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SECTION 2:

CIRCULATION

VOLUME III

HANDBOOK OF PHYSIOLOGY

A critical, comprehensive presentation
of physiological knowledge and concepts

SECTION 2:

Circulation

VOLUME III

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Integrated aspects of cardiovascular regulation

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CHAPTER CONTENTS

THE PRIMARY FUNCTION OF THE CIRCULATION is to furnish an adequate blood flow through the tissue capillaries allowing thereby a satisfactory exchange of metabolic materials with the tissue cells. The huge surface area of the capillaries, everywhere in close contact with the tissue cells, facilitates this diffusion exchange. In essence, all other parts of the cardiovascular system subserve the regulation of capillary flow, which is made possible by the establishment of a pressure gradient between the end points of the different circuits.

The problem of maintaining the tissue blood supply lies essentially in keeping up the output of the cardiac pump. This in turn presupposes an adequate return of blood from the periphery. Blood flows back to the heart from the capillaries via veins which offer little resistance to its passage. Due to the huge venous capacity, however, alterations of venous caliber can profoundly modify the absolute volume of blood actually returned to the heart. The right heart pumps blood through the pulmonary circuit for gaseous exchange with the external environment across the pulmonary capillaries; oxygenated blood is delivered to the left heart for subsequent ejection. The rhythmic contraction of the left heart which expels blood into the aorta allows the development of a mean pressure of some 100 mm Hg in this and other arteries. The central venous pressure measured in the vicinity of the right atrium is only 1 or 2 ml H_2O above atmospheric. Despite extensive variations in circulatory conditions, such as may be seen in heavy exercise,

this pressure gradient between the central systemic arteries and the right atrium ordinarily remains remarkably constant in healthy man. By means of elastic arteries serially coupled with smaller muscular arteries the rhythmic ejection of blood by the heart is converted into a steady and quantitatively well-adjusted flow through the systemic capillaries which, as already mentioned, form the key point of the cardiovascular system.

I. HISTORICAL DEVELOPMENT

The concepts of the mechanisms and function of the circulation outlined above have been developed slowly. The accompanying historical survey purports to show how these concepts were reached rather than to provide a detailed documentation which can be found in Volume I, Chapter 2 of this *Handbook*.

In perhaps the greatest discovery in the whole of medical science William Harvey in 1628 proved that the heart pumped blood around the circulation (65). He was well aware that the circulation provided a means of nourishing the tissues, but not of how the nutrient materials were distributed to the cells. In Chapter 14 of *De Motu Cordis*, he writes of blood which "forcibly ejected to all parts of the body, therein steals into the veins and porosities of the flesh, flows back everywhere through those very veins . . . to the auricle of the heart." Only in 1661 did Malpighi describe the capillaries (92), and Lavoisier was not to perform his classic research on oxidative metabolism for another 150 years.

Harvey's own experimental results on the importance of the venous capacity for heart performance were considerably extended by his pupil Richard Lower who brilliantly interpreted the effects of gravity on the blood content of the veins. "The veins of human beings are enlarged by *inter alia* the weight of the blood itself, or by a relaxed tone of the veins (*relaxato venarum tono*)" (90). Lower understood that the filling of the heart was grossly reduced by venous dilatation.

These pioneer experiments yielded a simple picture of the circulatory mechanism; but the very simplicity of the concepts served to show clearly the primary role of the heart as a pump, its function in supplying the tissues with blood, and its dependence upon an adequate venous return for its performance. Many years were to elapse before the output of the pump could be measured. Meanwhile in 1733 Stephen Hales recorded the arterial blood pressure and the venous pressure and accounted for the loss of pulsation in the veins (61). His ideas of peripheral resistance were greatly developed in 1830 by Poiseuille who first formulated the laws governing the flow of blood in a system of tubes, showing that the resistance to flow varied inversely with the fourth power of the radius of the tube (98). Poiseuille introduced the mercury manometer for pressure recording, and in 1847 Ludwig gave physiology his classic method of graphic registration. The kymograph record of blood pressure allowed a systematic analysis of factors which affected the circulation, but the absence of data on cardiac output meant that changes of pressure were usually identified with alterations of total peripheral resistance. Ludwig and his pupils did develop methods for the measurement of regional flow, but such results as were obtained were interpreted mainly in terms of changes of resistance, the role of the veins receiving little attention in these years.

The concept of a nervous control of the heart and circulatory system came in the middle of the nineteenth century. In 1845 the vagi were shown to depress the heart by Weber & Weber (118) and von Bezold observed in 1863 that the sympathetic fibers had an excitatory influence (115). The tonic vasoconstrictor influence of sympathetic nerves was shown during 1852 and 1853 by Bernard (16), Brown-Séquard (23) and Waller (117), although the pioneer in this field was Pourfoir du Petit in 1727 (99). Ludwig & Thiry (91) later showed the importance of the splanchnic nerves in maintaining vasoconstriction of the abdominal circulation.

Profound alterations of the arterial blood pressure caused by the stimulation of afferent nerves suggested the presence of a nervous center which was excited or inhibited by such sensory messages. Claude Bernard showed that spinal transection caused a marked fall of blood pressure, and Ludwig's pupil Owsjannikow (96) described the site of the vasomotor center in the medulla as lying above the tip of the calamus scriptorius. Destruction of this region caused systemic hypotension, recognized to be due to the interruption of a tonically active mechanism normally causing vasoconstriction. The lateral funiculi of the spinal cord furnished the pathway of nerve fibers from the vasomotor center which coursed down to synapse with the intermediolateral cell bodies of the sympathetic preganglionic neurons (87).

Goltz (53) was one of few at this time who paid attention to the vasomotor control of venous tone and hence capacity, showing in 1863 that destruction of

the medulla and spinal cord produced venodilatation resulting in syncope.

One of the more dramatic discoveries of Bernard was his demonstration in 1858 of the vasodilator function of the chorda tympani with respect to the submaxillary salivary gland which established the concept of vasodilator nerves (17). For a considerable period after this it was assumed that such nerves provided an essential mechanism for increasing local tissue blood flow. Only during the late years of the nineteenth century did the realization grow that vasodilator "metabolites," produced by the tissues themselves, constituted by far the most important means of increasing local blood flow. The nature of these "vasodilator metabolites" is still a matter of debate.

Bernard's finding did indeed lead to an intense search for other vasodilator nerves resulting in the discovery of the nervi erigentes by Eckhardt (38) and of the dorsal root dilator fibers by Stricker (112). Following Bayliss's interpretation of nervous vasodilator mechanisms in 1902 and 1908 (14, 15), text books until quite recently stated that the vascular bed was under a tonic reciprocal nervous control like that of the heart. It has only slowly been appreciated that vasodilatation of the arteries and veins by nervous mechanisms is ordinarily due solely to a release of vasoconstrictor tone. It is realized nowadays that the parasympathetic vasodilator nerves serve purely local mechanisms and, further, that their field of distribution is far more restricted than was earlier believed. It is of course arguable that the contribution to reproduction function made by the nervi erigentes makes these nerves the most important vasomotor fibers in the organism, but their activity places little strain on the cardiovascular system as a whole. Sympathetic vasodilator nerves have been shown to be restricted to the skeletal muscles and possibly to the myocardium. The activity of such fibers is aroused from corticohypothalamic centers in the "alert" reaction. This has been shown only recently (see below). The dorsal root dilator fibers subserve no efferent function at all, but form the background of the axon reflex mechanism of thin afferent fibers, essentially pain fibers (45).

As to reflex control mechanisms, the tonic discharge of inhibitory afferent impulses to the vasomotor center was not fully appreciated until 1923. Although de Cyon & Ludwig (37) had discovered the depressor nerve by showing that its stimulation evoked systemic hypotension and bradycardia, they opined that these nerves were not tonically active because section of both of them did not alter the level of mean blood pressure. The discovery of the carotid sinus nerves by Hering in 1923, however, provided an explanation of Ludwig's findings; Hering appreciated immediately that these buffer nerves, as they are called nowadays, tonically controlled the heart and blood vessels (67). Section of the aortic depressor nerves caused little if any change in blood pressure simply because the remaining buffer nerves of the carotid sinus continued to manifest their inhibitory activity.

Ludwig and de Cyon thought that the depressor nerve arose from endings in the heart, and they discussed the advantages to the heart which such a regulatory mechanism would provide. If the heart were overloaded, then sensory messages from the cardiac walls increased and caused reflex inhibition of vasomotor tone and reflex vagal slowing of the heart itself. It is now known that although the depressor nerves arise from the aorta they subserve such a reflex function as Ludwig described. However, cardiac sensory nerves of "proprioceptive" type do exist. The first hint of their presence was provided in 1868 by von Bezold & Hirt (116), but it was not until 1940 that Adolf Jarisch (76) proved that the Bezold effect of bradycardia and hypotension resulted from a veratrine-provoked, abnormally intense stimulation of cardiac vagal sensory endings which ordinarily exert a tonic inhibition of the cardiovascular system by their response to rhythmic deformation.

The chemoreceptors shown to exist by Heymans in 1926 and 1930 (70) were proved to have little effect on the normal resting circulation, but were found to be of primary importance in situations of hypoxia and acidosis.

The enormous interest in reflex circulatory regulation by means of deformation receptors placed strategically in sites of both the high and low pressure vessels was unfortunately again directed too exclusively to the reflex effects which these nerves exerted on the level of mean blood pressure. This was once more due to slowness in the development of methods for measuring cardiac output. The method suggested in 1870 by Fick (42) was used before the turn of the century of Gréhant & Quinquaud (58) and by Zuntz & Hagemann (121) with direct sampling from the right heart, but accurate measurements of cardiac output have been available only since 1930. Since that time it has become increasingly obvious that the neural regulation of the cardiovascular system is subtly achieved *a*) by reflexes which adjust heart output itself, both directly by cardiac motor nerves which influence both the force and rate of con-

traction and indirectly by variations of vasomotor discharge to the veins which alter their capacity; and *b*) by reflexes which alter the arteriolar resistance. The familiar equation usually written as blood pressure = cardiac output × peripheral resistance can better be expressed as cardiac output = blood flow = blood pressure/peripheral resistance. This serves to underline the primary duty of the circulation, namely, provision of blood supply to the tissues.

2. BASIC CONSIDERATIONS

A. Functional Differentiation of the Cardiovascular System

Although this review is devoted primarily to the integrative aspects of cardiovascular function, it is perhaps justifiable to give a brief résumé of the basic characteristics of the components of the circulatory system. For details the reader is referred to the quoted review articles and to earlier volumes of this *Handbook*. In addition, some recent results relating to cardiovascular control are documented.

The pump system consists of the right and left heart designed to deliver rhythmically their outputs into the low-pressure pulmonary and the high-pressure systemic circuits, respectively. Their output volumes are ordinarily equal—the inherent characteristics of heart muscle epitomized in Starling's law of the heart are probably responsible for this automatic equation of delivery by each ventricle.

The pulmonary vascular bed is homogeneous, but that of the systemic circuit is complex, being divided up into a number of parallel-coupled circuits which are both morphologically and functionally somewhat differentiated (54). These parallel-coupled circuits are in the main tailored to provide a sufficient flow capacity to meet the maximal metabolic requirements of the organs or tissues which they respectively supply (see chapters on regional blood flow in Volume II, Section 2, of this *Handbook*). Some circuits provide notable exceptions to this general statement; thus the kidney and most glands receive a huge blood supply which subserves the function of providing raw material for their respective secretions in addition to fulfilling the immediate demands of the nutritional requirements of the gland cells. In the excessive sweating of heat stress, the skin circulation may reach figures close to 5 to 7 liters per min in man, where the blood flow fulfills the primary requirements of heat loss, which far exceed the trivial metabolic needs of the cutaneous tissue. In a way the skeletal muscles provide an exception in the opposite direction; their large tissue mass and their immense increase of metabolism during maximal activity make it physically impossible for the cardiovascular system, notably the pump, to satisfy such enormous blood flow demands immediately. Accordingly, their vascular circuit is certainly underdimensioned in relation to their maximal nutritional needs. As a compensation, anaerobic energy derived from local stores can cover the costs of such intense activity for short periods.

Each individual parallel-coupled circuit consists of series-coupled functionally defined sections (93), i.e. windkessel vessels, resistance vessels, sphincter vessels, capillaries or exchange vessels, capacitance vessels and, in some cases, shunt vessels.

Windkessel vessels convert the rhythmic pump output to a fairly smooth blood flow to the tissues. These vessels correspond approximately to the large arteries which possess in addition to smooth muscle a generous amount of elastic tissue in their walls (28, 63). Their elasticity, which serves to damp the oscillations in the arterial system, can be adjusted by centrally controlled vasomotor nervous effects on their smooth muscle cells, often with only minor shifts in their dimensions (8).

Resistance vessels comprise a major precapillary (essentially small artery and arteriolar) section and a quantitatively less dominant, but functionally by no means less important, postcapillary section (essentially the venules and small veins). Their sum constitutes the total flow resistance, whereas their ratio forms one of the main determinants of mean capillary pressure and hence of filtration exchange (93, 100). Changes in the luminal diameter of these vessels are virtually solely responsible for changes in regional blood flow, for the tube length of any regional vessels and the blood viscosity do not vary appreciably and the provision of a steady mean systemic arterial pressure and hence perfusion pressure is an outstanding characteristic of cardiovascular control. The functional activity of the individual regional resistance vessels is ordinarily adjusted so that the relevant organ or tissue receives a blood supply according to its needs. The vasodilator effects of metabolites produced by the tissues themselves secure this. However, blood pressure could hardly be sustained if these local needs were allowed to dominate the resistance control completely. The competitive influence of centrally directed vasoconstrictor nerves to the resistance

vessels allows the adjustment of vascular resistance appropriately so that a relative constancy of arterial blood pressure is thereby secured. This extrinsic restricting influence on the caliber of the resistance vessels, the extent of which varies from one tissue to the other, means that local blood supply of any one tissue may temporarily be reduced, thus providing flow primarily to vital organs when the organism as a whole more urgently requires it. Variations in the ratio between pre- and postcapillary vessel resistance automatically affects the all-important fluid balance between the intravascular and extravascular compartments of body water (93, 100). Resistance vessels are structurally designed in such a way that major changes in blood flow can occur without causing other than minor alterations of blood content of this section; such an arrangement is vital if regional blood flow and blood volume are to be independently adjusted. In addition the arteriolar vessels, in which occur the greatest changes in resistance to flow, can effect such changes of resistance by only moderate shifts in the tone of the smooth muscles contained in their walls, thanks to the high wall-to-lumen ratio which they possess. The smooth muscles of the precapillary resistance vessels show an often considerable myogenic activity which provides the basis of "basal vascular tone" and probably also of the "flow autoregulation phenomenon" (see below).

Sphincter vessels, besides forming a part of the precapillary resistance vessels, constitute an important specialized section in their own right, for their smooth muscle "sphincters" determine the density of the capillary network actually patent for blood flow. Thus they subserve a local function in determining the capillary surface area available for the tissue in its exchange with the blood as well as modifying the average diffusion distance between the blood stream and the tissue cells. Moreover, they modify the time available for transcapillary diffusion, for the more capillaries that are patent to a given volume flow of blood then the longer will be the average capillary passage time. The smooth muscles of the sphincters are primarily, but not entirely, locally controlled and are thus well adapted for these functional demands.

The capillaries are exchange vessels, consisting only of endothelial tubes and lacking any contractile elements in their walls. They provide a huge porous surface over which the blood stream is spread out for diffusion and filtration exchange, thereby securing the constancy of the milieu intérieur (86, 100). The pulmonary capillary section, which of course receives the same volume flow as that of the systemic circuit, is of far smaller area. However, normally the pulmonary capillaries convey passage only of the respiratory gases, whereas the systemic exchange vessels convey, in addition to O_2 and CO_2, the "pore"-restricted passage of all lipoid insoluble ions and molecules. This "pore"-restricted diffusion and filtration implies that only a small fraction of the surface area is available for such substances as glucose, while the lipoid-soluble oxygen and carbon dioxide molecules appear to pass directly through the endothelial cells. The capillaries are not capable of active luminal changes. Changes of capillary surface and flow resistance are secured indirectly by adjustment of the smooth muscle tone of the precapillary and postcapillary vascular segments; such changes apparently do not affect the porous capillary walls themselves.

[But see also Chapter 30 by Mayerson in Volume II of this treatise. ED.]

Capacitance vessels correspond structurally with the voluminous venous compartment. Here changes of lumen, which are too small to greatly affect flow resistance, have a profound effect on venous capacity and hence the filling of the pump and its subsequent output (4, 60, 93). Such vessels can be considered as a functional part of the pump system rather than as subserving any local function. Such specialization requires centrally integrated control, with minimal allowance for such changes as are induced by local reactions. Correspondingly the smooth muscles of the venous walls exhibit little myogenic activity and are subordinated to potentially powerful constrictor control by the thoracolumbar sympathetic nerves (see below). In a broad sense of the term, the capacitance vessels should include the venous side of the pulmonary circuit.

Shunt vessels occur in large numbers in parts of the skin which are concerned in the regulation of homeothermia. These specialized shunt vessels, like the capacitance vessels and to some extent the windkessel vessels, fulfill general needs of the organism as a whole. In keeping with this concept, the myogenic activity displayed by the smooth muscle of their walls is minimal (like that of the capacitance vessels) and is centrally governed by a dense distribution of sympathetic vasoconstrictor fibers. As a corollary, vessels which serve the local needs of the tissue exhibit marked myogenic activity (see below). Shunts are described in several other tissues, but here their functional significance is largely unknown (19, 119).

B. *Principal Characteristics of Cardiovascular Effector Cells*

The myocardium with its inbuilt pacemaker syncytial type of arrangement, and propagation network of specialized conducting muscle tissue is well designed for pump activity. Functional characteristics such as the all-or-none nature of the contraction response, the long refractory period, and the automatic adjustment of stroke work to diastolic volume, with an additional dual control by vagal and sympathetic nerves, ensure a wide range of variation in heart rate, and the sympathetic innervation of the ventricles can markedly affect their contractile force and speed (101, 104).

With regard to the vessels, in addition to the features that have already been mentioned which imply differentiation, there remains the important question as to whether the smooth muscle which comprises part of the vessel walls is functionally differentiated so as to suit the specific demands on the various regional sections. Vascular smooth muscle cells, as those elsewhere in the body, exhibit automaticity, but this is by no means equally developed either in vessels of different regional parallel-coupled circuits or even in the components of any one series-coupled circuit. The "primitive" smooth muscle cellular characteristic of automaticity, evidenced by spontaneous changes of membrane potential which lead to intermittent depolarizations and contractions (8, 20, 24), is almost nonexistent in some vascular sections; in such sections contraction of the smooth muscle cells is secured solely by extrinsic factors such as vasoconstrictor fibers and is correspondingly centrally dominated. The capacitance vessels (49) the cutaneous shunt vessels (45), and the windkessel vessels provide examples of this phenomenon. Such blood vessels as these subserve no direct local needs, but rather those of the body and the cardiovascular system as a whole; it is correspondingly notable that centrally governed reactions effect changes in these vessels with a minimum of interference caused by local effects. Vascular smooth muscle of this type may be compared with the so-called multiunit (8, 20) muscles, being related, for example, to the intrinsic smooth muscles of the eye, the reactions of which are also centrally directed without any allowance for local changes.

Sharp contrast is provided by the smooth muscles contained in the walls of the smallest arterial vessels and precapillary sphincters, especially in those circuits supplying vitally important tissues where centrally induced vasoconstriction cannot be tolerated. Such vessels are only feebly supplied by vasomotor nerves; the deep cerebral vessels are an excellent example. The smooth muscles of such vessels, particularly those in the immediately precapillary region, often exhibit considerable automaticity (8, 49) and resemble in this respect the "visceral muscles" described by Bozler (20). This precapillary myogenic activity expresses itself as "basal tone" which, though primarily independent of, is nevertheless to some extent affected by extrinsic excitatory influences. However, such basal tone is of course influenced by local environmental factors, as is any cellular activity. The phenomenon of "autoregulation" of blood flow, implying that an increased vasodilatation compensates for primary decrease of pressure and blood flow through a vascular circuit and the converse changes, is apparently due to inherent precapillary myogenic tone. Clearly the flow-dependent changes in chemical environment tend to cause this type of adjustment of tone, but the transmural pressure changes per se seem to contribute also (46, 49), as was first stressed by Bayliss (13). The phenomenon of autoregulation when demonstrable in a vascular circuit is often even more vivid when local nervous connections are entirely blocked, and cannot be ascribed to "intrinsic nervous connections," the very existence of which is in any case doubtful (72). The myogenically active precapillary smooth muscles function as active "receptor-effector units" in this respect, with their rhythmic inherent activity partly dependent on the facilitatory influence of the transmural pressure and capable even of moderately propagated response. This intrinsic capability compares to the control of skeletal muscle by the monosynaptic myotatic reflex arc.

It is not yet definitely known how transmural distending pressure-dependent flow changes and myogenic activity interact to accomplish autoregulation. However, a reasonable hypothesis (46, 49) can be advanced based on the actual events which follow stretching nonvascular smooth muscle (20, 24, 27), namely, that distention increases the rate of spontaneous contractions, implying that the muscle cells serve as tension receptors. Such factors as the refractory period of muscle cells would set an upper limit on the contraction frequency evoked by a given mechanical stimulus, thereby restricting the range of the obtainable resistance increase when pressure is raised. Such a hypothesis would suggest that vascular circuits in which the smooth muscle elements show little or no spontaneous myogenic activity would not manifest autoregulation. Thus the larger arteries, the

A-V shunts of the skin, and the venous sections, which all lack significant intrinsic automatic activity and depend for control almost entirely upon extrinsic factors, do not demonstrate the autoregulation phenomenon (27). They have no significant background activity that can be facilitated by transmural distending pressure, a relatively weak stimulus, although strong stimuli such as pinching may induce response.

Maintenance of flow resistance is basically due to and resides in the resistance sections, in which smooth muscle elements manifest myogenic activity and in which this inherent rhythmic activity is continuously facilitated by the distending pressure itself. This inherent "tone," well developed only in the precapillary resistance vessels, can be markedly influenced by extrinsic regulatory factors; but such extrinsic factors achieve complete domination only in vascular sections which exhibit little or no inherent tone.

C. Extrinsic Regulatory Mechanisms

The dual nervous control of the heart provides a striking example of extrinsic regulatory influence on an inherently rhythmic structure. Sympathetic drive may cause such changes of rate and force of contraction as to overshadow the inherent "Starling's law" behavior of the ventricular muscle (101, 104). Such a finding does not lessen of course the importance of this basic characteristic of cardiac muscle behavior.

Tonic neurogenic control of the vessels is exercised by sympathetic vasoconstrictor fibers governed mainly by discharge of the medullary vasomotor center. Circulatory homeostasis does not ordinarily involve activity of specific vasodilator fibers; vasodilatation is achieved by inhibition of vasoconstrictor discharge. Adrenal catecholamine liberation is ordinarily of little importance in cardiovascular control compared with the effects of variations in tonic activity on the vasoconstrictor nerves (30).

The neurogenic constrictor influence, superimposed on the basal tone of the resistance vessels, creates a dynamic "blood flow reserve"; this reserve is most marked in circuits where the ratio of maximal to minimal metabolic rate is large. The flow reserve can be mobilized by appropriate inhibitory mechanisms of which local chemical changes induced by increased tissue activity are dominant. The chemical substances so liberated are still labeled noncommittally "vasodilator metabolites," such is our ignorance of their chemical nature. The combined effects of several chemical substances seem to secure the blood supply for a tissue appropriate to its needs; however, some of these substances may be quantitatively more important than others. Moreover, there is already evidence that different vascular circuits show quantitatively varying responses when individual chemical effects are tested. Cerebral vessels are much more sensitive to changes in pCO_2 than to changes in pO_2 (80); conversely, coronary vessels are only mildly responsive to pCO_2, but dilate almost maximally during severe anoxemia (57). In skeletal muscles potassium ions released from the muscle cells during depolarization probably play a role in exercise hyperemia (35, 81). Secretory fibers to digestive and sweat glands release the potent vasodilator polypeptide bradykinin (73) which reinforces vasodilatation caused by the usual "metabolite" factors, perhaps to ensure sufficient vasodilatation to satisfy the double flow requirements of both secretion and increased metabolism.

Some vascular circuits receive vasodilator fibers, of which there are three general types. The first type provides parasympathetic vasodilator innervation, e.g., the nervi erigentes which supply erectile tissue of the genitalia (45, 112). The second includes "dorsal root" vasodilators which probably are simply nociceptor C fibers subserving no efferent function whatever; these afferent C fiber nerve endings are most abundantly distributed to the skin, and they respond to noxious stimuli and, via axon reflexes, local vasodilatation is elicited (45). Third are the sympathetic vasodilator nerves (114) which are distributed to the arteriolar section of the resistance vessels within muscles (48) and are governed by corticohypothalamic discharges apparently activated in the alarm-defense reaction (see below).

Vasodilator nerves are not tonically active in any reciprocal balance with the constrictor fibers as was earlier believed (45, 114).

In summary, total vascular resistance is determined largely by a balance between the effects of central vasoconstrictor discharge, in cooperation with basal tone of the vessels, and those of locally produced chemical vasodilator substances. This balance varies not only among the several parallel-coupled circuits, but also among the various segments of the series-coupled vessels of any one circuit. In parallel-coupled circuits, the resistance vessels of brain and myocardium are little affected by neurogenic vasoconstriction or by blood-borne vasoconstrictor agents and are very responsive to vasodilator metabolites. Their blood supply is therefore not compromised by a

generalized discharge of vasoconstrictor sympathetic nerves; indeed, the cerebral and myocardial blood flow is maintained and bolstered in emergency situations by the vasoconstriction which affects the other vascular circuits.

In considering the responsiveness of the different series-coupled segments of a vascular circuit, it seems generally true that local chemical factors more easily overcome neurogenic vasoconstrictor influence within arteriolar and precapillary sphincter sections than within the postcapillary venous section (47). This general trend of preponderance has the net result that tissue needs, at least to some extent, control their own blood supply, whereas a competent central control of the venous compartment with its capacitance and postcapillary resistance function can be better maintained in states of intense sympathetic discharge. In most normal circumstances this type of balance is favorable both for the organism as a whole and for the individual tissues, although in some specific pathophysiological situations it may have its drawbacks (47).

3. PRINCIPLES OF REFLEX AND CENTRAL NERVOUS REGULATION OF THE CARDIOVASCULAR SYSTEM

The neural regulation of the circulatory system can be conveniently considered as comprising two mechanisms, the reflex control devices (*A*) and the influence emanating from the higher autonomic centers in the upper brain stem and cortex (*B*).

A. Reflex Control Mechanisms

Reflex control of vasomotor and cardiac efferent mechanisms is exercised mainly by the mechanoreceptor afferent nerves having endings in strategically important sections of the cardiovascular system, like the walls of the large veins, the cardiac chambers, and the pulmonary, aortic and carotid arteries. A recent review listing the pertinent literature should be consulted for details (70).

It is an oversimplification to regard these afferent systems as engaging in synaptic connections only with the medullary vasomotor and cardiac centers, for they also furnish afferent fibers which depress the activity of the ascending reticular system of the brain stem, although in general the medullary connections appear to be dominant in importance. The medullary cardiovascular integration stations are therefore often labeled the "vasomotor center" and the "cardioinhibitory center" to stress their key position in the system. The vasomotor center maintains a tonic discharge over the sympathetic vasoconstrictor fibers which supply the vascular system. Such sympathetic discharge is of a low frequency, some 1 to 2 impulses per sec; even during marked vasomotor activity this vasoconstrictor discharge rarely exceeds 8 to 10 impulses per sec (45, 114). In most vascular compartments this narrow range of sympathetic vasomotor discharge exerts virtually full command of the smooth muscle effector cells. In the past it has usually been considered that the sympathetic vasoconstrictor nerves evinced a reasonably uniform discharge to all parts of the vascular system, but recent studies cast doubt on this belief. Thus central autonomic neuron pools, which control the tonic efferent discharge to the different vascular circuits, appear to exhibit different excitability levels, some being even "subliminal" with regard to tonic activity in the intact resting organism, for example, the neuron pools controlling renal vessels. When exposed to strong excitatory drives or to the summated effect of several individual subliminal excitatory influences, such neuron pools may also evince intense and continuous activity. Hence there seem to exist mechanisms which allow not only an intense and massive discharge in appropriate circumstances, but also a finely graded differentiated activity of the autonomic control of the circulation, established by quantitative differences in excitability level of the neuron pools controlling the functionally different vascular circuits (47, 89). Moreover it is possible that quantitative differences of a similar kind also exist between the tonic constrictor fiber control of the resistance and capacitance sections. The analogy with the organization of the respiratory center, with its different thresholds for the neuron pools controlling the various respiratory muscles, is striking.

The reflex control mechanisms are mainly operated by afferent nerve endings in the arteries and veins which act as deformation receptors and which are responsive both to a mean degree of deformation and to the phasic amplitude of such distortion as they are subjected to in the ordinary course of circulatory events. Impulse traffic from all such receptors causes qualitatively similar reflex responses; an increase of their activity depresses arteriolar and venomotor tone owing to their inhibitory effect upon the medullary vasomotor center and to cardiac slowing and perhaps to weakening of the ventricular force of contraction due to their synaptic effects on the medullary cardiac centers.

The neurogenic inhibitory influences on the neuron pools controlling the sympathetic discharge to the different cardiovascular compartments all appear to be relayed via medial parts of the bulbar reticular formation—the so-called "depressor area"—whether they are derived from the cardiovascular receptors or from higher centers (89). They depress the tonic sympathetic activity wherever present, but very little is known so far as to whether the different types of mechanoreceptors, independent of their location within the low-pressure or the high-pressure cardiovascular sections, always inhibit the efferent discharge pattern in exactly the same way. More restricted sympathoinhibitory mechanisms do exist, as exemplified by the highly selective influence of the hypothalamic heat loss center on the vasoconstrictor discharge to the cutaneous vessels (113). Considering the fact that the tonically active centers themselves appear to exhibit a certain differentiation, it is not unlikely that the receptors too are specialized insofar as they may adjust the tonic discharge to the various cardiovascular sections somewhat differently in extent, depending on the receptor location and its adequate stimulus. The possibility should be kept in mind that the afferent fibers from some mechanoreceptors within the low-pressure sections (e.g., "volume receptors") might converge somewhat more on the neuron pools controlling the discharge to the capacitance sections than is the case with the tension receptors situated within the arterial high-pressure section. Even slight quantitative differences in these respects imply control mechanisms of considerable specificity, allowing for fine adjustments of the different functional cardiovascular compartments, relating to aspects like pump performance, fluid balance, flow distribution, and the like. For instance, suppose that in a depressor response caused by a generalized inhibition of constrictor fiber tone the neurons controlling one vascular circuit are only somewhat more inhibited than those serving the remaining circuits. Hemodynamically the consequence may be a selective flow increase in this circuit. The introduction of quantitative concomitant recordings of the events taking place within the functionally different compartments of the cardiovascular system may thus open up new aspects of the cardiovascular control organization.

Chemoreceptor afferent nerves found in the carotid body and aortic body do not exert any significant tonic effect on the resting circulation. They become important, however, in conditions of circulatory insufficiency, anoxic anoxia, and perhaps in severe exercise. These chemoreceptors provoke arteriolar and venous constriction, and a rise in blood pressure and possibly in cardiac output. The exact organization of the efferent excitatory pattern induced is, however, at present only sparsely documented (70, 84).

MECHANORECEPTORS. These may be classified according to their site: systemic arterial, pulmonary arterial, cardiac, and central venous.

Systemic arterial receptors. The main receptors are found in the walls of the aortic arch and the carotid sinus, with some accessory receptors in the root of the right subclavian artery, in the common carotid artery, the thoracic aorta and mesenteric arteries (55, 70).

Although the aortic nerves were discovered first, by far the most information concerning the nature, behavior, and reflex effects of stimulation of this type of mechanoreceptor is derived from studies of the carotid sinus area, for this can be vascularly isolated and perfused without disturbing the local innervation or compromising the circulatory condition of the animal as a whole. Hence the functional characteristics of the carotid sinus reflexes will be described in detail; with trivial reservations, the other systemic arterial receptor sites can be considered to exert a similar qualitative role in monitoring circulatory activity, although quantitatively their individual stimulation may not cause exactly the same reflex response pattern. The details of the discharge response of the various regional efferent nerves in terms of impulse traffic are not yet at hand.

The carotid sinus mechanoreceptors (also called baroreceptors or pressoreceptors) are found in the wall of the carotid sinus. The nerve endings arborize widely in the arterial wall. Both myelinated and unmyelinated sensory fibers pass from the sinus via the sinus nerve to the glossopharyngeal nerve and thence to the medulla. These sensory nerve endings are stimulated by deformation (stretch), and this is ordinarily occasioned by the pulsatile expansion of the arterial wall. Indeed, if this expansion of the arterial wall be prevented by a rigid cast, then the sinus nerve impulse traffic becomes unresponsive to the luminal pressure of blood within the carotid sinus. For this reason it is undesirable in some ways to designate these nerve endings as baroreceptors or pressoreceptors. The preferable term is mechanoreceptors, or stretch receptors.

Any abnormal form of stretch will stimulate the nerve endings. Tugging on the adjacent vessels during surgical operations or external pressure on the overlying skin will evoke massive discharges which cul-

minate in reflex cardiovascular syncope. Similarly the topical application of vasoconstrictor drugs to the sinus will provoke abnormally powerful reflex effects.

In an anesthetized or nonanesthetized animal, section of the carotid sinus and aortic depressor nerves causes a rise of blood pressure which is sometimes very marked, providing proof that these nerves are tonically active in restraining circulatory activity. Occlusion of both carotid arteries below the sinus mimics the effects of section of the sinus nerves; the reflex hypertension seen during carotid occlusion is due to lowered impulse activity in the sinus nerves. Conversely a rise of perfusion pressure in the vascularly isolated, but innervated and perfused, sinus causes bradycardia and systemic hypotension. Atropinization, which almost abolishes the bradycardia seen during high-pressure perfusion of the carotid sinus, does not abolish the systemic hypotension which is thus partly, if not mainly, due to reduction of arteriolar and venomotor tone owing to inhibition of vasoconstrictor fiber activity. In addition, tonic sympathetic activity to the heart is inhibited. Again it is not known whether the inhibitory influences exerted on the sympathetic neuron pools controlling the resistance and capacitance section and on the heart are of equal degree.

The mechanoreceptors of the carotid sinus and presumably of the cardiovascular system generally resemble those elsewhere in the body in being responsive to the magnitude and rate of displacement from their "resting" position. If the carotid sinus be vascularly isolated and subjected to a series of steady hydrostatic pressures, recordings from a preparation containing a single fiber or a few fibers of the relevant sinus nerve show that the impulse frequency is increased at each steady mean pressure up to a maximum frequency at some 200 mm Hg.

Of more interest is the response of the sinus nerve endings to pulsation about each mean pressure, for the arterial circulation is, after all, pulsatile. It is very simple to insert a T cannula into the carotid artery below the sinus. By connecting the T cannula to an air reservoir, which serves as a damping chamber, the normal pulsation delivered via the carotid artery to the carotid sinus can be almost completely suppressed without affecting the mean pressure in the lumen of the carotid sinus. Simultaneous recordings of preparations involving a few fibers of the sinus nerve in these conditions reveal two notable facts. *a*) When steady pressure is converted into pulsatile pressure, the individual units change from steady firing to rhythmic firing in time with the arterial pulse. During these rhythmic bursts the peak frequency far exceeds that shown during maintenance of steady pressure. *b*) Changing from nonpulsatile to pulsatile conditions at the same mean pressure causes recruitment of individual receptor units (70).

These findings indicate that pulsatility and mean arterial pressure jointly determine the degree of cardiovascular inhibition exerted via arterial mechanoreceptors. In the vagotomized cat, mere conversion of the carotid pulse into steady pressure delivered to the carotid sinus provokes a reflex rise in systemic blood pressure. Thus the normal pulsatile stimulation of the carotid sinus mechanoreceptors causes a much more effective inhibition of the cardiovascular efferent nerves than does a steady pressure of an even higher mean value. Hence the variations of control available to arterial receptors alone are more subtle than if such receptors were responsive only to a mean arterial pressure. In slow hemorrhage the mean blood pressure may be maintained for a long time by means of compensatory arteriolar and venomotor constriction which helps to offset the failing cardiac output. The basis of this reflex compensation is the progressive enfeeblement of the pulsatile stimulus delivered to cardiovascular mechanoreceptors in these circumstances.

All arterial mechanoreceptors behave qualitatively as a functional unit insofar as their cardiovascular reflex effects are concerned. Their quantitative effects on individual vascular circuits may, however, differ somewhat as mentioned above. The curious distribution of these receptors in the arterial tree has been accounted for by Koch (82) who suggested that these areas represent surviving remnants of the gill arch vessels of the fish. If this be so, there is nothing to suggest that branchial arch systems should have developed individual preferential reflex connections with the neuroeffector mechanisms controlling the circulation. The term "Blutdruckregler" introduced by Kahn (79) was admirably descriptive of one of their functions, but Samson Wright came closest to the perfect description with his term "buffer nerves." This implies that they minimize circulatory changes however induced. It does not imply that they prevent such changes entirely. Just as a physicochemical buffer system has an optimal pH range and can be rendered relatively ineffective by the addition of such amounts of hydrogen or hydroxyl ion as take the final pH out of this range, so the mechanoreceptor reflexes are most efficient in combating cardiovascular changes which cause departures from either side of the normal blood pressure level; but they can be outweighed,

e.g., by the delivery of massive corticohypothalamic impulse discharges to the medullary neurons. Such an event, which occurs at the onset of heavy exercise, may be considered a biological necessity for survival and escape when events require the fulminant conversion of the circulation into a simple mechanism providing maximal blood supply to muscles by a maximally active pump (see below). In such circumstances reflexogenic control may go by the board, but in the period ensuing upon such fulminant activity, when central drive has decreased or ceased, the mechanoreceptors must play an important role in recovery adjustments.

The functional role of the separate arterial mechanoreceptor mechanisms can be simply demonstrated by observing the response to aortic nerve stimulation before and after cutting the sinus nerves. After sinus nerve section, the reflex hypotension provoked by aortic stimulation is far more dramatic.

As stated early in this chapter, reflexogenic effects of arterial mechanoreceptor stimulation have usually been expressed in terms of the arterial blood pressure response obtained; there is no inherent fault in this, provided that the fall in blood pressure is not further described only in terms of a reduction of arteriolar resistance. Arteriolar resistance as a whole is undoubtedly lowered by arterial mechanoreceptor reflexes, and experiments on artificially perfused organs or limbs have provided evidence of individual contributions of these various circuits to the over-all drop in total peripheral resistance. Recent studies have here provided some quantitative information on the effects of such reflexes on the resistance vessels of individual circuits (89). However, our knowledge about the quantitative response of the capacitance section components of the individual regional circuits, as compared with the resistance section, is almost nonexistent. Ample qualitative evidence exists that these mechanoreceptor reflexes cause venodilatation, but the subtle parceling of quantitative effects in the various compartments is undocumented to date. Lastly, the arterial mechanoreceptor reflexes influence the pump itself, slowing and weakening the stroke. Daly & Luck (33) found that systemic hypotension provoked by a pressure rise in isolated, innervated, and perfused carotid sinuses is associated with reduction in cardiac output measured as total pulmonary flow in open-chest animals. In their experiments the right atrial pressure rose during sinus hypertension; this is not a common feature of the cardiovascular responses to such reflexes in closed-chest, normally breathing animals. If venodilatation be vivid in the reflex response, then one would hardly expect a rise of right atrial pressure unless the heart were failing as a pump. Complicated circulatory changes indeed may result from such sinus hypertension. It must be remembered, for instance, that sinus hypertension provokes a reflex fall of mean systemic pressure and hence of coronary perfusion pressure, so that the efficiency of the ventricle may well be secondarily affected in these peculiar experimental circumstances, quite apart from more direct reflex nervous influences exerted on its chronotropic and inotropic performance. In the intact circulation an exaggeration of arterial mechanoreceptor stimulation can occur only when the mean blood pressure level or its pulsatile amplitude increases due to primary changes of arterial resistance, of cardiac output, or of both. Failure of provision of an adequate coronary driving pressure could hardly eventuate. The experimental circumstances necessary for analysis of the sinus reflexes on the heart output are perhaps too artificial and involve too many different factors—the balance of which may vary considerably due to the experimental conditions—to give us even qualitative information as to the responses which ordinarily occur. Mechanoreceptors have been identified in other vascular areas, but the sinoaortic mechanoreceptors are still the main known means of the homeostatic regulation of the systemic arterial pressure.

Pulmonary arterial mechanoreceptors. These are found in the adventitia of the wall of the main pulmonary trunk and its branches. Their impulse activity occurs with the rise of pressure during systole and is affected by the pulse amplitude (70). Their reflex function is naturally more difficult to determine quantitatively, but Aviado & Schmidt (7) have described systemic hypotension and bradycardia as a reflex response to raised pressure in the perfused pulmonary artery. Whether the systemic hypotension is due mainly to reduction of cardiac output or to arteriolar dilatation and venodilatation is not known. Little too is known of the reflex influence which the impulse traffic from these nerve endings exerts on pulmonary resistance and capacity. It would seem likely that sensory messages from these nerve endings would be affected by any imbalance between right and left heart output, so that if the pulmonary circuit were suddenly overloaded by a temporary increase of right heart output reflex pulmonary venodilatation by increasing pulmonary vascular capacity might assist the other cardiac and systemic effects which these pulmonary mechanoreceptor reflexes simultaneously produce.

Cardiac mechanoreceptors. These are found as vagal

nerve endings in the subendothelial layer of the walls of both atria; ventricular vagal endings are also probably subendothelial in their site. These nerve endings are tonically active.

The atrial receptors have been classified as "A" and "B" receptors (70), according to their discharge characteristics. A receptors discharge during atrial systole and again during the venous filling wave of the atrial pressure curve. B receptors discharge only during the venous filling wave of the atrial pressure curve and are ordinarily silent during atrial systole.

This subdivision of atrial receptors is perhaps too restrictive. Although the single fiber discharge patterns described can often be found, the firing characteristics may be markedly changed by altering the venous return or the intrapulmonary pressure. An A receptor may completely alter its firing pattern during increased venous return simulating the discharge characteristics of a B receptor (94). On the other hand, a B receptor during positive pressure inflation of the lung may then simulate A receptor discharge. Although it is possible that these two sets of receptors do exist and that there is real significance in the difference in their respective patterns of discharge, to date there is no evidence that they subserve qualitatively or quantitatively different reflex mechanisms. Indeed the reflex response obtained by the stimulation of these atrial fibers is by no means clearly defined owing to the peculiar difficulty of stimulating them separately from other cardiovascular sensory endings. Such evidence as has been obtained of their reflex activity has been derived from studies of deformation of the right or left atrium and of reflex response to intracoronary injection of minute amounts of veratridine (which simultaneously stimulates ventricular vagal receptors). None of these methods has yielded any information whatever that the right or left atrial receptors cause reflex tachycardia. All the results, incomplete though they may be, indicate that these atrial receptors cause reflex bradycardia, systemic hypotension, and venodilatation. The effects of their activity on cardiac output are quite unknown with the obvious reservation that profound bradycardia, which their stimulation may reflexly produce, may lead to cardiac asystole and hence to a fall of output to zero. In addition, the right and left atrial receptors have been identified as fingers of afferent arms of reflexes which adjust the output of the adrenocortical (aldosterone) and antidiuretic hormones and hence may exert a "long-term" influence on blood volume (see below).

The ventricular receptors are relatively sparse compared with the number of atrial and central venous receptors. Paintal (97) first demonstrated their impulse activity proving that they discharge shortly after the Q wave of the ECG, attaining a peak frequency some 25 to 70 msec after the Q wave. They are strongly stimulated by veratridine. As veratridine in minute doses evokes reflex bradycardia when injected into the anterior descending branch of the left coronary artery (which supplies only the left ventricle), some at least of the Bezold-Jarisch reflex is due to the stimulation of ventricular receptors. As the Bezold-Jarisch effect consequent upon the stimulation of the cardiac vagal nerve endings is abolished by cooling the vagal trunks to 9 to 11 C (36), this suggests that the atrial and ventricular receptors which are excited by the drug discharge over fibers of the A group.

The ordinary function of the ventricular receptors is presumably proprioceptive, signaling information of overloading of the heart. The reflex response of bradycardia and hypotension presumably includes venodilatation, but there is no direct evidence of this.

CHEMORECEPTORS. These (70) are found near the aortic arch and the root of the subclavian arteries, and in the carotid bodies. They consist of highly vascular clumps of epithelioid cells which receive a rich sensory innervation. The carotid body is supplied by the sinus nerve and the aortic bodies by the vagi. The blood flow through the carotid bodies is fantastically high—some 2000 ml per 100 g per min—although as the carotid body weighs only 2 mg in the cat, the absolute blood flow is 40 mm^3 per min in this species.

Heymans and his co-workers (70) proved that the carotid and aortic bodies were stimulated by anoxia, hypercapnia, and acidemia. De Castro had suggested, on morphological grounds, that the carotid bodies might signal information via the sinus nerve of changes in the chemical composition of the blood (see 70).

The response of the chemoreceptors to anoxia is of vital importance to the body; after denervation of the chemoreceptors, anoxia causes respiratory depression and death, whereas if they are intact anoxia induces reflex hyperpnea and reflex cardiovascular excitation. Chemoreceptor stimulation by hypercapnia or by acidemia induces reflex hyperpnea which reinforces that provoked by the effect of these chemical changes on the medullary respiratory center itself.

Of the four types of anoxia only anemic anoxia is incapable of inducing chemoreceptor activity; anoxic,