description below it will be considered at first. Current concepts of local control mechanisms are more hypothetical.

##### A. Remote control

Remote control systems subserve general circulatory homeostasis by adjusting cardiovascular functions so as to maintain a normal arterial blood pressure and a normal blood volume. They are further engaged in other homeostatic

functions of importance for the organism as a whole, such as thermoregulation. Remote control systems also mediate circulatory adjustments that occur as integrated components of certain specific patterns of behaviour, like the defence-alarm reaction, the sexual response, the diving reflex, etc.

There are two principles in the remote control of the blood vessels, the nervous control exerted by the different vasomotor fibre systems and the humoral control exerted by blood-borne vasoactive agents.

### *1. The sympathetic adrenergic vasoconstrictor fibre system*

Previous reviews have dealt with the representation of the sympathetic constrictor fibre system and its organization at different levels in the CNS (92, 112, 113, 333) and with the peripheral autonomic organization (176). Synaptic mechanisms in autonomic ganglia appear to be more complex than previously believed with multiple cholinergic as well as adrenergic processes involved (336). Inhibition of ganglionic transmission might be mediated by adrenergic synaptic terminals but their possible impact on activity in efferent pathways such as the vasoconstrictor fibres is not clear. A reflex inhibition of vasoconstrictor tone at a ganglionic site has been suggested, however, on the basis of indirect evidence (147).

The degree of constrictor control exerted on the vascular smooth muscle effector is intimately dependent upon the density of the postganglionic nerve terminals ("synapses *en passant*"). Uneven distribution of the innervation to the parallel-coupled and series-coupled vascular sections would constitute one morphological basis for differentiated neurogenic response patterns. Various types of experimental study have suggested quantitative differences in the vasomotor nerve supply to different organs (112). The recent histochemical fluorescence technique of Falck and Hillarp (102, 103) offers a unique possibility for detailed analysis of the distribution of adrenergic nerve terminals. Investigations have demonstrated the presence of adrenergic innervation to vessels throughout the body, although regional quantitative differences are apparent. For example, the mesenteric vessels receive a rich supply, whereas intracerebral vessels show an extremely sparse adrenergic innervation (59, 91, 102). With regard to the consecutive sections of the vascular beds, adrenergic endings have been identified in all of them, except for the true capillaries (91). Precapillary vessels show, in general, a rich innervation. Arterial vessels are characterized by a plexus of nerve fibres located on the outside of the media, and only few branches penetrate into this layer and then for very short distances (91, 102). Such arrangement could be traced down to the smallest precapillary vessels but here the number of fibres is quite small. The differentiation of the muscle coat into an outer innervated and an inner noninnervated layer may have interesting functional implications (134). On the postcapillary side, the venular segments seem to have a sparser nerve supply than larger veins, which, in turn, have fewer adrenergic fibres than the precapillary vessels (102, 143). In large cutaneous veins, the fibres often penetrated into the deep layers of the media. It appears that further studies, specifically directed towards a systematic exploration of the adrenergic fibre

distribution in the circulatory system, would help to a better understanding of neurogenic control.

Mechanisms involved in the synthesis of the noradrenaline transmitter and its storage in the vesicles of the axoplasm are beyond the scope of the present review. The amount of transmitter liberated at the nerve terminal is related to discharge rate and to transmitter release per impulse. Maximal physiological impulse frequency in these fibres may reach phasically 15 to 20 per sec, but there is much evidence to indicate that, over prolonged periods of time, the discharge rate rarely exceeds 8 to 10 impulses per sec, a fundamental characteristic of autonomic nerves which has been discussed at length by Folkow (111, 112). Quantitative information about the transmitter release at the vasoconstrictor nerve terminals in skeletal muscle was recently obtained (120). This study indicated that the quantity of noradrenaline released per stimulus did not correspond to the amount present in one varicosity granule but was, in fact, less than 5% of this. Further, it was calculated that the noradrenaline concentration in the junctional gap between varicosity and smooth muscle cell would nevertheless exceed 1  $\mu\text{g}/\text{ml}$  at physiological rates of discharge. Transmitter concentrations of the same order of magnitude were obtained in a study on an isolated nerve-muscle preparation of rat portal vein (236). Transmitter inactivation after release is a prerequisite for precise neurogenic effector control, and the mechanisms for the transmitter elimination were briefly reviewed and further elucidated in the above study (120). Re-uptake of noradrenaline into the varicosities by a "membrane pump mechanism" seems to be the dominant principle. Elimination *via* the blood stream is usually quite small in resting skeletal muscle, but transmitter "overflow" can be greatly increased in muscle exercise and also during sympathetic stimulation at supraphysiological rates. Local enzymatic inactivation of the released transmitter appears to be of little importance, at least in skeletal muscle.

The concept of two separate adrenergic receptor mechanisms, the  $\alpha$ - and  $\beta$ -receptors (6), has become a useful model for characterization of cardiac and smooth muscle responses to the sympathetic transmitter and other adrenergic agents. In the vascular system both  $\alpha$ - and  $\beta$ -receptors are present and their activation leads, in principle, to vasoconstriction and vasodilatation, respectively. Certain aspects of the vascular smooth muscle responses to  $\alpha$ - and  $\beta$ -receptor stimulation will be dealt with below in connection with the adrenomedullary hormonal system.

Noradrenaline release from the nerve terminals leads to an  $\alpha$ -adrenergic vasoconstriction with the possible exception of the coronary vascular bed (163). Sympathetic stimulation after  $\alpha$ -adrenergic blockade produces marked vasodilatation in adipose tissue and this response can be abolished by  $\beta$ -blocking agents (264). Increased blood flow produced in myocardium and fat by sympathetic activation may to a considerable extent be related to accompanying changes in tissue metabolism.

The restriction of the vasoconstrictor innervation to the outermost layers of the media implies that only a small portion of the muscle cells are in proximity to the sites of noradrenaline release, and the effectiveness of the vasoconstrictor

fibre control is remarkable in view of this morphological arrangement. Myogenic spread of excitation can contribute to the effectiveness of the neurogenic influence on the vascular smooth muscle (196, 198).

*Effects on vascular functions in skeletal muscle.* Studies with methods that permit simultaneous recordings of the various vascular functions in skeletal muscle have revealed the following general pattern of response to activation of the sympathetic vasoconstrictor fibres: a sustained constriction of resistance and capacitance vessels, an increased ratio of pre- to postcapillary resistance, and a transient constriction of precapillary sphincters. These vascular adjustments are considered in greater detail below.

Supramaximal electrical stimulation of the regional adrenergic vasomotor fibres of skeletal muscle in the cat can elicit a maximal constriction in the *resistance vessels* corresponding to an 8- to 10-fold increase in flow resistance (20, 62, 111, 248). At a constant arterial pressure of 100 mm Hg such a change implies a blood flow decrease to about 1 ml per min  $\times$  100 g tissue from the resting level of 6 to 10 ml in the denervated muscle. These data refer to muscles with mainly "white" fibres such as gastrocnemius. In "red" muscle (soleus), maximal stimulation of constrictor fibres increased resistance only 2 to 2.5 times the control level (121).

Curves relating the resistance response to the frequency of sympathetic stimulation show a hyperbolic configuration with a steep rise at low impulse rates. Maximal constrictor response is reached at 15 to 20 impulses per sec (62, 111). With intact vasomotor innervation, blood flow in resting skeletal muscle is 3 to 5 ml per min  $\times$  100 g in anesthetized cats and dogs and somewhat less in man (20). These data and others demonstrate the existence of a tonic sympathetic vasoconstrictor fibre discharge at rest, which has been estimated to range from 0.5 to 2 impulses per sec (111, 239). This tonic activity, emanating from central autonomic structures, forms the basis for reflex inhibition of vasoconstrictor tone, which, in fact, is the most common mechanism of neurogenic vasodilatation.

The extent of the adrenergic resistance control in skeletal muscle and the possibility for eliciting precise adjustments by grading the rate of discharge is clearly demonstrated by the effects of direct sympathetic stimulation. Reflex studies have shown that the muscle resistance vessels are important targets in the nervous control aiming at maintenance of circulatory homeostasis. Thus, the resistance effects are often especially pronounced in this tissue during reflex adjustments elicited from arterial baro- and chemoreceptors and from receptors in the heart and in the low pressure system (123, 237, 262), as well as in more integrated reflex patterns, such as those elicited in hemorrhage (68, 122, 239, 262). Receptors on the low-pressure side of the intrathoracic vascular bed appear to be of particular importance for reflex vasomotor responses in skeletal muscle of man (32, 281, 285). In the diving reflex, there is a remarkably great increase in skeletal muscle flow resistance which, in the duck, to a significant extent is due to constriction of the large conduit vessels (118).

The influence of the vasoconstrictor fibres on the *precapillary sphincters*, and hence on the size of the functional capillary surface area, has been studied in

muscle by measurements of PS (277) and CFC (69). These studies were performed on denervated muscle, and the effects of maximal excitation of the sympathetic nerves were observed. Since PS is flow-dependent it was determined during constant flow, whereas CFC, being largely independent of flow, could be studied in the face of the flow reduction caused by resistance vessel constriction. PS was found to decrease to about  $\frac{1}{3}$  to  $\frac{1}{4}$  of the prestimulatory control value, and this response was sustained during prolonged stimulation (10 min). CFC similarly showed a decrease to about  $\frac{1}{3}$  of control but, in contrast to PS, it returned to, or rose slightly above, the control level after a few minutes of continued stimulation. Thus, these two independent methods indicated that by sympathetic influence on precapillary sphincters the functional capillary surface can be reduced to about  $\frac{1}{3}$  of that available at rest.

The foregoing differences in PS and CFC during prolonged stimulation most probably can be ascribed to the different flow situations in the experiments. When flow is permitted to decrease, as in the study of CFC, there will be a fall of transmural pressure in the precapillary sphincter section and, gradually, an accumulation of "vasodilator metabolites" in the tissue. Both these events are known to cause pronounced precapillary sphincter relaxation (see below), an effect opposing the neurogenic constrictor influence; this can explain the return of CFC during prolonged stimulation. With constant flow such interference with the constrictor effect should be less pronounced and, therefore, the PS reduction can be maintained. Since, under normal circumstances, there are relatively small changes in blood pressure, activation of the constrictor fibres to skeletal muscle will be associated with decreased regional flow. Therefore, although the precapillary sphincters are under the control of vasoconstrictor fibres, the net result of such influence might not be too significant in this section. The same conclusion was reached from studies on both experimental animals and man when sympathetic constrictor fibre discharge was reflexly increased by a reduction of the circulating blood volume or by asphyxia (65, 239, 254, 262). A maintenance of the functional capillary surface area in the face of sustained neurogenic constrictor fibre discharge might be considered an important compensatory mechanism facilitating capillary exchange in situations of reduced blood flow.

In muscle vasoconstrictor fibre activation produces, at constant central arterial and venous pressures, a 2-fold or greater increase in the *ratio of pre- to postcapillary resistance*, which at rest is about 4/1 (248, 262). This relatively more pronounced increase in precapillary resistance is one example of differentiation in the vascular response. The greater luminal reduction in the precapillary resistance vessels can be ascribed, at least partly, to their greater wall/lumen ratio (248). The functionally important aspect of this response is the resulting net transcapillary absorption of fluid into the circulatory system (248, 250) which is due to a fall in mean hydrostatic capillary pressure (section II). In other words, this adjustment forms the basis for reflex vasomotor control of plasma volume by determining the fluid distribution between the extravascular and the intravascular spaces. Quite small decreases of blood volume elicited reflex transcapillary absorption and, conversely, overfilling of the circulatory system led to net ultra-

filtration in skeletal muscle (262). Arterial baro- and chemoreceptors as well as heart receptors were shown to be involved in these adjustments. The reflex transcapillary fluid absorption is facilitated by the fact that precapillary sphincters relax during prolonged sympathetic excitation, a phenomenon tending to enlarge the capillary surface area available for fluid exchange (262). Maximal stimulation of vasoconstrictor fibres in cat skeletal muscle led to an absorption of about  $0.3 \text{ ml/min} \times 100 \text{ g muscle}$ , corresponding to a decrease in mean capillary pressure of some 10 mm Hg (248).

In the human forearm the rate of transcapillary fluid absorption in response to a 700-ml reduction of the circulating blood volume amounted to about  $0.5 \text{ ml/min} \times \text{kg tissue}$  (254). On the assumption that fluid absorption at this rate occurred in all skeletal muscles, a reflex increase in plasma volume of 150 to 175 ml in a 10-min period of time can be deduced for an adult person. This is an impressive "autotransfusion" of tissue fluid from the muscles, which, indeed, can play an important role in hemorrhage. In fact, the values deduced above for reflex fluid absorption agree fairly well with data on blood volume restoration in man after moderate bleeding (210). The fluid absorption is not an event resulting from a passive fall in capillary pressure consequent to arterial hypotension, even if this fall might reinforce the effect of the reflex resetting of the pre- to postcapillary resistance ratio.

The response of the *capacitance vessels* in cat skeletal muscle to graded sympathetic vasoconstrictor fibre stimulation has been studied by volumetric recording of regional blood volume translocation under circumstances of constant arterial inflow pressure and venous outflow pressure, the latter kept at about 10 mm Hg (248). Maximal sympathetic activation led to an expulsion of 25 to 30% of the total regional blood volume. An analysis of the active and passive components of the response revealed that under the existing conditions this mobilization of blood was mainly due to venoconstriction. The relative contribution of the active and passive mechanisms to the neurogenic capacitance response at different levels of venous pressure has been subjected to a systematic investigation with the same technique (263). Total amount of blood expelled by standardized vasoconstrictor fibre stimulation was greatest at low venous outflow pressures (5 to 10 mm Hg) and gradually declined at higher pressures. The passive component comprised more than 50% of total response at a venous pressure of 2 mm Hg and decreased rapidly at higher pressures. At 10 mm Hg it was about 20% and at 20 mm Hg less than 10%. Blood mobilization due to active venoconstriction was most pronounced in the venous pressure range of 5 to 20 mm Hg and then declined because of "overstretch" of the muscle elements or simply the increased load. It may be emphasized that venous pressure will seldom exceed 20 mm Hg in the cat, whereas it can be much higher, for instance, in the legs of man. The muscle layer of the veins in the extremities of man is quite thick (226) and can probably constrict efficiently even when exposed to great hydrostatic load.

The curve relating the capacitance volume response to the rate of sympathetic stimulation obtained in studies with constant central arterial and venous pressures is quite steep in the low frequency range and shows maximal response

at about 6 to 8 impulses per sec (248). The corresponding curve for the resistance function, based on simultaneous blood flow recordings in the same muscle region, was displaced to the right of the capacitance curve and maximal resistance response was reached first at about 15 impulses per sec. Such representation of the data may aid in the understanding of the functional organization of the neurogenic circulatory control; for example, it shows that at given discharge in the low frequency range, there is a more complete "recruitment" of the capacitance function than of the resistance function. Only at high physiological discharge rates (8 to 10 impulses per sec) is the resistance effect more fully developed; this might sometimes be necessary for blood pressure regulation but at the same time has the consequence that regional blood flow will become severely reduced. The frequency-response curves should not be taken to represent directly the actual degree of shortening of the smooth muscle cells in the two vascular sections or their sensitivity to the transmitter. This is because the two curves represent different mathematical power functions of the changes in vessel radius and because they are influenced by such factors as the wall/lumen ratio of the respective vascular sections. In fact it was computed in the above study (248) that the luminal reduction of an "average" resistance vessel was greater than that of an "average" capacitance vessel at any rate of sympathetic stimulation mainly because of the higher wall/lumen ratio of the resistance vessels.

In a more recent investigation (51), frequency-response curves for resistance and capacitance vessels were reported to resemble each other closely, and thus showed no signs of the functional differentiation outlined above. This difference between the two studies might be ascribed to methodological factors. In the later investigation (51), the venomotor responses were studied in the lower leg of the dog in terms of pressure changes monitored from the saphenous vein during periods of arrested hind leg circulation. The resistance responses were studied in the entire hind limb with constant flow technique. Both these methods have considerable limitations for investigations of this kind (section II). For example, the full range of resistance responses to sympathetic stimulation will not be properly reflected in the pressure changes obtained with constant artificial perfusion, because of the abnormally high transmural pressures elicited especially during strong constriction. In fact, it can be deduced from the figures given in that paper (51) that the resistance increased no more than about 100% above control in response to stimulation at 10 impulses per sec. Flow studies under constant pressure, which correspond better to the normal situation, show resistance to increase by at least 500% after such a stimulus (see above). It is thus doubtful whether the frequency-response curves reported in the later paper (51) reflect the normal characteristics of resistance and capacitance vessels, especially considering that the data were obtained from different vascular areas.

Reflex adjustments in the vascular bed of muscle usually involve the capacitance vessels, but it should not be taken for granted that there will always be a uniform discharge to the various consecutive vascular sections. Diminution

of baroreceptor activity, for instance, elicits a pattern of response that can differ quantitatively from the response observed upon direct stimulation of the regional constrictor fibres. Moderate reduction of carotid sinus pressure led to a more pronounced constriction of resistance than of capacitance vessels in cat skeletal muscle; this indicated a reflex discharge rate to precapillary vessels about twice as high as that to postcapillary vessels (170). A similar differentiation reported for dog hind limb (50) suggested even greater differences between discharge rates to resistance and capacitance vessels. However, resistance and capacitance phenomena were recorded from different vascular areas in this study. A comparatively large fraction of the tissue from which venous effects were recorded consisted of skin, and cutaneous vessels are relatively little engaged in the baroreceptor reflex (*e.g.*, 237). It might be emphasized that in cat skeletal muscle strong reflex vasomotor activation led to a fully developed capacitance response. In contrast to the situation in skeletal muscle the resistance and capacitance responses in intestine were equally pronounced at all levels of reflex constrictor fibre activation (170).

The functional significance of the above differentiation, occurring in skeletal muscle during moderate reflex sympathetic discharge, might be appreciated by considering the situation in hemorrhage. Although a strong capacitance response in skeletal muscle would seem an adequate compensatory reaction in the acute stage, it does not imply permanent restoration. No doubt there is in this tissue some capacitance response, a significant fraction of which is passive, due to precapillary constriction. The more adequate compensatory reaction to blood loss is, however, the plasma volume replacement due to reflex resetting of pre- to postcapillary resistance ratio as discussed above. This important recuperative process would seem to be hampered if strong venoconstriction occurred, since this would lead to concomitant augmentation of postcapillary resistance.

Topical stimulation of central nervous structures has failed to reveal any selective engagement of the sympathetic vasoconstrictor fibres supplying resistance and capacitance vessels, respectively (23).

In *summary*, experimental evidence may suggest the following functional significance of skeletal muscle vasoconstrictor fibre control. Skeletal muscle is one of the main targets for vasomotor reflexes concerned with the maintenance of general cardiovascular homeostasis. It appears that skeletal muscle, with its large total tissue mass and its tolerance to drastic vascular adjustments, is particularly well suited for subserving such homeostatic regulation. The peripheral vascular functions of primary importance for such a control are those executed by the pre- and postcapillary resistance vessels and the capacitance vessels. The resistance function is directly involved in the regulation of arterial blood pressure. Reflex transcapillary fluid movement influences plasma volume, and variation in regional blood content affects venous return and cardiac filling. The insignificant nervous influence on the precapillary sphincters is consistent with the idea that they are primarily involved in local microcirculation. Maintenance of functional capillary surface area in the face of constrictor fibre discharge tends to facilitate nutritional exchange but, besides this primarily local affair,

it contributes to the general homeostatic adjustment by promoting transcapillary fluid exchange, *i.e.*, the fluid absorption resulting from an increased pre- to postcapillary resistance ratio.

*Effects on vascular functions in skin.* Activation of the sympathetic adrenergic vasoconstrictor fibres supplying a skin region produces constriction of resistance and capacitance vessels and of arteriovenous shunts. The changes in pre- to postcapillary resistance ratio and in precapillary sphincter activity may resemble those occurring in skeletal muscle, *i.e.*, an increased ratio and a transient increase in precapillary sphincter tone, but the data available for these vascular functions in skin are sparse and sometimes conflicting.

The adrenergic vasoconstrictor fibres exert a very strong influence on the total resistance function of the cutaneous vascular bed. This is evidenced, for instance, by the observations that sympathetic stimulation at rates as low as 0.25 impulses per sec produces clear-cut reductions of blood flow in the denervated cat paw and that a frequency of 10 impulses per sec can cause a 100-fold increase in skin flow resistance (63, 135). Increased tone in the *resistance vessels* of the nutritional pathways in the cutaneous circulation contributes to the blood flow decrease, but constriction of the arteriovenous *shunt vessels* plays a dominant role as indicated, for instance, by a marked flattening of the frequency-response curve after ligation of the pads, the major site of the shunt channels (135). The pronounced influence of the adrenergic vasoconstrictor fibres on the resistance function of the cutaneous vascular bed was ascribed mainly to the high wall/lumen ratio of the arteriovenous anastomoses.

In view of the steepness of the frequency-response curve of the cutaneous vessels it is clear that the low discharge rate normally prevailing in the constrictor fibres will keep skin blood flow well below its maximum. Changes in body temperature and thermal or electrical stimulation of diencephalic thermoregulatory structures produce large variations in cutaneous flow by increase or decrease of skin constrictor fibre activity (159, 190, 320). The increase in paw blood flow obtained by stimulation of the hypothalamic "heat loss area" in the anesthetized cat is often comparable to that produced by acute regional sympathectomy; this reflects complete inhibition of the prevailing constrictor fibre discharge (190). Intra-arterial infusion of vasodilator agents, like acetylcholine, increases blood flow in the denervated paw by only some 50 to 100 %, and this indicates a low "basal tone" in this vascular bed (63).

The greatly enhanced blood flow in the human hand and forearm skin observed in response to body heating is also closely related to inhibition of prevailing sympathetic activity (12, 284), but release of vasodilator material associated with sweating is an additional factor in cutaneous dilatation (see section V A 3). The total skin blood flow of an adult person can amount to 3.5 to 4 l/min in a hot environment, and since cardiac output often increases more than this, the blood flow must increase in some deeper tissues as well in response to heat stress (56). It is also evident from these figures that, during prolonged strenuous muscular exercise, the gradually increasing thermoregulatory demands for redistribution of flow to the skin can offset a circulatory steady state situation prevailing in the early period of work.

Reflex alterations in cutaneous blood flow can be induced by variations in baro- and chemoreceptor activity and by stimulation of afferents in the spinal nerves, but these responses are generally small in comparison with the thermo-regulatory reactions considered above (190, 237).

There is little information available on the adrenergic vasoconstrictor control of *precapillary sphincter vessels* in skin. Measurements of CFC in cat paw after ligation of the pads indicated that moderate reflex variations in constrictor fibre activity produce little or no change of functional capillary surface area in the cutaneous vascular bed (262). No study has been made to evaluate possible changes in cutaneous capillary surface area in response to direct graded sympathetic nerve stimulation.

The effects of the sympathetic constrictor fibres on the *pre- to postcapillary resistance ratio* have not been studied extensively in cutaneous preparations. Studies of segmental flow resistance in the dog paw (214) and microscopic observations of skin vessels in the same region (232) led to the conclusion that sympathetic stimulation increased postcapillary resistance relatively more than precapillary resistance, and that neural activity could be a factor in the genesis of skin oedema. More recent studies do not support this view. For instance, reflex activation of the sympathetic vasoconstrictor fibres by unloading of carotid baroreceptors produced an absorption of fluid in the cat paw indicating an increased pre- to postcapillary resistance ratio (262). It appears therefore that reflex "autotransfusion" of extravascular fluid occurs in skin much as in skeletal muscle. Since the cutaneous vascular bed is characterized by relatively great capillary filtration capacity, an increased capillary pressure, related for instance to hydrostatic load, could lead to gross oedema (338). Protection against fluid accumulation seems to be accomplished mainly by local vascular control mechanisms (section V B 2).

Quantitative information about the responses of the *capacitance vessels* to graded sympathetic nerve stimulation is not available for cutaneous tissue specifically. However, indirect estimations were obtained from studies of the capacitance responses in cat hindquarters, some 20% of which consist of skin. It could be deduced that vasoconstrictor fibre stimulation at 6 to 8 impulses per sec led to maximal expulsion of blood, which amounted to about 1.5 ml/100 g skin (248). This capacitance response was about twice that of skeletal muscle.

A variety of vasomotor reflexes have been shown to influence cutaneous capacitance vessels in both animals and man. For instance, some reduction in regional blood content was noticed together with the increase of resistance in cat paw during hemorrhage or carotid artery occlusion (262). Deep inspiration produced transient venoconstriction in the human hand, shown either as a volume reduction in plethysmographic recordings or as a rise of venous pressure when hand circulation was arrested (327). Studies of pressure-volume curves in the vascular beds of the human hand and foot showed reduced venous distensibility when the subject was tilted from supine to erect posture, but this was a transitory phenomenon and there were no signs of sustained venoconstriction (326). Pressure measurements in occluded segments of superficial forearm veins indicated a short-lasting constriction in response to cooling of the contralateral hand, to

hypercapnia, and to emotional apprehension (85). It thus appears that reflex venoconstriction in the skin is often of quite short duration and that the cutaneous veins usually contribute little to sustained reflex mobilization of blood or prevention of pooling, a surprising result in view of the strong effects of direct sympathetic stimulation.

A summary of the adrenergic vasoconstrictor fibre control of the cutaneous vessels must emphasize its predominant role in thermoregulation. Increase in cutaneous blood flow on inhibition of the sympathetic discharge and reduction in flow at increased rates of discharge can be graded with remarkable precision because of the readiness with which the arteriovenous shunts react to the changes in nervous activity. Reflex adjustments concerned with circulatory homeostasis are much less pronounced in skin than in skeletal muscle in that only moderate or transitory variations in flow resistance, precapillary sphincter tone, pre- to postcapillary resistance ratio, and vascular capacitance occur.

*Effects on vascular functions in intestine.* Sustained activation of the sympathetic vasoconstrictor fibres of the intestine elicits the following general pattern of response: a transient pronounced constriction of the resistance vessels followed by secondary return of resistance toward the control level, a transient increase of the pre- to postcapillary resistance ratio and secondary return to control, a maintained decrease of the functional capillary surface area indicating increased precapillary sphincter tone, and a maintained constriction of capacitance vessels. This pattern of response has so far been studied mainly in cat intestine and it will be considered in greater detail below.

Total venous outflow from a segment of denervated small intestine "at rest" is about 40 to 60 ml/min  $\times$  100 g tissue at normal perfusion pressure (129). A characteristic response of the *resistance vessels* has been demonstrated upon supramaximal activation of the regional sympathetic adrenergic fibres (126). At constant pressure there was an initial pronounced decrease in flow, sometimes an almost arrested circulation (peak response) (cf. 156). Within 1 to 3 min of continued stimulation, flow returned toward or to the prestimulatory control level (steady state response) and this phenomenon was termed "auto-regulatory escape from vasoconstrictor fibre influence." At low stimulation frequencies (1 to 6 impulses per sec), flow in the steady state phase usually stabilized at a level 20 to 40% below control level, but occasionally the resistance response was somewhat better maintained. At higher rates (8 to 10 impulses per sec) the "escape phenomenon" was generally more pronounced resulting in steady state flow values close to, or sometimes even above, the control level. A similar pattern of resistance response is seen in the large intestine as well (186). Cessation of stimulation was regularly followed by a "reactive hyperemia," which was quite pronounced even when, in the steady state phase, total intestinal flow had returned to or above the prestimulatory level. This pattern of constrictor response and a poststimulatory reactive dilatation occurred also when constant flow methods were applied (84).

Reflex engagement of the vasoconstrictor fibres to the intestine induced by diminution of baroreceptor activity, chemoreceptor stimulation, or moderate

hemorrhage elicited a resistance response like that described above, and the resistance in the phase of autoregulatory escape was, as a rule, only 10 to 25% above the control level (262).

The vasoconstrictor fibre influence on resistance function in intestine is thus very different from that in skeletal muscle and skin, in which sustained constrictor responses are seen over prolonged periods of stimulation. On the other hand, neurogenic resistance effects resembling those in intestine have been observed in the kidney (105) and in the hepatic arterial circulation (162). Some aspects of the nature of the autoregulatory escape phenomenon in intestine will be discussed later in this section.

The sympathetic nervous influence on *precapillary sphincters* has been studied in terms of changes in CFC (127). Sympathetic activation caused a reduction of CFC which, in contrast to the situation in skeletal muscle, was maintained over prolonged periods of stimulation. Thus, a sustained reduction to 30 to 50% of the resting control value was observed in the steady state phase of constrictor fibre stimulation, *i.e.*, when blood flow due to autoregulatory escape had returned to a steady level not far from the control value. This indicates a corresponding decrease of functional capillary surface area. The fact that there was a decrease of the capillary exchange surface to values ranging from  $\frac{1}{3}$  to  $\frac{1}{2}$  of the control without a corresponding increase of resistance could indicate a redistribution of blood flow within the intestine in response to constrictor fibre excitation.

This hypothesis was supported by experiments in which the distribution of India ink was studied after intra-arterial administration. During the peak resistance response there were signs of pronounced constriction in the mucosal vessels and this constriction was fairly well maintained even in the phase of autoregulatory escape when the submucosal regions appeared hyperemic (127). Therefore, it appears that the observed decrease of CFC can be ascribed to closure of precapillary sphincters in the mucosa. It might also be an effect of strong constriction of small arterial vessels located in the basal mucosa since these have a particularly abundant adrenergic innervation (261). These data seem to provide strong circumstantial evidence for the hypothesis that at least part of the autoregulatory escape can be explained by a redistribution of intestinal blood flow, most probably from mucosal to submucosal vessels. The post-stimulatory reactive hyperemia seems consistent with the idea that constrictor fibre activation caused a maintained decrease in nutritional flow in some part of the intestine.

The question whether true nonnutritive arteriovenous anastomoses or *shunt vessels* exist in the intestinal vascular bed is of great physiological and pathophysiological interest. For example, a sudden diversion of flow to shunts from the exchange vessels of tissues with high metabolic demand might lead to ischemic lesions, a mechanism discussed for the development of gastric ulcer, intestinal necrosis, etc. (for ref. see 153, 323). From the data reported above, it seems likely that vasoconstrictor fibre engagement in the phase of autoregulatory escape brings about a diversion of flow from mucosal to submucosal structures

and that functional exchange surface in the mucosa is diminished. These adjustments *per se* would seem to result in decreased availability of oxygen and nutrients to the mucosal cells, but the important question whether prolonged sympathetic excitatory states can lead to tissue damage in the mucosa cannot be answered as yet.

Spanner (310) described a type of shunt vessel in the submucosal layer of intestine. Dynamic studies (235) in which the recovery of calibrated microspheres was determined indicated the presence of some fairly wide arteriovenous pathways in this tissue (see section IV), but such investigations do not, of course, rule out that these vessels still might have some exchange function. It is possible that during the phase of autoregulatory escape part of the flow is diverted to the submucosa by opening of low resistance vessels, but the question then arises whether or not these are true nonnutritive shunts.

From experiments in which blood flow and capillary filtration and diffusion capacity (CFC and PS) were determined simultaneously it was concluded that if low resistance vessels, like the shunts of Spanner, were involved in the flow recovery during autoregulatory escape, these vessels seem to permit diffusion exchange (83). Furthermore, data obtained from studies of oxygen consumption in the intestine in the period of autoregulatory escape gave no evidence for extensive arteriovenous shunting (19). No doubt, however, constrictor nerve activity can produce an uneven capillary flow distribution within the intestine. A maintained high flow in the face of a decreased number of open capillaries could lead to such an increase of capillary flow velocity that solute extraction would decrease. This would imply "physiological shunting" (section II), which should be distinguished from true shunting in nonnutritive vessels.

During the brief peak constrictor response there appears to be some transcapillary absorption of extravascular fluid, and this indicates an increased *ratio of pre- to postcapillary resistance*, as occurs in skeletal muscle and skin. In the steady state of the constrictor response, however, there is no significant net transcapillary fluid movement in the intestine, a finding that indicates a return of the ratio, and of capillary hydrostatic pressure, to the prestimulatory control level (162). This type of response is seen also during reflex excitation *via* baro- and chemoreceptors and during hemorrhage (262). The rapid return of the pre- to postcapillary resistance ratio seems dependent mainly upon local regulatory adjustments of vascular tone, which are probably related to the autoregulatory escape of the precapillary resistance vessels in the face of maintained constriction of the capacitance vessels (see below). The functionally important aspect of this reaction is that it implies an "autoregulation of intestinal transcapillary filtration" during vasomotor engagement. The absence of net fluid exchange may further be related to closure of precapillary sphincters in the mucosa, to maintained constriction within the portal venous system (162), and to changes in colloid osmotic and hydrostatic tissue pressures (203, 337). The capillary network in intestine shows a very large hydrodynamic conductivity as evidenced by the CFC value, which at rest is about 10 times higher than that in skeletal muscle. It is evident that only a slight change in intestinal capillary

pressure would lead to profound transcapillary fluid movements. The auto-regulation of transcapillary filtration must be an important mechanism protecting the intestine against severe dehydration or oedema formation and consequent dysfunction during increase or decrease of sympathetic discharge. Skeletal muscle and skin have lower capillary hydrodynamic conductivity and are voluminous organs with large total extravascular fluid volumes from which fluid absorption at moderate rates can occur in response to constrictor fibre discharge, apparently without impairing the tissue functions.

During the maximal response of the *capacitance vessels* to vasoconstrictor fibre stimulation there is an expulsion of 30 to 40% of the regional intestinal blood volume, which at normal venous pressure amounts to 7 to 9 ml/100 g tissue in denervated gut (126, 129). The active component of this response was well sustained even in the stage of autoregulatory escape of the resistance vessels. The magnitude of the passive component of the capacitance response was related to, and varied, accordingly, in parallel to the constrictor response of the precapillary resistance vessels. The passive component was quite pronounced at low venous transmural pressures, but fairly insignificant at high venous pressures. The maximum of the active capacitance constrictor response was reached at low rates of discharge (4 to 6 impulses per sec), as in skeletal muscle. Reflex studies similarly show sustained capacitance effects (262), and there is evidence that, in contrast to skeletal muscle, the reflex sympathetic discharge to the capacitance vessels equals that to the resistance section (170).

The mechanism behind the "*autoregulatory escape*" from vasoconstrictor fibre influence in the intestinal resistance vessels is not clear. The maintenance of the constrictor response of the intestinal capacitance vessels and of small precapillary vessels in the mucosa seem to indicate that there is no failure of adrenergic impulse discharge or transmitter release. Intra-arterial noradrenaline administration elicited essentially the same pattern of response as nerve stimulation (19, 84), whereas vasopressin produced a pronounced and well maintained resistance response without signs of an autoregulatory escape (84). The possibility of a distribution of the adrenergic  $\alpha$ -receptors and of the sympathetic nerve endings to particular "key sections" of the intestinal vascular bed was discussed on the basis of these findings (84).

The autoregulatory escape could not be related to excitation of cholinergic nerve fibres, since the flow pattern was not affected by atropine (126). Administration of a  $\beta$ -blocking agent (propranolol) seems to make the autoregulatory escape more sluggish in onset and somewhat less pronounced, but it does not abolish the phenomenon (251). If the arteriovenous pathways of Spanner are involved in the autoregulatory escape, an  $\alpha$ -adrenergic contraction of their longitudinal smooth muscle might lead to increased lumen and shortened length and hence to decreased resistance, but this possibility has not been tested experimentally. It would seem worth while to study the recovery of graded microspheres on the venous side in the phase of autoregulatory escape. The escape phenomenon is not related to passive effects on the circulation of a changed intestinal motility (19). It seems at present most likely that the escape is related

to some local regulatory mechanism, and it has some features in common with "conventional" flow autoregulation in response to varying perfusion pressure as seen in many tissues including intestine (202). For example, if perfusion pressure is decreased below the range in which autoregulation of intestinal flow occurs, the autoregulatory escape is much diminished or abolished (126). Locally produced vasodilator factors tending to reopen mucosal vessels or submucosal vessels, or both, might very well be involved in the escape phenomenon, but none has so far been identified. A local increase of the hydrogen ion concentration did not occur during the autoregulatory escape and thus cannot be the factor responsible (19). Future study is needed to clarify the mechanism and the functional significance of this interesting vascular adaptation.

The adrenergic control of all the vascular functions in the gut discussed above has so far been studied only in the cat. Although it should be emphasized that species differences may very well exist, several studies indicate that the pattern of adrenergic vascular response described above may occur in the dog and probably in man as well. For example, hemorrhage is generally associated with only slight increases of mesenteric resistance. This might indicate an autoregulatory escape phenomenon, whereas there is a maintained decrease of the splanchnic blood volume (*e.g.*, 45-47, 279). A sustained reflex constriction of intestinal resistance vessels, however, might be expected in hemorrhage if arterial blood pressure falls below the range in which autoregulation of blood flow occurs (*cf.* 126). If, on the other hand, a reflex activation of constrictor fibres is associated with a marked rise in blood pressure, as for instance, after carotid sinus denervation, intestinal flow resistance may become fairly pronounced even in the escape period (256), and this may be due to reinforcement of the response by the local myogenic mechanism (see below).

*In summary*, it may be emphasized that excitation of the abundant vasoconstrictor fibres to the intestine elicits a pattern of vascular response differing greatly from that in skeletal muscle and skin, and the general hemodynamic consequences are accordingly different. After an initial, short-lasting, strong constrictor response, there is an autoregulatory escape from vasoconstrictor fibre influence in the resistance vessels, particularly at high discharge rates, which, at least partly, seems related to a redistribution of flow from mucosal to submucosal vessels. At moderate rates of discharge, the maintained resistance effect, although small compared to that of skeletal muscle and skin, may play some role in homeostatic regulation considering the large fraction of cardiac output distributed to the gut. Since the intestinal capacitance constrictor response is sustained during prolonged sympathetic activation and since it can lead to mobilization of quite large amounts of blood for the central circulation, this response must be considered an important component in neurogenic vaso-motor adjustments aiming at a maintenance of cardiovascular homeostasis. In contrast to skeletal muscle and skin, the intestine does not participate in the neurogenic control of plasma volume by tissue fluid absorption, but shows, instead, an "autoregulation of transcapillary fluid movement" to maintain a Starling equilibrium.

*2. The sympathetic cholinergic vasodilator fibre system*

The existence of a vasodilator fibre system in the sympathetic nerves to the hind limbs of cat and dog was demonstrated by Bülbring and Burn (55) and Folkow and Uvnäs (136). Blockade of the dilator response by atropine gave evidence for the cholinergic nature of the system (119). It seems well established that these fibres are distributed only to the vessels of skeletal muscle (136), and the early suggestion that the coronary vascular bed might be supplied with a similar cholinergic innervation from the cardiac sympathetics is refuted by recent investigations (104). Marked species differences appear to exist with regard to the development of the dilator fibres to skeletal muscle (334).

A central representation of the sympathetic cholinergic vasodilator fibre system was demonstrated in the hypothalamus (93), and the sites of the brain structures from which active vasodilatation in skeletal muscle can be elicited have later been mapped out in greater detail (4, 184, 234). The peripheral efferents subserving the cholinergic skeletal muscle vasodilatation are thin, high-threshold fibres (125), and the demonstration of the dilator response by electrical stimulation of the sympathetic trunks therefore usually requires that the effect of the simultaneous constrictor fibre activation is first eliminated by  $\alpha$ -adrenergic blockade or by reserpination of the animal. The fact that the cholinergic response can be elicited by central stimulation, for instance in the hypothalamus, without previous adrenergic blockade, is clear evidence that we are dealing with a true dilator fibre system and not with a cholinergic effect of vasoconstrictor fibre activation as proposed by Burn and Rand (58). The functional differentiation of adrenergic and cholinergic fibres to muscle has also been established by other means (81).

Structures resembling nerve endings were recently demonstrated in arterioles 30 to 100  $\mu$  in diameter by staining skeletal muscle from dog, cat, and sheep for the presence of acetylcholinesterase (39). These structures were not found after chronic regional sympathectomy; therefore, they appear to represent the terminals of the cholinergic dilator fibres. Functional circulatory studies indicate a confinement of these fibres to the arteriolar section of the vascular bed in skeletal muscle (see below).

The mechanism by which the cholinergic transmitter inhibits vascular smooth muscle tone is not clear. Isolated preparations from large vessels, which have been used for investigating electrical and mechanical responses of vascular smooth muscle, often contract in response to acetylcholine and thus cannot serve as models for studying cholinergic vasodilatation. One possibility is that myogenic pacemaker activity or intercellular propagation in small vessels is inhibited by the cholinergic transmitter (79).

*Effects on vascular functions in skeletal muscle.* Apart from the early demonstrations of the decrease in muscle flow resistance produced by the cholinergic fibers, there are several recent investigations concerned with a more detailed and quantitative analysis of the vascular response. These have indicated a decrease in pre- to postcapillary resistance ratio but no dilator effect in precapillary sphincters or capacitance vessels.

Stimulation of the lumbar sympathetic trunks at 10 to 20 impulses per sec after  $\alpha$ -adrenergic blockade or reserpine causes a 5-fold increase of skeletal muscle blood flow in cat and dog hindlimbs. This response is at least 70% of the maximal *resistance vessel* dilatation produced by intra-arterial infusion of acetylcholine or by muscle exercise (132, 278). The resistance vessel dilatation obtained by cholinergic dilator fibre excitation, either in the periphery or in the hypothalamus, is often quite transient and followed by return of flow resistance despite continued stimulation. This recovery may be explained by assuming that the cholinergic transmitter produces the dilator response by blocking propagation of myogenic smooth muscle activity at some rather distinct section of the small precapillary vessels and that vascular tone is gradually restored by the appearance of spontaneity in potential pacemakers at more proximal levels of the arteriolar tree (79). Under conditions of "poor vascular reactivity" the responses to vasodilator fibre stimulation were shown to be well sustained.

Clearance of radioactive electrolytes from the muscle tissue did not increase in association with the flow augmentation produced by cholinergic dilator fibre excitation. This finding led to the suggestion that the dilator fibres might open up nonnutritional *shunt vessels* (187). This hypothesis, however, was not supported by experiments in which the transit of graded microspheres was determined (271). The above clearance data as well as the reduced oxygen uptake by the skeletal muscle during cholinergic vasodilatation have been explained, instead, as results of functional shunting attributed to uneven capillary perfusion (288). The *precapillary sphincters* seem to be devoid of cholinergic innervation as indicated by an unchanged capillary diffusion capacity during vasodilator fibre stimulation in experiments on skeletal muscle perfused at a constant flow (278). When flow was allowed to increase on stimulation of the sympathetic cholinergic fibres, CFC decreased, a result that indicates closure of precapillary sphincters (79). This was interpreted as a myogenic response produced by the increment in transmural pressure in this vascular section resulting from dilatation of the precapillary resistance vessels.

Net transcapillary fluid filtration accompanying the cholinergic blood flow increase indicates a decreased *pre- to postcapillary resistance ratio*, which implies a predominant effect of the vasodilator fibres on the arteriolar vessels (132). Regional blood content increased to some extent upon peripheral stimulation, but since this appeared to be an essentially passive phenomenon, it was concluded that the muscle *capacitance vessels* have little or no cholinergic fibre innervation. In fact, stimulation in the hypothalamic dilator area could elicit precapillary resistance vessel dilatation and concomitant capacitance vessel constriction (132). The integrated autonomic pattern upon topical stimulation of these hypothalamic structures includes activation of the sympathetic adrenergic fibre system as well, which leads to a variety of adrenergic responses, such as increased cardiac output and constriction of cutaneous, intestinal, and renal vessels (105, 128, 234). It is conceivable, therefore, that the capacitance vessel constriction in muscle described above results from the engagement of constrictor fibres supplying the veins.

As to the functional significance of the sympathetic cholinergic dilator system, it is generally agreed that these fibres are not involved in cardiovascular homeostatic reflexes of chemoreceptor or baroreceptor origin (333). Stimulation of the hypothalamic vasodilator area in awake animals with implanted electrodes leads to a behavioural response pattern of alerting, flight, or attack, indicating that activation of the cholinergic dilator fibres is part of the autonomic nervous adjustments associated with the alerting response and the defence reaction (4, 5, 334). A large increase in skeletal muscle blood flow has been demonstrated in people subjected to emotional stress (*e.g.*, 21, 149), but conclusive evidence as to the role (160), or even the existence (334), of sympathetic cholinergic vaso-dilator fibres in man seems still to be lacking.

### 3. Other nervous systems

Vasomotor fibre systems, other than those considered above, have not been analysed in detail with regard to their influences on peripheral vascular functions, and some of these systems must even be considered hypothetical.

Activation of autonomic fibres distributed by way of the cranial nerves produces vasodilatation in the pia mater, in the tongue, and in salivary glands, responses which have been ascribed to *parasympathetic vasodilator fibres* (for ref. see 112, 113, 333). These effects have been studied most extensively in the salivary glands (97), in which the secretory response elicited by maximal stimulation of the parasympathetic nerve supply is associated with a more than 10-fold increase in blood flow from a high resting value of some  $40 \text{ ml/min} \times 100 \text{ g tissue}$  (*e.g.*, 322). The fact that the vasodilator response is well maintained after this secretion is abolished by small doses of atropine demonstrates that the vascular reaction is not secondary to the change in glandular activity. Much research has been carried out to elucidate this dissociation between blood flow and glandular secretion (or oxygen consumption) seen after atropine and different mechanisms have been proposed to explain this persistent vascular response.

Studies by Hilton and Lewis on the submaxillary gland of the cat led them to the conclusion that the increase in glandular blood flow produced by chorda tympani stimulation was not due to activation of true dilator fibres supplying the vascular smooth muscle but was mediated by a kinin mechanism (181). They suggested that the nerve stimulation caused liberation of an enzyme which, in the interstitial fluid, released a vasodilator substance, probably bradykinin or some related polypeptide. Increase in the blood flow of the tongue upon stimulation of the chordolingual nerve was also attributed to kinin release in the glandular tissue of this region (182). The role of enzymatic kinin formation as a factor in neurogenic vasodilatation of glandular tissue as proposed by Hilton and Lewis has not received unanimous support, however, and Schachter and his associates have presented some evidence against the importance of kinins for vasodilatation in the cat salivary glands (31). It appears that the evaluation of the relative importance of true vasodilator fibres and of enzymatic kinin formation, respectively, for the control of glandular blood flow must await further investigation. Also, a satisfactory explanation for the relative refractoriness of

the parasympathetic vasodilatation to atropine must be given before the cholinergic nature of the response can be assessed.

Vasodilator nerve fibres are distributed to the genital organs, bladder, and large intestine by way of the sacral parasympathetic outflow. The fibres supplying the genital organs seem to be activated from quite discrete areas of the diencephalon and the limbic cortex as indicated by the appearance of penile erection in monkeys during topical stimulation in these parts of the brain (244). The mechanism of erection has been studied in dogs by stimulation of the pelvic nerves (82, 173). It was concluded in the more recent study (82) that interference with venous outflow by contraction of skeletal muscle or by venous constriction plays little or no role in the response, but that the dilatation of the resistance vessels, leading to a 20-fold increase in blood flow, is enough to raise venous pressure and maintain the filling of the cavernous tissue. The vasodilator response was reduced but not abolished by atropine. Close arterial acetylcholine infusion did not produce erection and it was concluded therefore that the normal neural response may contain a cholinergic link, but that some unidentified vasodilator substance may be the direct cause of the vasodilatation.

A pronounced vasodilatation is obtained in the descending part of the colon upon pelvic nerve stimulation and this response is also quite resistant to atropine (186).

Besides the cholinergic vasomotor innervation to skeletal muscle considered under section V A 2 above, other *sympathetic vasodilator systems* have been proposed to participate in the regulation of blood flow in skin and skeletal muscle.

The neurogenic vasodilatation elicited in the human hand during general body heating roughly corresponds to that obtained by regional nerve blockade. This indicates that the thermoregulatory response in this vascular bed can be accounted for by inhibition of sympathetic constrictor fibre activity (12, 284). In other skin areas, such as forearm and calf, the blood flow increase produced by body heating greatly exceeds that occurring after nerve blockade (90, 151, 283), and this result indicates direct or indirect participation of a neurogenic dilator mechanism. The pronounced vasodilatation in these areas is closely related in time to the activation of the sweat glands (90), although the two events can be dissociated by atropinization, which abolishes the sweating response but merely reduces and delays the increase in blood flow. There is experimental evidence that a bradykinin mechanism is operating in the sweat glands (137) and that it contributes to the vasodilatation in skin much as in salivary glands, as discussed above.

Stimulation of the sympathetic fibres to the cat's paw after adrenergic blockade does not seem to cause any increase of blood flow despite the presence of sweat glands in the pads (136), whereas active vasodilatation has been obtained in the paw of the dog (351). This latter response could not be abolished by atropine or antihistamines; nor did it seem to be related to release of bradykinin. In the tail of the muskrat, where sweat glands appear to be lacking, a 400-fold increase in blood flow occurred in response to body heating, and this effect was largely abolished by regional nerve blockade (189). The above examples may

serve to illustrate the relative roles of vasoconstrictor fibre inhibition and of vasodilator fibre activation respectively, as well as the variable relationship of active cutaneous vasodilatation to sweat gland activity during heat load in different species.

Reflex vasodilatation produced, for instance, by carotid baroreceptor stimulation is mostly looked upon as a result of inhibition of tonic sympathetic discharge, a view which receives substantial support from demonstrations of decreased electrical activity in the sympathetic efferents (*e. g.*, 148). It has been suggested, however, that such reflex vasodilatation involves, in addition, an active component mediated by histaminergic vasodilator nerve fibres distributed in the sympathetic nerves (25). Injections of noradrenaline or adrenaline into the systemic circulation produced reflex dilatation of resistance vessels in the hindquarters of the dog, and the magnitude of these transient responses exceeded the resistance decrease obtained by subsequent regional sympathectomy. Such comparisons do not seem to provide sufficient evidence for active neurogenic vasodilatation since local control mechanisms, for instance of myogenic nature, may modify the responses. The proposed active component of the reflex was reduced or abolished by antihistamines (25, 26). In animals given <sup>14</sup>C-histidine before the experiments, an increased release of <sup>14</sup>C-histamine could be detected in the venous effluent during neurogenic vasodilatation (331), but there is no experimental proof that this histamine is of neural origin. The proponents of neurogenic histaminergic vasodilatation have summarized their arguments in recent symposia (26, 49, 332) but the evidence for the existence of a sympathetic histaminergic vasodilator fibre system is still incomplete. A major problem seems to be that direct sympathetic nerve stimulation has failed to elicit effects that can be ascribed to such fibres; this has led to assumptions of complex autonomic interactions at peripheral sites (26). Further, there is so far no convincing evidence for increased electrical activity in sympathetic efferents during reflex vasodilatation. Recently, still another sympathetic vasodilator fibre system eliciting sustained dilatation has been proposed in the hindquarters of the dog (27), but its nature remains to be elucidated.

Antidromic stimulation of afferent C-fibres causes a pronounced and sustained vasodilator response, preferentially in the cutaneous vascular bed (*e. g.*, 64). It is now generally agreed that these "dorsal root vasodilator fibres" are not activated reflexly from the central nervous system, but that the afferent C-fibres may participate in local vascular effects, such as the flare of the triple response *via* an axon reflex arrangement. The "transmitter substance" mediating the vasodilator reaction is not known, but several possibilities have been discussed (113, 333). Even if these dorsal root vasodilators are not normally involved in the central nervous control of the peripheral circulation they seem to deserve attention because of their possible role in the repair of injured tissue.

#### 4. *The adrenomedullary hormonal system*

Release of catecholamines from the adrenal medulla into the circulating blood contributes, to some extent, to the control of the peripheral vascular functions.

Details concerning the functional organization of this system have been reviewed previously (99, 113). Both adrenaline and noradrenaline are produced in the adrenal medulla, but the ratio of the two catecholamines in the venous effluent from the suprarenal glands varies considerably in different species and also in the same animal under different conditions (99). There is some evidence to indicate that there are separate adrenaline- and noradrenaline-producing cells in the adrenal medulla and that the secretion of either substance may be controlled from separate structures in the central nervous system (for ref. see 113).

The physiological secretory capacity of the adrenal medullae was estimated in cats by Celander (62). He found a release of catecholamines of about  $5 \mu\text{g}$  per kg body weight and min during excitation of all the secretory fibres to the adrenals at a high physiological discharge rate (10 impulses per sec). Upon strong reflex sympathetic activation, the amounts of catecholamines seldom exceeded 2 to  $3 \mu\text{g}/\text{kg} \times \text{min}$  and under resting conditions the release was generally less than  $0.1 \mu\text{g}/\text{kg} \times \text{min}$  (62, 100). Before discussing the effects on the circulatory functions of the adrenomedullary hormonal system, certain aspects of the reactions of the vascular smooth muscle effector to adrenergic " $\alpha$ - and  $\beta$ -receptor" stimulation will be considered.

Vascular smooth muscles in which contraction is related to propagated action potentials (section III) show enhancement of spike activity in response to  $\alpha$ -receptor stimulation (71, 142, 194). The reaction of the agonist with the receptor sites appears to change the ionic membrane permeabilities in such a way that depolarization and increased firing rate occur. There is evidence, however, that the mechanical response to  $\alpha$ -receptor stimulation cannot be ascribed solely to the change in the pattern of electrical activity: a "positive inotropic action" of the adrenergic agent on the vascular smooth muscle appears to contribute to the increased tension development (71, 194). The latter effect is seen most clearly on the potassium-depolarized muscle, in which noradrenaline increases contracture tension without causing any measurable change in membrane potential (194). The  $\alpha$ -receptor stimulant may exert its inotropic action on vascular smooth muscle by improving the supply of calcium ions to the contractile apparatus. This, in turn, could result from increased membrane permeability augmenting the influx of extracellular calcium. But, since noradrenaline can restore electrical and mechanical activity in  $\text{Ca}^{++}$ -free medium when spontaneous spikes and contractions are abolished, there is reason to assume that enhanced liberation of bound calcium is involved in the  $\alpha$ -adrenergic response (194, cf. also 185). Such a mechanism might be of particular importance for eliciting constriction of vessels whose adrenergic response appears to be entirely unrelated to electrical events (section III).

Vasodilatation elicited by adrenergic agents can be due to direct stimulation of  $\beta$ -receptors of the vascular smooth muscle cells, but it may also be an indirect effect of changes in tissue metabolism produced by the adrenergic substances. Release of "vasodilator metabolites" from the parenchyma would be the immediate cause of the vascular response in the latter case. Changed metabolic ac-

tivity is undoubtedly of importance for the increase in coronary blood flow produced by adrenergic agents and the situation may be similar in adipose tissue. The role of metabolic products in the adrenaline vasodilatation of skeletal muscle has been evaluated in several experimental studies, but is still a matter of debate. This subject was recently reviewed (242).

Experiments on isolated vascular smooth muscle clearly demonstrate its ability to relax in response to a direct action of adrenergic substances and this effect is abolished by  $\beta$ -adrenergic blocking agents. Strips from small coronary arteries are peculiar in the respect that noradrenaline is a more potent stimulant of their  $\beta$ -receptors than is adrenaline (36). A recent study of the influence of isoprenaline (isoproterenol) on electrical and mechanical activity in the isolated rat portal vein has revealed quite a complex pattern of response (194). Stimulation of the  $\beta$ -receptors by this agent produced depolarization and an increase in the frequency of the bursts of action potentials that trigger contraction, but this "positive chronotropic effect" was accompanied by a reduced amplitude of contraction, partly attributable to a decreased number of spikes per burst. Isoprenaline inhibited tension development also by some mechanism unrelated to electrical phenomena. The  $\beta$ -adrenergic response of the portal vein resembled the changes in spontaneous activity obtained by reducing the calcium ion concentration of the medium. It is notable that adrenergic relaxation of the taenia coli is associated with hyperpolarization (54) in contrast to the depolarization found in the portal vein.

When evaluating the importance of the adrenomedullary hormonal system for peripheral circulatory control, the secretory capacity of the adrenal medullae should be taken into consideration. As mentioned above, the maximal amounts of catecholamines released under physiological conditions in the cat do not exceed 5  $\mu\text{g}/\text{kg}$  body weight/min. Strong reflex sympathetic activation as during hemorrhage can result in plasma concentrations of the catecholamines in the range of 25 to 50 ng/ml (see 58a). Under "resting" conditions, the corresponding figure is about 1 to 2 ng/ml (58a, 120). These moderate concentrations of blood-borne catecholamines should be contrasted with the local concentrations of more than 1  $\mu\text{g}/\text{ml}$  in the neuromuscular junctional gaps at vasoconstrictor nerve endings when these are activated at physiological impulse rates (120, 236). Since, however, the nerve endings have a fairly restricted distribution in the muscle layer of most vessels, circulating noradrenaline is likely to reach a much greater number of the vascular smooth muscle cells.

Celander (62) compared the resistance effects in several vascular beds evoked, on the one hand, by graded excitation of regional sympathetic constrictor fibres and, on the other, of the secretory fibres to the adrenals, and further, studied the responses to intravenous and intra-arterial infusions of adrenaline and noradrenaline when given in "physiological" amounts (up to 5  $\mu\text{g}/\text{kg} \times \text{min}$ ). He found with regard to constrictor effects that the resistance vessels were completely dominated by the vasomotor fibre influence and that during reflex discharge it made little difference whether the secretion from the adrenal medullae was eliminated or not. In one respect, however, the adrenomedullary secretion

is of great significance in circulatory control, *i.e.*, in evoking a  $\beta$ -receptor dilator response to adrenaline in skeletal muscle. Another important aspect is, of course, the metabolic actions of adrenaline.

On intravenous administration of *l*-adrenaline the dilator response of skeletal muscle resistance vessels was most pronounced at infusion rates of about 0.3 to 0.5  $\mu\text{g}/\text{kg}$  body weight  $\times$  min. This response was about 75%, or more, of a maximum dilator effect elicited by large doses of intra-arterially administered acetylcholine (62, 248). At higher rates of adrenaline infusion, the interference of the  $\alpha$ -constrictor effect became apparent and at doses exceeding 2 to 3  $\mu\text{g}/\text{kg}$   $\times$  min the response reverted to pure constriction. However, such high concentrations are probably released only under exceptional conditions in the intact organism, and a vasodilator effect of adrenaline in muscle is likely to be the more common response.

A quantitative analysis of the responses in the pre- and postcapillary resistance vessels and in the capacitance vessels to graded stimulation of the secretory fibres of the adrenal medulla and to graded infusions of adrenaline and noradrenaline was performed in cats in muscle as well as in a region consisting of both muscle and skin (248). These effects were compared to the responses elicited by graded excitation of the regional sympathetic vasoconstrictor fibres. With regard to constrictor effects, it was found that catecholamines in "physiological" amounts, whether released by graded stimulations of the adrenal medullary nerves or infused into the blood stream, induced responses in both the resistance and capacitance vessels that were generally only some 20 to 25% of those obtained by similarly graded stimulations of the constrictor fibres. Even so, the adrenomedullary hormonal control cannot be entirely neglected. With regard to other vascular functions, the constrictor effects of blood-borne catecholamines showed characteristics similar to those produced by vasoconstrictor fibre excitation. Thus, there was a moderately increased ratio of pre- to postcapillary resistance and an absorption of extravascular fluid to the circulatory system when perfusion pressure was kept constant. The fluid absorption may be less pronounced if blood pressure rises markedly upon catecholamine administration or release. Noradrenaline infusion can elicit a transient constrictor effect in pre-capillary sphincters, as evidenced by determination of CFC, but during prolonged infusion there is soon a reversal, so that the functional capillary surface area tends to increase above the control level (249). This is probably the result of competitive local control mechanisms, as discussed above in connection with vasoconstrictor fibre influence.

When adrenaline was administered in such amounts as to elicit a pronounced  $\beta$ -receptor dilatation in the muscle resistance vessels, there was little or no active dilatation of the capacitance vessels, whereas dilator drugs like acetylcholine always dilated both these vascular sections to a marked degree (248). In fact, it was possible to adjust the dose of adrenaline to evoke a clear-cut dilatation of the resistance vessels and a concomitant constriction of the capacitance vessels. Reduction of total flow resistance by adrenaline was associated with a decreased ratio of pre- to postcapillary resistance, leading to a filtration of fluid

from the intravascular to the extravascular space. These results might suggest that the  $\beta$ -receptors are localized predominantly in the precapillary vessels, whereas the  $\alpha$ -receptors are distributed to both the pre- and postcapillary sections of the vascular bed in skeletal muscle. Such a difference may also exist in the human forearm vessels (88, 302).

In skin, both adrenaline and noradrenaline evoke constriction of resistance and capacitance vessels and in all probability an increased ratio of pre- to postcapillary resistance (62, 248). The remarkably strong constriction of cutaneous arteriovenous anastomoses produced by noradrenaline is apparently not caused by a greater shortening of the smooth muscle elements in these vessels than in others but depends on the high wall/lumen ratio of these shunt vessels (135).

In intestine, noradrenaline elicits a pattern of resistance response in the cat like that seen during excitation of the intestinal constrictor fibres, *i.e.*, a relatively pronounced, but transient, peak constrictor effect followed by a return of resistance towards the control level (19, 84). This latter phenomenon, termed "autoregulatory escape" seems, at least partly, related to a redistribution of flow from mucosal to submucosal vessels, as discussed in section V A 1 above. Adrenaline has been reported to elicit constriction (155) as well as dilatation (161) of the intestinal resistance vessels, but in the former study a  $\beta$ -receptor dilator response could be revealed after  $\alpha$ -receptor blockade. Adrenaline evokes constriction of intestinal resistance vessels in man (154). There is indication that noradrenaline as well as adrenaline can increase venous tone in the intestinal vascular bed (*e.g.*, 7, 301). The effects of circulating adrenaline and noradrenaline on precapillary sphincters in skin and intestine do not seem to have been investigated.

The action of adrenaline and noradrenaline on the resistance vessels in the human forearm and hand has been extensively studied, and reviewed elsewhere (*e.g.*, 20, 341, 342). With regard to the direct effects on the vascular smooth muscle, the responses in man are usually similar to those observed in animals, but the pattern may often be modified by concomitant nervous reflex alteration of vascular tone.

##### 5. *The renin-angiotensin system*

The octapeptide angiotensin is the most potent biogenic vasoconstrictor substance known at present. Much work has been done, therefore, in order to elucidate its mode of action on vascular smooth muscle, its influence on the different peripheral vascular functions, its significance in normal circulatory control, and its possible role in the pathogenesis of hypertensive disease. Recent advances with regard to the formation of renin and its regulation, as well as the kinetics of angiotensin production, are beyond the scope of this presentation but have been reviewed elsewhere (269, 335).

Besides its direct influence on vascular smooth muscle considered below, angiotensin has been assigned a multitude of actions on the sympathoadrenal system and thus affects vascular tone indirectly through adrenergic mechanisms. A release of catecholamines from the adrenal medulla was demonstrated by

Feldberg and Lewis (106) and effects of angiotensin on central vasomotor structures, and on release or uptake of noradrenaline at the peripheral nerve endings have also been proposed (for ref. see 174, 269). Recent studies of blood flow reductions in the human hand and forearm produced by angiotensin infusions indicated that the response to intravenous administration was mainly due to an indirect action on the sympathetic system at a central locus, while the effect of intra-arterial infusion was mainly a direct one on the vascular smooth muscle (174, 297).

As to the mechanism of the direct influence of angiotensin on the vascular smooth muscle we have little definite information, but the data available leave no doubt that stimulation of electrical activity is involved at least in certain vessels (38, 71). Some investigators have attempted to define the action of angiotensin on smooth muscle in terms of ion fluxes between intra- and extracellular fluid. Thus, in a recent study, angiotensin contraction of uterine and aortic muscle was found to be associated with increased active extrusion of sodium from the cells whereas the passive influx of this ion was unaffected (330). These findings are in conflict with the thesis advocated by Friedman and Friedman that angiotensin and other constrictor agents cause vascular smooth muscle cells to take up  $\text{Na}^+$  in exchange for  $\text{K}^+$  (138). To contribute significantly to our understanding of the vasoconstrictor effect such ionic flux studies need to be paralleled by recordings of the electrical membrane events and by studies that define the consequences of the ionic shifts for the intracellular contractile machinery. Until this has been done, the functional significance of the above observations cannot be evaluated.

Vascular smooth muscle from different sites and species show striking differences in their responsiveness to angiotensin and in their tendency to develop tachyphylaxis to this agent (38, 207). An interesting observation that may bear on the kinetics of the interaction between angiotensin and its smooth muscle receptor is that angiotensinase can reverse tachyphylaxis to angiotensin (38, 217).

The influence of angiotensin on consecutive vascular sections was first studied in the cat skeletal muscle (124). When the two substances were given in doses eliciting equal resistance effects, noradrenaline caused a clear-cut decrease in regional blood volume, whereas the effect of angiotensin on the capacitance function was slight or absent. Experiments on dog foreleg, spleen, and intestine have also indicated a comparatively stronger influence of angiotensin on pre-capillary than on postcapillary vessels (33, 166). Other authors have reported, however, a constrictor effect of angiotensin on small veins of dog, cat, and monkey extremities (96). Comparative studies of the influence of angiotensin and noradrenaline on the overall systemic vascular capacity were done by Rose *et al.* (287) using a left ventricle bypass technique. Capacitance responses were quantified as translocations of blood between the systemic circulation and the reservoir of the perfusion system. Equipressor amounts of noradrenaline and angiotensin produced opposite effects on intravascular blood volume, *i.e.*, the former agent elicited a significant displacement of blood into the extracorporeal

reservoir whereas angiotensin infusion caused a slight or moderate uptake of blood by the vascular system. This is consistent with the idea that angiotensin is not a venoconstrictor.

The effects of angiotensin on capillary exchange functions as mediated by adjustments of the pre- to postcapillary resistance ratio and of precapillary sphincter activity have not been clearly established. At constant arterial pressure, noradrenaline causes a transcapillary absorption of extravascular fluid in muscle, but surprisingly enough this effect is much less obvious with angiotensin despite the marked increase in total regional resistance (124). This angiotensin response would have been interpreted as an approximately equal rise in pre- and postcapillary resistances if the very weak capacitance effect had not spoken against a strong postcapillary constriction. The response may be related in part to a precapillary sphincter constriction by angiotensin (251), reducing the capillary surface area available for fluid absorption.

The significance of the renin-angiotensin system in circulatory control cannot be decided at present. It is most likely that the vascular responses to angiotensin in the acute experiments, described above, were produced by concentrations of the agent that may greatly surpass those occurring endogenously under normal or pathological conditions. Angiotensin may play its major role in the body not as a direct regulator of vascular tone for the maintenance of circulatory homeostasis, but as a control system for aldosterone secretion or for intrarenal vascular adjustments (269).

#### *6. The vasopressin system*

Vasopressin plays its most important role in the body as a regulator of water reabsorption in the renal tubules, a function that is reflected in the more appropriate name for this polypeptide—the antidiuretic hormone. Normal plasma concentrations of this substance are probably insufficient to exert any direct vasoconstrictor ("vasopressor") effects and its major influence on cardiovascular function therefore can be considered secondary to its action on salt and water balance. As mentioned above the same may be true for angiotensin and, if so, it seems a stroke of irony that both these agents have received names indicating primary vascular control functions.

Vasopressin may still deserve some consideration in this context since the hypothalamo-hypophyseal liberation of the substance seems to be under reflex control from cardiovascular receptors (301a), the plasma concentrations under anesthesia may reach levels sufficient to influence vascular tone, and the hormone shows some remarkable differentiation in its actions on vascular smooth muscle (see below).

Isolated vascular smooth muscle preparations obtained from various sites, exhibit pronounced differences in their responsiveness to the naturally occurring vasopressins or to synthetic analogues. For instance, strips from the thoracic part of dog aorta show no response whatsoever to vasopressin, whereas in the abdominal section sensitivity increases gradually in the craniocaudal direction (306). No such differences were found between the aortic segments with regard

to their responsiveness to adrenaline or angiotensin. The contractile response of vascular smooth muscle to vasopressin depends on extracellular  $Mg^{++}$  concentration, and it was suggested that this ion increases the affinity between the hormone and the muscle receptor (308). Isolated strips from limb veins failed to respond to vasopressin in concentrations that produced strong contraction of small artery strips from the same region (37, 199), a result that again shows great differences in responsiveness.

From such data *in vitro* there is reason to expect interesting differentiated response patterns in the intact circulation. By observing segmental vascular resistances in the dog foreleg a constrictor effect of vasopressin was demonstrated in the arterial vessels, while there were no signs of any significant venoconstriction (167). Studies on cat hindquarters also revealed a clear-cut increase in regional flow resistance, but virtually no change in vascular capacitance (199), a pattern of response compatible with the different sensitivity of small arterial and venous strips to vasopressin. Despite the increase in regional flow resistance, vasopressin, like angiotensin, did not produce absorption of tissue fluid into the circulation. One possible explanation for this is a maintenance of the pre- to postcapillary resistance ratio, which could occur if the arterial constriction were associated with constriction of a limited section of postcapillary resistance vessels, having little influence on capacitance. This interpretation receives some support from the observation of strong venular constriction in the mesenteric microcirculation evoked by natural vasopressins (11). Studies on the intestinal circulation indicate differences in the resistance and capacitance responses to vasopressin which resemble those reported for the skin-muscle regions of the extremities (324). Vasopressin is able to elicit a well maintained constriction of the intestinal resistance vessels (84) in contrast to the effect of noradrenaline, which soon develops an "autoregulatory escape" (see section V A 4 above).

#### B. Local control

Local mechanisms in circulatory control seem primarily involved in the establishment of an optimal exchange function in the tissue. This, in turn, is achieved essentially by proper adaptation of regional blood supply and capillary blood flow distribution. The resistance vessels and precapillary sphincters are, therefore, important targets for the local control systems. There are local factors that promote nutritional flow to the region, for example, when tissue metabolism is increased. Further, there are local factors that tend to stabilize the blood supply during variations in perfusion pressure (autoregulation of flow). Local control mechanisms can also execute a protective function directed against deleterious circulatory effects in the tissue, such as gross oedema formation in situations of increased hydrostatic load on the vascular bed.

Many factors have been proposed to be responsible for local control but several of the concepts are still more or less hypothetical. There is much experimental evidence suggesting that changes in the chemical metabolic environment in the tissue, and myogenic smooth muscle reactions related to stretch play major roles in local vascular control. These two mechanisms will be considered in more detail below.

### *1. Chemical factors related to metabolism*

It is well known that increased metabolism in a tissue is associated with increased regional blood flow, *i.e.*, functional hyperemia. The adaptation of nutritional blood supply to the metabolic demand of a tissue is greatly dependent upon peripheral circulatory adjustments, and these are brought about by control mechanisms which are mainly local in origin. In approaching experimentally the problem of functional hyperemia it has seemed reasonable to assume that regional vascular tone should be inhibited by accumulation of metabolic products, or by lack of nutrients, so as to adjust tissue blood flow in relation to the increased metabolic activity. Such a feedback system was postulated almost a century ago by Gaskell (145), but despite intense research since then, several aspects of the ultimate causal connections between metabolic vasodilator factors and functional hyperemia remain to be established. The local chemical factors involved may very well vary in different organs owing, for instance, to differences in metabolic pathways, vascular smooth muscle responsiveness, *etc.* Other agents than the "true metabolites," such as histamine, acetylcholine, and bradykinin have also been discussed in connection with functional hyperemia.

Local chemical control may certainly be engaged in other circulatory adjustments than in functional hyperemia, such as reactive hyperemia and autoregulation of blood flow, but it cannot be taken for granted that vascular tone is regulated by the same agents in these different reactions. Several vascular beds show reactive hyperemia after a period of arrested circulation, and the mechanisms underlying the phenomenon have been discussed at length elsewhere (*e.g.*, 20, 163, 300, 341). Since the response pattern of reactive hyperemia does not seem to have been analysed in detail with regard to different consecutive vascular sections, this reaction will only be considered in passing. As to the mechanisms of blood flow autoregulation, chemical factors related to metabolism have received much attention, but emphasis has also been placed on myogenic smooth muscle responses to changes in transmural pressure. This phenomenon therefore will be discussed below when myogenic reactions related to stretch are presented. The whole problem of blood flow autoregulation was the subject of a recent symposium (201).

Functional hyperemia seems to be the vascular reaction most intimately related to local chemical factors. It may be seen in any tissue when cellular activity is increased and, if the hyperemia is pronounced and a large mass of tissue is engaged, it can lead to profound alterations in general cardiovascular hemodynamics. From this point of view, skeletal muscle is by far the most important tissue in the organism, since during intense exercise hyperemia, skeletal muscle may receive more than 80% of maximum cardiac output, whereas, normally, only 10 to 15% of resting cardiac output is distributed to this tissue (*cf.* fig. 2). Skeletal muscle exhibits a greater variability in metabolic rate than most other organs and experimentally this can be easily graded by somatomotor nerve stimulation. Functional hyperemia in this tissue has been studied extensively and at different levels of activity. In addition, the pattern of response within the various consecutive vascular sections in skeletal muscle during exercise hyperemia has been analysed in detail, and such studies have helped to evaluate the

significance of different chemical factors responsible for the reaction. Since these types of investigation have not been performed so far in other tissues, the differentiated vascular response to exercise will be presented below as an important example of local chemical control. Various aspects of exercise hyperemia with regard to resistance function have been reviewed previously (20, 178, 341).

*Pattern of vascular response to exercise.* The extent of vascular adjustments to exercise can be revealed from studies on "pure" skeletal muscle during stimulation of somatomotor nerves at intensities below the stimulus threshold for autonomic fibres under circumstances when vascular reactivity at rest is well maintained, and when the mechanical interference of muscle contraction on the circulation is negligible. There is little mechanical interference with flow as long as single twitches are produced (*e.g.*, 121) and therefore the vascular responses to exercise are most clearly revealed at low rates of somatomotor fibre excitation. Maximal vascular effects of exercise in "white" skeletal muscle are generally elicited already at stimulation rates of 4 to 5 impulses per sec, and below this, the reactions are roughly proportional to the stimulation frequency (69, 219, 276). The responses of the various consecutive vascular sections to exercise should be studied preferably with an experimental approach permitting simultaneous analyses of several vascular functions (see section II). Most of the data reported below were obtained from such simultaneous measurements.

With regard to the *resistance vessels*, exercise causes a dilator response, almost immediate in onset, and generally reaching a steady state within less than 90 sec. At a constant blood pressure of 100 mm Hg, flow increases with increasing rates of motor nerve stimulation and at 4 to 5 impulses per sec it reaches values of about 40 to 60 ml/min  $\times$  100 g tissue, *i.e.*, maximal resistance vessel dilatation for "white" skeletal muscle (20, 121, 219). Upon cessation of stimulation, flow returns to the control level within a period of time related to the extent of exercise performed, roughly following an exponential course (80). The physiological motor fibre discharge to a muscle like gastrocnemius can amount to 50 to 60 impulses per sec and then the mechanical effects of the tetanic contraction can significantly impede flow. The muscle blood flow was found to be only about 12 ml/min  $\times$  100 g at this rate of stimulation, despite the fact that the resistance vessels were completely relaxed, as could be revealed by brief interruption of exercise (121).

"Red" skeletal muscle, such as soleus, which has a resting blood supply more than twice as large as gastrocnemius (section IV), seems to dilate its resistance vessels relatively less in the low frequency range and maximal vasodilatation was not obtained until the upper physiological discharge rate of the nerve fibres to this muscle (20 to 25 impulses per sec) was reached (121). However, this fact is easily overlooked since the mechanical effect of tetanic contraction impedes flow significantly at stimulation rates exceeding 8 to 10 impulses per sec. Flow during contraction at 20 impulses per sec was about 50 ml/min  $\times$  100 g, but it more than doubled in the initial postcontraction period when the mechanical obstruction to flow was released.

Metabolic vasodilatation in skeletal muscle is associated with improved capillary exchange even at constant flow. This seems related to the opening of *precapillary sphincters* augmenting the size of the functional capillary surface area, since, as mentioned previously, there is no indication of increased capillary permeability in exercise (13). The extent to which functional capillary surface area increases during exercise has been studied by measuring changes in capillary filtration or diffusion capacity in terms of CFC or PS (section II). CFC was found to be three to four times greater during maximal exercise vasodilatation than at rest (69, 219) and PS, determined for  $^{86}\text{Rb}$ , rose by a factor of 2 to 2.5 during full metabolic dilatation (276). These studies on predominantly "white" muscle indicate, on the average, a 3-fold increase of the functional capillary surface area (*cf.* also 349). The effect, ascribed to an opening of precapillary sphincters, was found to be well graded with respect to the exercise performed at stimulation rates lower than 5 impulses/per sec. Measurement of CFC in soleus suggests that "red" skeletal muscle has a capillary surface area at rest about twice as large as that of "white" muscle and that during maximal exercise dilatation it also increases by a factor of about three (121). Stainsby and Otis (318) estimated the capillary density at rest and exercise from measurements of minimal oxygen tensions compatible with constant oxygen uptake and concluded that the number of perfused capillaries could increase by a factor of 17, thus far exceeding the surface increase indicated by the studies described above. However, their experimental approach is fairly indirect and the deduced capillary density in cross-section of muscle at rest ( $40/\text{mm}^2$ ), in particular, seems extremely low compared to morphological estimates (*e.g.*, 246).

Exercise is associated with a relatively more pronounced dilatation of precapillary than of postcapillary vessels, which can be ascribed at least in part to the fact that on the precapillary side there is a higher resting myogenic "basal tone" on which inhibition can act (section IV). Thus, one effect of exercise is a decrease of the *pre- to postcapillary resistance ratio*, increasing hydrostatic capillary pressure which leads to a net transcapillary loss of fluid from the intravascular to the extravascular space (222). Opening of precapillary sphincters facilitates this fluid transfer. The fluid loss was found to be quite rapid in the initial stage of exercise, but it declined with time with successively increasing tissue pressure, as fluid accumulated in the extravascular space (188). In view of more recent investigations, this fluid loss can be ascribed not only to hydrostatic forces alone, but also to osmotic effects, since exercise was associated with considerable increases of regional osmolality involving primarily the extravascular space (252).

The ineffectiveness of the dilator factors of exercise on postcapillary vessels becomes even more apparent when studying the *capacitance vessels*. By methods that permitted distinction of passive and active components in the capacitance response it was shown that exercise led to virtually no active venodilatation (219), whereas a superimposed intra-arterial infusion of acetylcholine appears to cause the veins to dilate (251).

When the vascular bed of skeletal muscle is simultaneously subjected to the

antagonistic dilator influence of exercise and constrictor influence of adrenergic vasomotor fibre activity, the various vascular sections exhibit a high degree of differentiation in their response. The resistance vessels and especially the precapillary sphincters are dominated by the vasodilator factors, whereas the capacitance vessels are more sensitive to the constrictor influence, so that blood flow and capillary flow distribution are determined mainly by metabolic demand, while accumulation of blood in the active muscles is prevented by the vaso-motor nerves (220). Increased transmural pressure is known to elicit a myogenic constriction of both resistance vessels (115) and precapillary sphincters (255) in resting skeletal muscle (see below), but during exercise this response is abolished in the larger resistance vessels whereas it is fairly well maintained in the precapillary sphincters (243).

*Aspects of the role of metabolic factors in exercise hyperemia.* If some factor related to tissue metabolism is involved in the establishment of exercise hyperemia, it would be released most probably from the contracting skeletal muscle fibres into the interstitial compartment. From here it could influence vascular tone directly, since this space forms the immediate environment of the vascular smooth muscle effectors. An alternative possibility would be a primary metabolic change in the vascular smooth muscle itself, caused, for instance, by oxygen lack.

Diversion of the venous effluent from a contracting skeletal muscle into the artery of a muscle at rest can elicit vasodilation in the latter (e.g., 290, 295). The dilatation, however, is usually less pronounced than that of true exercise hyperemia, at least in short-term experiments. This fact does not, of course, invalidate the metabolic dilator hypothesis, since such an experimental approach does not guarantee a rapid establishment of similar concentrations of the presumed dilator metabolite at the site of action in the resting muscle as in the active one, owing to a multitude of factors, such as possible slow transcapillary diffusion, high rate of elimination, or dilution of the metabolite.

Some suggestions with regard to the elimination of the dilator factor in exercise were presented by Dornhorst and Whelan (80) from their observations on post-exercise hyperemia. Among other things, they found blood flow in the post-exercise period to decrease towards the control level in an approximately exponential manner both under normal circumstances and during mechanical reduction of flow or arterial hypoxia. The rate of recovery of flow was not very different in these three situations. They concluded that if postexercise hyperemia was related to the local concentration of some metabolite, its removal or destruction could not be critically dependent upon the rate of flow or upon the local oxygen tension. Moderate deviations from an exponential decline can, of course, be easily overlooked when plotting such a complex function as total blood flow, and possible adaptive changes in the microcirculation cannot be revealed by flow measurements alone. It is quite likely that the elimination of the dilator factor in exercise can depend upon several different processes.

Numerous attempts have been made to reveal the local chemical factor responsible for exercise hyperemia. The most common experimental approach

has been to add the test substance to, or decrease its concentration in, the arterial blood supplying a skeletal muscle region at rest. Such a mode of administration does not, of course, mimic exactly the normal appearance of local chemical changes in exercise but it might nevertheless offer valuable information, provided due attention is paid to rheological artifacts of infusion, interference with normal constituents of the blood, transintimal vascular effects, capillary and interstitial distribution problems, etc., and some of these factors may be difficult to control.

When trying to evaluate the various factors proposed to be involved in exercise hyperemia, we are faced with the same problem as previous reviewers (20, 178) that the current concepts are largely based on circumstantial evidence. A brief discussion will be given of a few criteria to be satisfied for a proposed metabolic factor to play an *important* causal role in exercise hyperemia. Some of these have direct relation to the type of study concerned with the functional differentiation of the vascular bed.

(a) The substance should belong to the group of agents naturally occurring in skeletal muscle tissue and it should be possible to demonstrate at least traces of the substance, or its breakdown products, in the tissue or the venous effluent during exercise. The concentration of the substance should bear some quantitative relation to the degree of vasodilatation. (b) Intra-arterial administration of the test substance in similar amounts as are known, or believed, to be released during exercise should elicit in resting muscle the same pattern of vascular response as that of exercise itself, *i.e.*, a pronounced and graded dilatation of precapillary resistance vessels and precapillary sphincters, a decrease of the pre-to postcapillary resistance ratio, no change in capillary permeability, and no significant active dilatation of capacitance vessels. (c) During administration of the test substance, a superimposed engagement of other vascular control systems, nervous or myogenic, should elicit the same type of differentiated response as seen in exercise under corresponding conditions. (d) If the dilator factor of exercise is believed to influence the vascular smooth muscle from the interstitial compartment, then, the test substance should elicit a pronounced hyperemia when administered directly into this space. (Technical difficulties are encountered, but a crude approach might be to study local hyperemia by clearance methods after intramuscular injection of the test substance.) (e) The importance of the dilator factor would seem to be strengthened if the inhibitory action of the test substance on vascular tone could be satisfactorily explained by its effects on electrical and mechanical activity on proper vascular smooth muscle preparations *in vitro*. (f) The recovery of vascular tone and the mode of elimination of the dilator factor after infusion should be compatible with the approximately exponential decrease of flow seen in the postexercise period. (g) If a more general role of the factor is proposed, it should be shown to elicit vasodilatation in several species, including man.

Few substances have been tested with regard to all these points. Several presumed candidates, however, may be ruled out from the discussion because they do not fulfil some of the more important criteria listed above, or for other rea-

sons. Some factors have too weak dilator effects on the resistance vessels to be of much significance. Increased  $P_{CO_2}$ , lactate, several other carbohydrate metabolites, and reduced pH are factors belonging to this group (for ref. see 20). Several potent vasodilators elicit vascular effects in skeletal muscle that are not consistent with the vascular response to exercise itself, and this makes their role in exercise hyperemia quite doubtful. Thus, acetylcholine and ATP have been shown to produce active venodilatation, and histamine and bradykinin appear to evoke increased capillary permeability (*e.g.*, 223). Further, there is no evidence for bradykinin release from muscle in exercise (10, 179, 340); and exercise hyperemia is not altered by atropine or antihistamines (177). The histamine-forming capacity was recently shown to be increased in skeletal muscle in mice during exercise (150), a circumstance that might suggest a possible role for histamine in this species. However, there are species differences since such a change was not found in rats. Among several phosphorylated nucleotides tested, only ATP and ADP were found to have strong vasodilator actions (180), but it is not known for sure if any of these are released from contracting skeletal muscle into the interstitial space, a process that would be a prerequisite for an effect on vascular tone. Adenosine was not found in normal or anoxic skeletal muscle and would therefore not be a factor controlling skeletal muscle flow, but it may play a role in the regulation of coronary circulation (29, 209). Several of the Krebs intermediate metabolites may elicit slight to moderate dilatation in the arterioles upon intra-arterial administration (139), but their significance in exercise hyperemia remains to be shown.

There are three factors that, at present, seem to deserve particular attention in exercise hyperemia, namely, oxygen lack, regional increase of extracellular potassium concentration, and regional hyperosmolality.

It has long been agreed that severe oxygen lack can bring about relaxation in vascular smooth muscle, but this does not necessarily imply that hypoxia serves an important physiological role in exercise hyperemia. Recently, Guyton and his associates studied vascular effects in the dog's hindlimb during severe hypoxia (101). They occluded the arterial inflow for 3 to 10 min and, on release of occlusion, the limb was perfused with blood that had all its oxygen removed. Under these circumstances, there was no recovery from the reactive hyperemia, nor any continuously increasing dilatation, but vascular tone quickly returned towards control upon shifting to oxygenated blood perfusion. This may indicate that oxygen lack is intimately connected with local vasomotor control, but it does not rule out the possibility that inhibition of smooth muscle might be caused at least in part by some vasodilator factor released from the tissue by anoxia. The vasodilatation of the resistance vessels in the postocclusion period was not very marked in these experiments, since at a pressure of 100 mm Hg flow increased on the average from a control value of 3.6 ml to only about 11 ml/min  $\times$  100 g tissue, whereas maximal flows are known to be in the range of 40 to 60 ml. It would have been interesting to know if superimposed exercise could have produced a further increase of flow in the period of anoxia in these experiments.

The change of blood flow in a resting hindlimb of the dog has been studied when oxygen tension in the arterial inflow was decreased to the levels seen in venous blood during exercise (290). This was done by admixing to the perfusate of the resting test muscle region the venous effluent from an exercising or resting muscle. Hence, the test vascular bed was exposed not only to reduced oxygen tension but also to other possible dilator factors delivered from the working muscle. The augmentation of flow was moderate and on average about 30 to 35% of the exercise hyperemia. The exercise hyperemia itself was not marked in these experiments, with average flow values 2.7 times the flow at rest. Skinner and Powell (304), using constant flow perfusion, also demonstrated moderate changes in vascular resistance to variations in  $P_{O_2}$ . Nicoll and Webb (260) showed a pronounced relaxation of precapillary sphincters in response to anoxia. The importance of oxygen tension for smooth muscle activity has also been demonstrated *in vitro*. The contractile response of aortic smooth muscle strips to adrenaline was found to be closely dependent on the  $P_{O_2}$  of the medium up to a partial pressure of 100 mm Hg (76).

These experiments, and others reviewed by Barcroft (20), seem to suggest that oxygen lack, or factors secondary to hypoxia, can be involved in the establishment of functional hyperemia. The available quantitative data on resistance function seem to strongly indicate, however, that oxygen lack cannot be the sole factor responsible for exercise hyperemia.

The hypothesis of Dawes (74) that an increased potassium concentration in the interstitial space might be partly responsible for exercise hyperemia has received experimental support in recent studies by Kjellmer (221). The efflux of potassium ions from contracting striated muscle, measured in the venous blood, was reported to be related to the work load at low rates of somatomotor fibre stimulation (222). During maximum exercise dilatation the venous plasma concentration of potassium rose to levels twice that at rest. Intraarterial infusion of isotonic potassium salts to resting muscle in amounts producing changes in venous potassium concentration like those observed during graded levels of work, elicited a pattern of response in the consecutive sections of the vascular bed identical to that of exercise. The dilatation of the resistance vessels recorded under constant flow perfusion was found to be 25 to 65% of the exercise hyperemia at corresponding levels of venous hyperkalemia. Infusions giving venous potassium concentrations exceeding those seen in exercise caused little or no further dilatation of the resistance vessels. Instead, very high venous potassium levels (above 20 mEq/l) caused a constrictor response and this effect seems to be confined to the larger arteries (95, 221).

More recently, Skinner and Powell (304) studied with a constant perfusion technique the combined effects of potassium ions and of oxygen deficiency on the resistance vessels. They found vascular resistance in resting muscle to decrease only moderately when either the venous oxygen tension was reduced to the levels encountered in exercise or the potassium concentration in blood was increased to values twice the normal. Additive effects, or possibly even some potentiation of the response, were observed when both these factors were changed simul-

taneously. Further, the rate at which vascular resistance decreased was more rapid when oxygen tension and potassium concentration were altered together than when only one factor was varied. A decrease of the potassium concentration below the normal level was shown to elicit a constriction, but with oxygen-deficient blood the effect reverted to vasodilatation. During perfusion with oxygen-deficient blood a rise in venous potassium concentration to a level encountered in heavy exercise (about 6 mEq/l) resulted in a resistance decrease to about 30% of the control resistance in resting muscle.

The constant flow method can adequately reveal small to moderate decreases in resistance, as produced, for instance, by hyperkalemia, but it is not well suited for quantitative analysis of changes in resistance when the dilatation is large or maximal as during heavy exercise, since the pressure will then fall to abnormally low levels. The full extent of the dilatation therefore may not be truly revealed by the calculated change of resistance during maximal dilatation (section II). If moderate dilator effects of a test substance are observed and if these are expressed in percent of the maximal vasodilator response such handling of data may lead to overestimation of the relative effect of the test substance. It might be necessary to consider such methodological aspects when evaluating the vasodilator effects of potassium alone or in combination with hypoxia reported above. It is worth noticing that when a constant pressure method was used, a potassium infusion that gave a venous concentration twice the normal increased flow to only about  $\frac{1}{3}$  of that recorded during muscular work producing similar degrees of venous hyperkalemia (218). It was postulated, however, that a transcapillary gradient for potassium existed and that therefore the role of this ion in exercise hyperemia was underestimated.

The inhibitory effect on vascular smooth muscle of increased extracellular potassium concentration may seem paradoxical considering that it would lead to a decreased gradient of  $[K^+]/[K^+]_o$ , which should be expected to cause depolarization and enhanced activity. However, *in vitro* experiments have shown that the high contraction frequency of strips from small arteries, produced for instance by noradrenaline or plasma, can be reduced by elevation of  $[K^+]_o$  (191). This "negative chronotropic effect," tentatively ascribed to an increased membrane permeability to potassium, caused relaxation of the vascular smooth muscle strip. In the isolated rat portal vein, which has myogenic rhythmicity, there is under certain conditions a pronounced but only transient inhibition of this activity when the potassium concentration of the external medium is suddenly increased (193). These data might be reconciled with a vasodilator effect of potassium, and the studies *in vivo* seem to suggest strongly a role of potassium in exercise hyperemia. The mutual influences of hyperkalemia and tissue hypoxia may vary depending on the work load. The mechanism behind the proposed potentiation of the vasodilator response in the presence of both these factors is, as yet, not clear.

The fact that infusion of hypertonic and hypotonic solutions can elicit vascular effects has been known for some time (140, 245, 265, 316, 317), but a direct physiological corollary of hyperosmolality, with specific regard to exercise hyperemia, was suggested so recently (152, 252) that the hypothesis can hardly be

reviewed in proper perspective. Yet, experimental evidence has accumulated to indicate a role for this factor in the vascular response to exercise, some of which will be presented below.

Exercise was shown in experiments on cats to be associated with a considerable increase in regional osmolality above the level at rest and this was reflected in the venous effluent from the muscle (252). This environmental change is in all probability due to release of osmotically active particles from the contracting striated muscle fibres (*cf.* 22, 175). The extent of venous plasma hyperosmolality was related to the work performed and could amount to 40 mOsmol/kg above the resting control level when the somatomotor fibres were stimulated at 4 impulses per sec. Intra-arterial infusion of hypertonic glucose or xylose solutions to the resting skeletal muscle at slow rates, producing changes in venous osmolality like those observed in exercise, evoked a pattern of response within the various consecutive vascular sections that was identical to that of exercise itself (152, 252). The extent of the resistance vessel dilatation during such experimental hyperosmolality was usually quite significant and sometimes approached that of exercise hyperemia at comparable levels of venous osmolality. Exercise at 4 twitches per sec producing blood flow rates of 35 to 55 ml/min  $\times$  100 g tissue at a pressure of 100 mm Hg was associated with increases of venous osmolality ranging from 15 to 40 mOsmol/kg. Experimental hyperosmolality of similar magnitudes produced by hypertonic infusion to resting muscle gave flows usually in the range of 15 to 30 ml/min  $\times$  100 g (251). Maximal flows, however, could be observed at still higher levels of tonicity and it is possible that in exercise, measurement in venous plasma gives an underestimation of interstitial osmolality.

Hypertonic infusion and simultaneous vasoconstrictor fibre excitation led to the same differentiated pattern of vascular response seen on sympathetic stimulation during exercise (152). Also, the myogenic responses of the vascular bed to transmural pressure changes appeared to be altered in the same way during experimental hypertonicity and exercise (251).

Interstitial deposits of  $^{133}\text{Xe}$  in resting muscle were found to be cleared at faster rates when the tracer was dissolved in hypertonic than in isotonic medium (152). This can be taken to indicate a local microvascular dilator response occurring when the hypertonicity primarily involves the extravascular space. The clearance rates obtained during local experimental hypertonicity in resting muscle often equalled those observed at corresponding levels of hyperosmolality produced by exercise.

In man, strenuous forearm or leg exercise was associated with an increase of regional venous osmolality of up to 30 mOsmol/kg (152). Infusion of hypertonic solutions into the brachial artery in amounts raising regional venous osmolality by 10 to 15 mOsmol/kg, caused a clear-cut decrease of forearm flow resistance, sometimes to about 20 to 30% of the control value. In absolute figures, this corresponded to an increase in flow from about 2.5 to 8 to 12 ml/min  $\times$  100 g.

The mechanisms responsible for the inhibitory action of hyperosmolality on vascular smooth muscle were elucidated by recording electrical and mechanical activity in the isolated, spontaneously active rat portal vein (192, 252). It was

shown that increased osmolality caused pronounced and sustained relaxation by inhibiting myogenic pacemaker activity. This, in turn, was ascribed to changes in transmembrane ionic concentration gradients and in membrane permeabilities to ions produced by osmotic reduction of smooth muscle cell volume. Pronounced hyperosmolality also interfered with propagation and with excitation-contraction coupling. *In vivo*, exercise leads to hyperosmolality apparently by release of particles from the striated muscle fibres into the interstitial fluid space and this change in the environment of the smooth muscle may inhibit vascular tone by the mechanisms discussed.

The experimental evidence presented above suggests that hyperosmolality may play an important role in exercise hyperemia, and it appears that this factor deserves further investigation. Perhaps it should be looked upon as a "non-specific" dilator principle, and as such, it seems quite simple from the point of view that any osmotically active product invading the interstitial space could contribute to the vascular effect.

Functional hyperemia in skeletal muscle is a vascular response which is undoubtedly established in large part by local chemical control mechanisms. It should be clear from the discussion that no single factor is likely to account fully for the reaction. Current research does not seem to indicate a great significance of "specific" dilator agents, but lends more support to a role of factors more intimately related to tissue metabolism. It appears that three factors, hypoxia, potassium, and hyperosmolality, deserve special attention. As far as they have been tested these factors seem to fulfil the specific criteria listed above. They are not by any means mutually exclusive, but, instead, may act synergistically to enhance the hyperemia response. Their relative importance may vary under different phases of the response and also under different muscular work loads.

Functional hyperemia in other tissues may well be mediated by some of the mechanisms considered for skeletal muscle, but there is much to indicate that the local chemical control factors can vary in different vascular circuits.

## 2. Myogenic reactions related to stretch

The calibre of a blood vessel is determined, from the mechanical point of view, by the balance between two opposing forces, the transmural distending pressure and the tangential wall tension. At equilibrium the relationship between these forces and the radius of the vessel is given by the law of Laplace. Recent reviews (16, 52) have been devoted specifically to the biophysical aspects of wall tension and vessel calibre as influenced by the complex interactions between the smooth muscle and the passive elements of elastic and collagenous tissue. Such aspects are beyond the scope of this article, but the possibility that vascular distension, in itself, can act as a stimulus for smooth muscle activity makes it necessary to consider the responses of the vessels to passive stretch among the mechanisms for local vascular control.

The idea that increased transmural pressure may cause enhancement of vascular tone was originally put forward by Bayliss (24) and it has received strong experimental support in more recent years beginning with the investigations by

Folkow (109). "The Bayliss mechanism" now forms the basis of the myogenic theory of blood flow autoregulation (see below) and seems to be an important factor for the establishment of basal vascular tone in general. Before considering the influence of such reactions to stretch on the different functions of the peripheral vascular beds it may be appropriate to discuss the underlying cellular mechanisms in the light of current knowledge of smooth muscle physiology. Bülbring (53) showed that intestinal smooth muscle from the guinea-pig taenia coli increases its frequency of action potentials in response to a passive stretch. This implies that the contractile system becomes activated at a higher rate. There is consequently a rise in active tension opposing the applied external force. An increased rate of activation due to passive stretch is observed also in other smooth muscles of the single unit type (43, 44). It thus appears as if the cellular machinery of this type of muscle is characterized not only by an electro-mechanical coupling, *i.e.*, contraction in response to action potentials as discussed in section III but also by a mechanoelectrical coupling, *i.e.*, spike discharge in response to deformation (*cf.* 192). Stimulation of vascular smooth muscle by passive stretch has been demonstrated by recording contractile responses of isolated vascular preparation *in vitro* (73, 191, 311), by microscopic observation of terminal vascular beds, for instance in the bat wing (260, 346), and by studies of peripheral vascular functions in circulatory experiments (see further below).

The role of transmural pressure as a normal stimulus for vascular smooth muscle tone and thereby as a regulator of peripheral vascular functions in different regions and sections of the circulatory system has been the subject of many investigations. It was pointed out in section IV above that the vascular tone "at rest" (*cf.* fig. 2) is established, to a significant extent, by myogenic automaticity in the "single-unit" smooth muscle of the resistance vessels. With the probable exception of arteriovenous shunts and large veins, such basal myogenic tone is present within all sections of the vascular tree but there is evidence that basal tone is higher in precapillary than in postcapillary vessels (133, 255). On the venous side the myogenic activity may be restricted in general to the small venules (291, 343) and to large veins in the splanchnic area (see 196), the latter constituting a special case since they are interposed between two capillary networks. The myogenic responsiveness of the vessels to changes in transmural pressure seems to parallel their level of basal tone.

Transmural pressure as a factor influencing the smooth muscle tone of the *resistance vessels* is intimately related to the problem of blood flow autoregulation. Autoregulation of flow implies, in the restricted sense of the words, the ability of an organ to maintain a relatively constant blood flow despite variations in perfusion pressure, a characteristic of several different vascular beds such as renal, cerebral, skeletal muscle, *etc.* The myogenic mechanism as an explanation for the autoregulatory phenomenon has been rejected *a priori* by some authors on the basis of two principal arguments. Firstly it has been argued that the myogenic response would imply a type of positive feedback leading to considerable instability in the cardiovascular system; any rise in arterial pressure would cause an

increase in peripheral flow resistance and hence a further increase in pressure stimulating the smooth muscle to further constriction, *etc.* One group of authors has recently abandoned the myogenic theory as an explanation of renal blood flow autoregulation (329). A reason for this was the fact that a primary regulation of vessel wall tension by a myogenic mechanism would not result in constancy of flow but in a rapid decrease of flow in response to elevation of arterial pressure. The second main argument against myogenic blood flow autoregulation is concerned with the consequences that occur if vessel calibre is the parameter primarily regulated. If the smooth muscle contracted in response to vascular distension, produced by an increase in blood pressure, it may seem that the resulting constriction would abolish the stimulus so that the muscle would relax again. This sequence of events might cause the vessel to oscillate around a diameter larger than the initial which would not suffice for autoregulation of flow.

In view of the complexity of the vascular walls, with passive elastic elements both in parallel and in series with the smooth muscle, and considering also the variations in contractile force related to initial fibre length (312, 314) neither of the two parameters, wall tension or vessel calibre, can be regarded as the primary factor regulated by the myogenic mechanism. Mathematical models may be devised that meet the above objections to myogenic blood flow autoregulation, but the proponents of the myogenic theory have developed their arguments mainly from knowledge of smooth muscle physiology and from circulatory studies. A description of the myogenic theory of autoregulation based on the characteristics of "single-unit" smooth muscle has been given by Folkow (115, 116). It implies, in principle, that distension increases the frequency of the rhythmic contractions initiated by the "pacemakers" and propagated to the adjacent cells of the smooth muscle units. In other words, distension increases the vasomotion of the small arterial vessels so that resistance to flow is enhanced. In this form the myogenic theory is in agreement with known characteristics of other types of single unit smooth muscle, and it can help to explain autoregulation without leading to the paradoxical situations described above. The tendency to positive feedback in this system is limited simply by the restricted frequency range of the pacemakers of the smooth muscle and also by the dilator influence of "metabolites" accumulating as a possible result of flow restriction. The latter implies that chemical control of vascular smooth muscle acts as a brake on the myogenic reactions to stretch so that in fact the metabolic and myogenic mechanisms operate simultaneously to accomplish a well balanced autoregulation of flow (115, 116).

Studies of blood flow variations in response to altered vascular distending pressure, produced by simultaneous and equivalent changes in arterial and venous pressure, represent the critical type of experiment for demonstration of myogenic autoregulatory responses. Elevation of transmural pressure in such experiments can lead to reduced blood flow, despite the constant perfusion pressure head; this result indicates an increase in total flow resistance due to vasoconstriction instead of an unchanged or decreased resistance, which would have occurred in rigid or passively distensible systems. Such active responses have been described,

for instance, in skeletal muscle, intestine, and kidney (*e.g.*, 109, 133, 172, 200, 202, 255, 339), suggesting a role for myogenic mechanisms in the autoregulation of blood flow to these tissues. Chronic denervation, reserpine, and local anesthesia have been used to rule out the possible participation of nervous vasomotor reflexes in the vascular reactions (109, 133, 172, 202). Since the autoregulatory phenomena persist after these procedures they can be regarded as myogenic reactions; local reflexes like the proposed "veno-vasomotor reflex" (144) do not need to be invoked in the explanation of the responses.

By using volumetric and gravimetric methods for studying changes in regional blood volume and in capillary hydrostatic pressure, the latter reflected by filtration or absorption of fluid, it has been possible to determine the localization within the vascular bed of the resistance response to increased transmural pressure. In skeletal muscle and small intestine the myogenic increase in resistance is an essentially precapillary event (133, 202, 255) which implies that the *pre- to postcapillary resistance ratio* rises on elevation of transmural pressure. For a rise of 50 mm Hg in mean vascular pressure, produced by corresponding increases in both arterial inflow and venous outflow pressures, the pre- to postcapillary resistance ratio in cat skeletal muscle increased by some 25% (255). Autoregulation of renal blood flow in response to variations in arterial pressure also seems to reflect variations in precapillary vascular tone as indicated by the fact that there is a proportional autoregulation of glomerular filtration rate (329).

Besides the importance of vascular distension as a regulator of total flow resistance and of pre- to postcapillary resistance ratio, the influence of this mechanical factor on precapillary sphincters and on capacitance vessels should be considered, although available information is more scanty in these respects. Increased transmural pressure is associated with a reduced capillary filtration capacity in the denervated vascular bed of cat skeletal muscle (255), a finding that indicates a decrease in the functional capillary surface area due to closure of *precapillary sphincters*. A similar reaction was found in the human foot, which showed a decrease in CFC by 50 to 85% when the subjects were tilted from the supine to the erect posture (255). This change in CFC was elicited, not to any significant extent by baroreceptor reflexes, but evidently by a local myogenic reaction of the precapillary sphincters to the increased hydrostatic load. The response was present also in exercising skeletal muscle (243). Together with the simultaneously induced increase in pre- to postcapillary resistance ratio, this reduction of the capillary surface area available for exchange may represent an important protective mechanism against oedema formation when a vascular bed is exposed to increased hydrostatic load. These two reactions, and especially the myogenic response of the precapillary sphincters, can thus establish an "autoregulation of transcapillary filtration" in skeletal muscle and skin in situations of increased vascular transmural pressure (250). These circulatory investigations indicating closure of precapillary sphincters in response to vascular distension are supported by microscopic observations of changes in "vasomotion" produced by pressure stimuli. For instance, increased arterial pressure caused a prolongation of the time during which the terminal arteriolar vessels of the bat wing stood contracted

(346). Similar autoregulatory patterns of periodic flow were demonstrated in mesenteric capillaries by a microphotometric technique for measurement of red cell velocity recently developed by Johnson and Wayland (205).

Increasing venous outflow pressure in experiments on cat hindlimb led to an immediate increase in regional blood content as shown by the rapid increase in tissue volume but this initial passive effect was not followed by any obvious secondary decrease of volume (133). It was concluded, therefore, that the raised transmural pressure did not initiate any significant smooth muscle contraction in the *capacitance vessels*. Studies on the isolated dog tongue indicated some myogenic reactivity in the capacitance vessels of this tissue (291). Passive distension also enhances myogenic automaticity in small veins as seen by vital microscopy and by venous pressure recordings (343, 344), but this ability of the post-capillary vessels to respond to passive distension appears to be of little hemodynamic significance.

The relative importance of the stretch response of vascular smooth muscle for autoregulation of the circulatory functions in different organs is a matter of debate. Besides the myogenic theory, there have been other mechanisms suggested to explain autoregulation of blood flow, and these have often been referred to as "the metabolic theory," "the tissue pressure theory," "the cell separation theory," etc. As indicated above, the different mechanisms may very well operate together in many vascular beds, but there is no general consensus as to their relative importance. A further analysis of blood flow autoregulation is beyond the scope of this review, but the reader will find a lively discussion of the whole subject in a recent symposium (201). It is very possible that the myogenic control of the precapillary sphincters and of the pre- to postcapillary resistance ratio leading to an "autoregulation of transcapillary filtration" is as important for the tissue as the autoregulation of blood flow. The former type of regulation would be a truly protective reaction serving as a defence against gross oedema formation. It seems adequate that this protective function is executed by a local mechanism restricting the vascular response to the very regions exposed to increased hydrostatic load. Should this regulation have been handled by the central nervous system it would have required a complex system of segmental autonomic reflex arcs.

### *3. Other local control systems*

It is very possible that local mechanisms other than those related to tissue metabolism and transmural pressure may participate in the control of vascular tone, but their roles in normal circulatory regulation are far from clear and therefore they will only be considered in passing.

Several potent vasoactive substances such as histamine, prostaglandins, and serotonin are present in various tissues, but their importance as "local hormones" for microcirculatory control under physiological conditions is a matter of debate. Schayer (292a) has suggested a central role for histamine in local adaptation of vascular tone, for instance in functional and reactive hyperemia and in vasomotion, but conclusive experimental evidence for this hypothesis is lacking (*cf.* 11a).

As mentioned in section V B 1 above, histamine given intra-arterially evokes a pattern of vascular response in skeletal muscle that differs from that caused by exercise. The main physiological significance of histamine formation in tissues may be represented by other events, for instance within the metabolic sphere (208).

The prostaglandins are a group of closely related substances (see 28) some of which are very potent vasodilators (*e.g.*, 60, 98). It remains to be clarified whether these vascular effects have any physiological corollary in the normal control of circulatory functions.

Serotonin (5-hydroxytryptamine) was reported to elicit vasoconstriction and oedema formation in the foreleg of the dog when administered intra-arterially (167). In man, serotonin may evoke a variety of vascular effects (see 341). Skin blood flow was usually reduced and there were also signs of cutaneous vasoconstriction. Infusion of large doses could lead to oedema formation. A vasodilator response to serotonin appeared to occur in skeletal muscle. Serotonin is present in certain tissues and in the thrombocytes, but its possible significance in normal circulatory control cannot be decided at present.

Local vascular responses mediated by neural mechanisms have been briefly referred to in the foregoing. The axon reflex vasodilatation in skin appears to be a well established phenomenon although the nature of the transmitter is still unknown (see section V A 3 above). Elevation of pressure in limb veins results in constriction of resistance vessels in the region, and this was taken to indicate the existence of a local "veno-vasomotor reflex" (144). As discussed above this response may be explained more correctly in terms of a myogenic smooth muscle reaction to stretch. In the isolated perfused dog intestine a reduction in arterial pressure caused an increase in venous flow resistance which was abolished by adrenergic blockade, local anaesthetics, and chronic denervation (172). It was concluded therefore that the vasoconstriction was produced by a local nervous reflex initiated from receptors on the arterial side.

A dilator response within a skeletal muscle region, produced for instance by exercise, is associated with a gradually developing "ascending dilatation" of the larger regional arteries as well even though their smooth muscles are not directly exposed to the metabolic dilator factors (179a). Several mechanisms have been proposed for this reaction but at present it seems most likely that the response is due to elimination of myogenic activity conducted from the periphery.

#### VI. INTERACTION BETWEEN DILATOR AND CONSTRICTOR MECHANISMS

Vascular smooth muscle is commonly exposed to simultaneous influences from several of its control systems, which can lead to modified effector responses by synergistic or antagonistic interactions. Experimental evidence indicates that a broad spectrum of differentiated vascular response patterns can ensue from such interference, a few examples of which will be outlined.

Synergism between constrictor mechanisms may occur, for example, in response to increased transmural pressure and augmented sympathetic constrictor fibre discharge. Stretch of the smooth muscle would lead to myogenic constrict-

tion mainly of precapillary vessels, and the sympathetic influence both to a reinforced constriction of these vessels and also to excitation of the smooth muscle in the postcapillary vessels (see above).

It is possible that the constrictor fibres mainly engage the smooth muscle situated in the outer layer of the media in the precapillary vessels, since these are the only ones that have direct contact with the adrenergic nerve endings (section V A 1), whereas the inner muscle layer is more subordinated to other control systems. This arrangement could lead to interesting types of differentiation of the vascular response, as first suggested by Folkow (116, 134). The myogenically active smooth muscle of the inner layers would be responsible for "basal vascular tone" and could effect responses to passive stretch and to local chemical factors. On the other hand, intensification of vasoconstrictor fibre activity with its main action on the outer layer would lead to a "centralization" of vascular control at the expense of local mechanisms (see 116, 198). The localized release of the adrenergic transmitter in the outer cell layers may indirectly affect the inner sheath of vascular smooth muscle as well, since the neurogenic excitation may spread by myogenic propagation to noninnervated cells. Neural and myogenic mechanisms have been shown to interact in this way in sparsely innervated but rhythmically active vascular smooth muscle studied *in vitro* (198).

Synergistic actions between dilator mechanisms may occur, for example, in the defence-alarm reaction, when the sympathetic cholinergic fibres lead to prompt dilatation of the larger precapillary resistance vessels of skeletal muscle. Since, in the intact animal, this behavioural response involves increased activity of the skeletal muscles (4), the associated production of dilator "metabolites" would soon be able to reinforce the neurogenic vascular response and, in addition, lead to relaxation of the precapillary sphincters. This vascular reaction pattern may be further complicated by concomitantly increased constrictor fibre discharge (see below).

There are several situations in which the peripheral vascular bed is simultaneously exposed to the antagonistic actions of adrenergic constrictor fibre activity and local chemical dilator influence. One example of such interaction is seen during increased sympathetic discharge to exercising skeletal muscle, as mentioned in section V B, when the "metabolites" strongly suppress the constrictor responses in the precapillary vascular sections while the constrictor effect of the capacitance vessels is well maintained (220). The neurogenic constriction can override the metabolic dilator influence of exercise in species which have an abundant adrenergic innervation of large conduit vessels. Such interaction has been observed in the duck during the diving reflex (118).

An interaction between neurogenic constriction and local chemical dilator factors can be observed in the vascular bed of skeletal muscle during hemorrhagic shock. This may lead to important hemodynamic consequences (233, 239, 253; cf. also 40). In this situation, the reflex constriction of the resistance vessels in muscle and the fall in blood pressure may reduce muscle flow to such an extent that a relative accumulation of "metabolites" occurs. Early in hemorrhage, the neurogenic constriction persists in all consecutive vascular sections, but with

time, as the local metabolite concentration increases, the dilator effect becomes apparent despite the fact that the increased sympathetic discharge is largely maintained (for details see 239). The precapillary resistance vessels and the pre-capillary sphincters, being particularly sensitive to metabolites, will then dilate gradually, whereas the neurogenic constriction is maintained in the postcapillary resistance and the capacitance vessels for considerable length of time. The important neurogenic compensatory response in terms of absorption of extra-vascular fluid due to increased pre- to postcapillary resistance ratio is established in early periods of shock but, owing to a secondary gradual decline of this ratio, capillary pressure rises in later stages, so there is a reversal, and plasma fluid is lost by ultrafiltration. One can calculate that in this stage of shock an adult person might lose as much as 0.5 l of plasma fluid per hour, which must be an undesirable effect in this primarily hypovolemic situation. Sympathetic blockade at this stage eliminates the postcapillary neurogenic constriction and hence prevents further fluid loss, and this finding may help to explain the reported beneficial effect of  $\alpha$ -adrenergic blocking agents in the treatment of shock (259).

The "autoregulatory escape from vasoconstrictor fibre influence" of the intestinal resistance vessels in the face of a maintained constriction of the capacitance vessels appears to be another example of differentiated vascular response resulting, at least partly, from competitive actions of local and remote control systems (see section V A).

Apical skin regions exhibit a gradually developing vasodilatation during prolonged exposure to cold. This cold vasodilatation might be related to the action of an axon reflex liberating a dilator substance, which opposes the thermoregulatory neurogenic constriction of the cutaneous vessels (see 160). This effect has also been ascribed to an impairment of vascular reactivity to the adrenergic transmitter when tissue temperature approaches the freezing point (211). It appears that cold vasodilatation is quite a complex vascular reaction, which can depend on a number of different mechanisms (117a).

Simultaneous influences from various remote control systems can also lead to differentiation or modification of the peripheral vascular response. Thus, competitive effects of adrenergic constrictor and cholinergic dilator nerves have been observed in the vascular bed of skeletal muscle upon topical stimulation in the hypothalamic "defence area". The outcome of these interactions can be a dilatation of precapillary resistance vessels and a constriction of capacitance vessels (132). Further, during moderate or severe arterial hypoxia a transient reflex constriction of the resistance vessels in skeletal muscle is observed as a result of chemoreceptor engagement. Later, however, this effect is decreased or even reverted to a dilatation, which can be ascribed, at least in part, to release of adrenaline from the adrenal medullae exerting a  $\beta$ -receptor dilator action (67).

The precapillary resistance vessels and precapillary sphincters in skeletal muscle are normally quite sensitive to the local metabolic as well as the local myogenic control mechanisms (section V B). In situations of simultaneous strong influence of both dilator metabolites and myogenic constrictor stimuli (*e.g.*, exercise during increased vascular transmural pressure) the metabolic factors

can override the myogenic response in the resistance vessels, while the precapillary sphincters are still able to constrict (243). These competing stimuli will thus elicit differentiated responses within these two vascular sections. During severe exercise the resistance vessels behave passively in response to increased transmural pressure. This indicates an abolition of the myogenic autoregulation of blood flow. By the maintained myogenic constrictor response of the precapillary sphincters in exercise, increased hydrostatic load leads to a decrease of the functional capillary surface area. Thus, the phenomenon of "autoregulation of transcapillary filtration" is still present during muscle activity and may be quite important to protect dependent limbs against gross oedema formation when exercise is performed in the upright posture.

Studies of the interaction of various vascular control systems have thus revealed many differentiated patterns of vascular response. Further investigations of such problems would seem rewarding and may help to a better understanding of peripheral circulatory control in normal and pathophysiological situations.

#### VII. ACTIONS OF DRUGS ON PERIPHERAL VASCULAR FUNCTIONS

From the foregoing chapters it is clear that the peripheral circulatory state is determined by a multitude of factors, such as the level of basal smooth muscle tone in the different vessels, the degree of activity of the various physiological control systems, and their synergistic or antagonistic interactions. Such factors must also be important determinants for the circulatory effects elicited by administration of vasoactive agents. The types of differentiation described with regard to the vascular smooth muscle effector, as well as to the patterns of peripheral vascular response to physiological stimuli, may be expected to be displayed to some extent also in the circulatory effects of drugs. Indeed, numerous studies of blood flow have revealed different influences of drugs on the resistance vessels of various organs. The importance of the other vascular functions for general cardiovascular homeostasis and for local tissue nutrition was emphasized above, and it would seem necessary to define the pattern of response within the various consecutive sections of the vascular bed also when characterizing the circulatory actions of vasoactive substances. This approach has been used in pharmacological research in recent years, though so far only in a limited number of studies. Some of the results obtained from such investigations will be considered below with particular attention to agents that have revealed a quantitative or qualitative differentiation in their patterns of vascular response.

Besides the biogenic vasoactive substances whose effects upon administration were described in connection with the various control systems above (*cf.* also 169), some chemically related substances, certain blocking agents, and a few other vasoactive drugs have been subjected to the type of analysis already mentioned.

The effects of adrenergic agonists on the different peripheral circulatory functions depend to a great extent on the relative potency of the respective agents in stimulating  $\alpha$ - and  $\beta$ -adrenergic receptors and also on the relative distribution of these receptors in the various sections of the vascular beds. As mentioned in

previous chapters, noradrenaline produces  $\alpha$ -adrenergic constriction of both resistance and capacitance vessels in skeletal muscle, skin, and intestine. Skeletal muscle shows in addition constriction of the precapillary sphincters, but this response, like the resistance vessel constriction in the gut, is quite transient because of interference by local control mechanisms. Noradrenaline has frequently been used as a reference substance when other constrictor agents have been examined with regard to their effects on peripheral vascular functions. A number of sympathomimetic drugs were tested on a skeletal muscle region of the cat, and their relative influences on resistance and capacitance vessels were expressed as a ratio of resistance/capacitance constrictor response (224). It was concluded that for substances with predominantly  $\alpha$ -adrenergic action, such as phenylephrine, methoxamine, and N-ethyl-norphenylephrine, this ratio was higher than for substances like adrenaline and corbadrine, which also stimulated  $\beta$ -receptors. In another study on cat skeletal muscle the effects of noradrenaline and N-ethyl-norphenylephrine on the resistance, capacitance, and precapillary sphincter vessels and on the ratio of pre- to postcapillary resistance were compared. Both agents showed similar patterns of response and, at comparable levels of constriction in the resistance vessels, they evoked effects in the other vascular sections which were of about the same magnitudes (249).

Blockade of the  $\alpha$ -adrenergic receptors may be expected to affect the circulatory functions of a peripheral vascular region in essentially the same way as when tonic vasoconstrictor fibre activity is abolished by acute sympathectomy. However, phenoxybenzamine administered intra-arterially dilated the small vessels also in the denervated, artificially perfused hindlimb of the dog (77). This response was accompanied by constriction of digital veins. It was concluded that these effects of phenoxybenzamine may be due to local release of histamine (cf. 165).

Dihydroergotamine can exert, besides its  $\alpha$ -adrenergic blocking influence, a direct constrictor effect on the vascular smooth muscle. The direct effect seems to be especially pronounced in skin tissue, at least in the cat, where it can produce strong constriction of resistance and capacitance vessels and an increased pre- to postcapillary resistance ratio resulting in absorption of extravascular fluid. The precapillary sphincters appear to be largely unaffected (251). The direct constrictor effects of dihydroergotamine seems to be much less marked in cat skeletal muscle. Whether cutaneous constrictor effects can explain the reported beneficial effects of dihydroergotamine in orthostatic hypotension in man remains to be shown.

Although it is agreed that stimulation of  $\beta$ -adrenergic receptors by the administration of isoprenaline can evoke dilatation of precapillary resistance vessels, for example, in skeletal muscle and intestine, different effects on the capacitance vessels have been reported in various studies. In the human forearm, the translocation of blood from the veins and a decrease in venous distensibility found in response to intravenous isoprenaline indicated constriction of the capacitance vessels (87). Secondary neurogenic constriction of the veins due to reflex sympathetic activation may have contributed to this response (1). Studies of the capaci-

tance function of the entire systemic vascular bed in dogs by a complete cardio-pulmonary bypass technique also indicated a venoconstrictor action of isoprenaline (208a). The response was not due to secondary vasomotor reflex adjustments, as evidenced by its persistence in animals treated with ganglionic blocking agents. The constrictor effect of isoprenaline on the systemic capacitance vessels of the dog was abolished by  $\beta$ -adrenergic blockade. It was concluded therefore that the  $\beta$ -receptors in the venous bed are constrictor in nature.

Other investigations have given opposite results, indicating a  $\beta$ -adrenergic venodilator response to isoprenaline. Thus, in studies on the dog foreleg using the segmental resistance technique, intra-arterial administration of isoprenaline was found to reduce venous resistance to flow (1). Dichloroisoproterenol and pronethalol abolished the response. It was suggested by those authors that the decrease in total systemic capacitance observed in the dog in response to this agent (see above) might have resulted from relaxation of the hepatic venous sphincters. Plethysmographic studies on the hindquarters of the cat have shown an increase in regional blood volume to intra-arterially administered isoprenaline (206). This capacitance effect was partly due to passive distension of the veins as a result of the evoked dilatation in the precapillary resistance vessels, but there was also a true inhibition of tone of venous smooth muscle. In comparison with nitroglycerin and sodium nitrite, however, the dilator effect of isoprenaline on the capacitance vessels was quite weak.

It thus appears that isoprenaline does produce a dilation of capacitance vessels by a  $\beta$ -adrenergic influence but there may be a more sparse distribution of  $\beta$ -receptors on the venous side than in precapillary vascular sections, at least in skeletal muscle (206, 248).

The effects of isoprenaline on precapillary sphincters produced by close arterial infusion of the agent have been examined by studying the changes in capillary filtration capacity. In the human forearm the dilatation of the resistance vessels was not accompanied by any significant change in CFC (48), whereas in cat skeletal muscle and intestine CFC increased, a result indicating inhibition of precapillary sphincter activity (129, 206).

The  $\beta$ -adrenergic blocking agent propranolol administered intraarterially in therapeutic doses to the resting human forearm evoked a slight decrease of blood flow. This indicates the presence of some  $\beta$ -receptor stimulation of the resistance vessels under normal circumstances (205a). Another  $\beta$ -adrenergic blocking agent, H 56/28 [*dl*-1-(*o*-allyl-phenoxy)-3-isopropylamino-2-propranolol-hydrochloride] did not produce this decrease of blood flow, a result attributed to the fact that this substance also has a slight  $\beta$ -receptor stimulating action. In higher doses, both agents significantly increased forearm blood flow. This response was not related to their effects on the  $\beta$ -receptors, but might be ascribed to local anesthetic action.

Synthetic analogues of neurohypophyseal hormones have been analysed to some extent with regard to their influences on consecutive vascular sections. Microscopic observations of the mesenteric terminal vasculature indicated that natural vasopressins had a stronger constrictor influence on venules than some of the synthetic agents (11). Plethysmographic studies of resistance and capaci-

tance responses in the hindquarters of the cat indicated a strong constrictor effect of phenylalanin-lysine-vasopressin on the venous vessels whereas the resistance vessels were relatively less affected (66). Natural vasopressin has little effect on capacitance function in this vascular region (199).

Intra-arterial infusion of acetylcholine to cat skeletal muscle at rest elicits a pronounced dilatation of resistance vessels, precapillary sphincters, and capacitance vessels, and a decrease of the pre- to postcapillary resistance ratio leading to net transcapillary fluid filtration (3, 223, 249, cf. also 18). The fact that this response is different from that evoked by excitation of the cholinergic dilator fibres indicates an uneven distribution of these nerves within the vascular bed of skeletal muscle (section V A 2). Under special circumstances acetylcholine may lead to closure of the precapillary sphincters. This was observed, for instance, during muscular exercise under conditions of constant flow, and there was some indication that this response of the precapillary sphincters was related to a reinforced myogenic reaction to stretch in the presence of acetylcholine (309). The contractile force of the skeletal muscle was depressed by this substance under these circumstances, an effect that, at least partly, may be due to constriction of the sphincters. Infusion of acetylcholine to the human forearm at rest dilated resistance vessels but had no significant effect on precapillary sphincters (48).

Hydralazine exerts its main dilator effect by a "direct" action on the vascular smooth muscle. This effect was found to be almost entirely confined to the pre-capillary resistance vessels. It therefore produced a decrease of the pre- to post-capillary resistance ratio and ultrafiltration, whereas the capacitance vessels were hardly affected at all. These responses were evoked both in cat skeletal muscle and in the human forearm (2, 3). Similarly, diazoxide seems to exert its main dilator action on the small precapillary resistance vessels, as shown in the fore-limb of the dog (292).

Sodium nitrite elicits a pattern of vascular response in skeletal muscle that differs in several respects from those of most other dilator agents. Thus, there is a moderate dilatation of resistance vessels and an unusually pronounced dilatation of capacitance vessels in both cat and man (2, 3, 206, 303). The sites for the resistance decrease seem also unusual in that, besides the dilatation of the small precapillary resistance vessels common to most dilator agents, there appears to be quite a marked dilatation of large arteries and of postcapillary resistance vessels (3, 292). The pre- to postcapillary resistance ratio seems unchanged by this drug and, hence, there is no significant net transcapillary filtration (3). The precapillary sphincters are not much affected by nitrites and nitroglycerin (206). The relaxation of large arteries, and especially the pronounced venodilatation, which can lead to an "unloading" of the heart, may help to explain the effects of nitrites in relieving angina pectoris.

In a comparative study of the effects of acetylcholine and butyl-nor-synephrine performed on cat skeletal muscle at comparable degrees of dilatation of the resistance vessels, the former substance was found to cause more venodilatation, whereas the latter elicited a more marked relaxation of precapillary sphincters and a more rapid net transcapillary filtration of fluid (249).

Among the large number of synthetic vasodilator drugs now available, few

seem to have been analysed in detail with regard to other peripheral vascular functions than flow resistance. It would seem important to know, in addition, the effects on the precapillary sphincters, which influence capillary flow distribution and, hence, tissue nutrition, and also the effects on the capacitance vessels and on capillary fluid transfer, which affect general cardiovascular homeostasis. Net transcapillary fluid movement may also improve the transfer of solutes from tissue to blood (240).

Studies devoted to such problems may be required not only on normal vascular beds but also under conditions resembling those in which they may be used, *i.e.*, in vascular disease. This is because vascular reactivity can be drastically changed in an ischemic region, such as that distal to an obliterated artery. The vascular bed of such a region, in which blood supply is small and transmural pressure low, may be dilated almost maximally because of accumulation of "vasodilator metabolites" and loss of myogenic basal tone. Further, the collaterals may have low tone due to the presence of "ascending vasodilatation" (*cf.* 328). Administration of dilator drugs into the general circulation under these circumstances may be of limited value, since further vasodilatation in the ischemic area cannot be accomplished, but may occur in other regions, leading to decreased perfusion pressure and to impaired nutrition of the region with obliterative vascular disease. Various physiological aspects of this problem were discussed in a recent paper by Folkow (117).

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