THE CONTROL OF THE CIRCULATION OF THE BLOOD

SUPPLEMENTAL VOLUME

BY

VARIOUS AUTHORS

ARRANGED BY

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PREFACE TO SUPPLEMENT

THE original volume of the *Control of the Circulation* was destroyed in the great fire of London on 29th December 1940, in spite of the fact that Messrs. Longmans had taken precautions to disperse their store in two separate places, but the subsequent demand for it has been such that it has now been reprinted. Incorporation of all new material now available would have been too costly, but a supplement has been added in those sections of the subject in which there have been major advances in the last seventeen years. In the preparation of it I have been fortunate in securing the co-operation of a number of distinguished specialists who have undoubtedly made the supplement much more valuable than it otherwise would have been. The slight overlap it has produced has also the special value of showing that on several points there is a considerable divergence of view. It is, for example, very difficult to reconcile the older work on histamine with the view that the capillaries are inert tubes acting passively. It is a pity that so many of the earlier workers are no longer able to reply to many modern views, which in their time received due consideration.

The discovery of the chemoreceptors, of noradrenaline, of the stimulating action of acetylcholine in the heart, of the importance of the maintenance of the sodium-extruding mechanism in relation to function and permeability and the realisation of a sympathetic vasodilator outflow has necessitated a re-interpretation of many facts referred to in Volume I, to which this volume is essentially a sequel, and it must be read in that sense. Much study has been devoted to other fields, notably that of the afferent pathways from the heart and lungs, but fortunately that has been made the subject of several recent reviews or books and therefore it has not been included. These reviews have, however, been listed, as it is the intention of the volume to be a guide to the literature and make it more readily available to young workers. In the years to come perhaps a new supplement volume will be added.

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THE NERVOUS CONTROL OF THE BLOOD VESSELS

by

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(1) Introduction

SINCE the first edition of this monograph was published in 1938, many important papers dealing with the nervous control of the blood vessels have been published, which to a considerable extent have widened our knowledge concerning the regulation of the peripheral circulation. In this review an attempt will be made to sum up the present state of knowledge concerning the different types of nervous mechanisms which control the blood vessels.

Some vasomotor reaction patterns can be distinguished which operate continuously and mainly serve the organism as a whole in the general purpose of maintaining its integrity. In states of emergency it is possible, for example, by means of these mechanisms to secure a supply of blood primarily to tissues of the utmost importance for the maintenance of life. The vasomotor control of the blood pressure belongs to this group, and also the nervous adjustments of the cutaneous blood flow, which are of prime importance for the regulation of the body temperature. Such centrally controlled circulatory adjustments seem to be exclusively effected by way of the sympathetic vasoconstrictor fibres, which therefore form a relatively distinct functional unit.

In other reaction patterns that are elicited under special circumstances, centrally controlled vasodilator fibres, distributed to restricted tissue areas, provide an increased blood flow to these tissues. Both the sympathetic and parasympathetic vasodilator fibres can be said to belong to this group, though they are otherwise not closely related in function, as will be seen later on.

Lastly, some nervous adjustments of the blood flow are exclusively peripheral in nature and therefore more or less strictly localised in the region where the stimulus is evoked. It will be found that the so-called dorsal root vasodilator fibres belong to this group of mechanisms. Further, it is at present much discussed whether there exist peripheral independent nervous networks in the vascular walls, by which local vascular responses are integrated.

Therefore, following these main lines it is possible to present the papers dealing with the nervous control of the blood vessels

according to a system that is based both on the morphological and on the functional arrangement of the vasomotor fibres:

Each section is divided into subdivisions with special titles, and these subdivisions are given consecutive numbers to facilitate references both in the text and in the bibliography.

Only papers that provide definitely new information about the functional organisation of the vasomotor fibre control of the blood vessels will be discussed. The author is well aware of the fact that in the attempt to select such papers many important contributions may have been overlooked.

(2) Some Principal Characteristics of the Effector Cells

Before the vasomotor fibre control of the blood vessels is discussed it is of importance first to outline briefly the functional characteristics of the effector cells on which the vasomotor nerves exert their action.

It is now generally accepted that vascular contractility, at least in mammals, is dependent on the vascular smooth muscle cells, but there is much evidence which suggests the "true" capillaries in some areas act as passive tubes, and that changes in their lumen are secondary to hydrostatic factors. Now and then a slow swelling of the capillary endothelium cells has been reported with a bulging of the cells into the capillary lumina (see Krogh's monograph). Probably such changes are to be looked upon as passive

osmotic effects rather than as true active contractions (for further references, see Zweifach 1939, Fulton and Lutz 1941–42, Clark and Clark 1943, Chambers and Zweifach 1944, 1946, 1947, Nicoll and Webb 1945–46, Nelemans and Nauta 1948, and Lutz *et al.* 1950).

It is important to stress that the activity of the vascular smooth muscle cells is in no way solely dependent on the vasomotor fibres. It is now generally accepted that the automaticity of the heart is principally independent of, though modified by, nervous factors, and there is in fact almost as good evidence for a corresponding automaticity of myogenic origin in many types of smooth muscle cells (see e.g. Bozler 1941, 1942, 1948, and Evans and Schild 1953). Thus completely nerve-free smooth muscle strips show spontaneous activity, which of course is dependent on a normal environment like all types of cellular activity, but nevertheless difficult to ascribe to specific stimulating factors in the environment. There are in fact good reasons for assuming that the vascular smooth muscle cells to some extent also exhibit automaticity (for a discussion of the literature, see e.g. Folkow 1952–53). Thus the rhythmical but unsynchronised changes in tone of the smallest vessels, often called "vasomotion", are said to be basically independent of, but modified by, the vasomotor fibres (Nicoll and Webb 1945–46, Lutz *et al.* 1950, and Webb and Nicoll 1952). It has long been known that this rhythmical activity is especially pronounced in the small veins of the bat's wings, where rapid, almost heart-like contractions may be observed (Nicoll and Webb 1945–46). The fact that these rhythmical reactions seem to be completely unsynchronised, even in closely adjacent smooth muscle cells, makes it somewhat improbable that they should be ultimately due to e.g. an activity in a local syncytial nerve cell plexus in the vascular walls as has sometimes been suggested (see 3). Further, there is no definite need of such a nervous interlink to explain these particular reactions. It is just as easy (or difficult) to imagine an inherent automaticity of the smooth muscle cells proper, and to imagine that these cells respond directly to external factors. Whichever is the case, rhythmical unsynchronised contractions of the denervated smooth muscle cells must create a basal tone of the vessels, in principle independent of external nervous control, though of course markedly influenced by central nervous and humoral mechanisms. The extent of such a basal tone in a vascular area, where the vasomotor nerves are cut and the catechol secretion from the suprarenal glands is eliminated, has been approximately evaluated in a recent study (Celander and Folkow 1953a). From the difference between the blood flow during "resting" conditions and during induced maximal vasodilatation, the basal tone may be estimated in terms of relative peripheral resistance units. It

has then been found that the vessels of e.g. the paw of the cat, where there is an abundance of arterio-venous anastomoses, exhibit a very low basal tone. The muscular blood vessels of the cat, on the other hand, seem to have a pronounced basal tone, which is in accord with studies on man, where muscular work may considerably increase the blood flow, even in acutely sympathectomised limbs (Barcroft *et al.* 1943–44). Therefore the extent of the inherent activity of the vascular smooth muscle probably varies markedly from region to region. The vasomotor fibres should then be looked upon more as potent adjustors of an inherent vascular smooth muscle activity than as the ultimate initiators of vascular tone.

There is in many vascular regions evidence of a wide range of vasomotor nerve control of the effector cells, often most pronounced where the inherent vascular activity is insignificant. Thus, vascular reactions, which for their exact performance need an intimate central control with little margin for local interference, seem to be completely dependent on the vasomotor nerves with a minimal inherent activity of the vascular smooth muscles, as is necessarily also the case with e.g. the ciliary or the pupillary smooth muscles. The control of the cutaneous arterio-venous anastomoses, governed by the hypothalamic heat regulating centre, is a good example. At the other extreme there are vascular areas serving the metabolic needs of vitally important tissues, such as the brain or the myocardium, where the vasomotor fibres exert only minimal control over the blood flow. These blood vessels seem to be regulated mainly by the local interaction between a relatively pronounced basal tone and vasodilator metabolites produced by the tissue. Obviously the inherent vascular tone is marked in these tissues, as it is known that, even when all nervous influences have been eliminated, anoxia for example is still able markedly to increase the blood flow. In such vascular regions the basal tone may be said to create a locally controlled "vascular reserve", which is immediately mobilised to the extent needed by e.g. changes in the local concentration of vasodilator metabolites. At intermediate levels between these two extremes the other vascular regions are found. Many of these points are brought out in Volume I of this book.

It has been pointed out by Rein *et al.* (1939–40) that the influence of the constrictor fibres is always more or less counteracted by locally produced vasodilator metabolites. Therefore, even in regions with a relatively extensive supply of vasoconstrictor fibres, the tissue is to some extent protected against centrally induced constrictor influences. When the production of vasodilator metabolites is increased, as in muscular work, this local factor may completely overpower even a marked constrictor fibre discharge.

FIRST SECTION: CENTRALLY CONTROLLED VASOMOTOR FIBRE SYSTEMS

I. THE SYMPATHETIC VASOMOTOR FIBRES

(3) General Principles of the Organisation of the Neuro-Effector Complex

As regards the sympathetic neuro-effector organisation, two fundamentally different schools oppose each other. On the one hand it is claimed—with minor modifications—that the sympathetic vasomotor fibres end in a terminal reticulum with a syncytial arrangement, which according to many investigators is formed by primitive peripheral ganglion cells. This peripheral nerve plexus would then constitute the ultimate nervous control of the vascular smooth muscles (Leeuwe 1937, Coujard 1943, Champy *et al.* 1945–46, Nelemans 1948, Feyrter 1952, Schaefer 1952, Meyling 1953, and Cannon *et al.* 1954). According to Meyling (1953) the hypothetical local nerve plexus is responsible for the "spontaneous" activity of the blood vessels (see the monographs of Langley and of Krogh). Further, the postganglionic sympathetic neurones are said to exert their action entirely by way of these local ganglion cell plexuses, which means that a third neurone link would exist in the sympathetic innervation of the blood vessels. In that case it is strange that ganglionic blocking agents do not even diminish the effect of postganglionic stimulation, if an additional synapse must be passed before the effector cells are excited (see e.g. Moe and Freyburger 1950). The evidence hitherto adduced to support the existence of such peripheral neurones and independent nerve plexuses is for many reasons not entirely convincing. Further, an arrangement of this type is by no means necessary or even helpful for explaining the effect of the postganglionic sympathetic fibres on the vessels or the "spontaneous" activity of the vascular smooth muscle cells. When later on local reflexes are discussed this question will be further dealt with (see 39).

In contrast to this concept other investigators claim that the postganglionic sympathetic neurone makes direct contact by axon ramifications with a group of smooth muscle cells, thus forming a "motor unit" analogous to the innervation principle of the skeletal muscle. Such a view is supported by electrophysiological studies of the nictitating membrane in the cat (Eccles and Magladery 1937a, b) and by direct observations of the vascular reactions following stimulation of single vasomotor nerve fibres (Fulton and

Lutz 1941–42, Lutz *et al.* 1950). Fulton and Lutz also observed that direct microstimulation of the vascular wall still caused a contraction of the same group of smooth muscle cells when the effect of nerve fibre stimulation was abolished by local cocainisation. As nervous elements should now be blocked, this reaction could hardly be due to a local nerve plexus. The observation may indicate some type of syncytial arrangement of the smooth muscle cells within the "motor unit".

Langworthy and Hesser (1940) claim that after sympathectomy practically all nervous elements in close contact with the vascular walls degenerate, except true afferent fibres, which are not eliminated until after section of the dorsal roots. Had there been any local ganglion cells a peripheral nerve plexus would still have been found.

Hillarp (1946, 1949), in an extensive study of the functional organisation of the postganglionic sympathetic innervation, presented strong evidence in support of the "motor unit" arrangement. Further, a pronounced divergence and convergence principle seems to exist in the organisation of these neuro-effector units, as is known to be the case also with the synaptic arrangement in the sympathetic ganglia. According to Hillarp there is no syncytial arrangement of the postganglionic fibre ramifications and no peripheral ganglion cells. On the other hand, a syncytially arranged Schwann plasmodium is found, through which the postganglionic axon ramifications pass without forming true nervous interconnections. Technically, investigations of this type are very difficult, however, and the above mentioned arrangement of the postganglionic nerve endings and the Schwann plasmodium might easily be mistaken for a syncytial nerve plexus with tiny primitive ganglion cells. From extensive studies of the sympathetic innervation of the cutaneous blood vessels, Weddel and Pallie (1954) were also unable to find evidence of peripheral nerve cells or independent syncytial nerve plexuses in the vascular walls.

A somewhat different theory concerning the sympathetic neuro-effector organisation has been put forward by Cannon and Rosenblueth and their collaborators (see Rosenblueth 1950). They claim that only a fraction of the effector cells—the "key cells"—are directly innervated by the postganglionic fibres, from which the adrenergic transmitter is said to reach the surrounding non-innervated effector cells by diffusion, a view which is criticised by Hillarp. The evidence presented to support the "key cell" theory is on the whole also valid for a postganglionic fibre arrangement of the type Hillarp describes. It also seems strange that the effector cells should have such a sparse innervation from the postganglionic neurones when there is an extensive divergence and

convergence organisation of the preganglionic fibres in the sympathetic ganglia.

If one compares the evidence now available in support of an independent syncytial nerve plexus with peripheral ganglion cells as contrasted to a "motor unit" arrangement, the latter theory seems to be based on more solid ground. It should be realised, however, that it is dangerous to make definite statements when technical problems of this extreme complexity are involved.

(4) Fibre Types in the Sympathetic Vasomotor Nerves

It is generally agreed that the preganglionic sympathetic axons belong to the thinly myelinated B-fibre group while the post-ganglionic axons are unmyelinated C-fibres. This fact in no way excludes the possibility, however, that within these fibre groups a relatively wide variation of fibre diameter may exist with correlated differences also in transmission rate, discharge capacity, etc. Maltesos and Schneider (1938–39a, b, c, d) and Hensel (1950) estimated the threshold of the sympathetic vasomotor fibres to stimulation with alternating current at different frequencies. They observed a considerable variation even for fibres distributed to the same vascular region, with a tendency for the threshold values to aggregate in distinct groups. The threshold of nerve fibres to electrical stimulation is generally related to the fibre diameter and also to other characteristics of the fibres. It is therefore not impossible that e.g. the discharge rates of the vasomotor fibres, and possibly also the characteristics of their subordinated effector cells, may vary within reasonable limits in one and the same vascular area.

A. THE SYMPATHETIC VASOCONSTRICTOR FIBRES

(5) The Route of Vasoconstrictor Fibre Distribution

The general principles of the distribution and the pathways of the vasoconstrictor fibres are well known and described in detail in earlier sections of this book. It should be mentioned that Wrete (1935, 1941, 1943), Pick and Sheehan (1946), and Boyd and Monro (1949) have demonstrated the existence of "intermediary" sympathetic ganglia in close connection to the ventral roots. Many of these small ganglia may remain intact after extirpation of the sympathetic chain. An interesting new contribution in regard to the vasoconstrictor fibres has recently been made by Alexander *et al.* (1949), Kuntz and Alexander (1950), Randall *et al.* (1950b), Ehrlich and Alexander (1951), and Cox *et al.* (1953). They were able to show that both in dogs and in man a fraction of the constrictor fibres seem to reach the blood vessels without ever joining

the sympathetic chain or leaving the ventral roots and the spinal nerves. Probably the synapses with the postganglionic neurones are situated in or in close proximity to the ventral roots or the spinal nerves. These constrictor pathways will therefore remain intact after a complete sympathetic ganglionectomy of the type normally performed, and may explain why in some cases it has been possible to elicit vasomotor reflexes in animals after extirpation of the sympathetic chains (see 12a).

Randall *et al.* (1950a) have traced the segmental distribution of the postganglionic vasoconstrictor fibres to the paw of the dog. Most of the fibres are derived from ganglia at the vertebral levels of L6 to S1 and the maximal inflow of preganglionic fibres appears to be between L4 and L6. Bowling *et al.* (1953) found that practically all vasomotor fibres of importance for the regulation of the muscular blood flow in the hind limb in the dog seem to run in the sciatic nerves.

(6) The Transmitter at the Vasoconstrictor Nerve Endings

No detailed survey of the large number of papers dealing with the nature of the adrenergic transmitter will be given here, as many excellent reviews of recent date specifically deal with this question (see e.g. Rosenblueth 1950, Euler 1950, 1951, 1954, and Holtz 1952). Only some investigations which specially deal with the vasoconstrictor fibres will be discussed in this connection. It is known, predominantly from the investigations of Euler and his school (see Euler 1950, 1951, 1954), that high concentrations of noradrenaline, often with a small admixture of adrenaline, can be extracted from sympathetic nerves and sympathetically innervated tissues but not from the nerve-free placenta. Degeneration of the postganglionic sympathetic fibres markedly reduces this noradrenaline content. Schmiterlöw (1948) was able to extract high concentrations of noradrenaline from the vascular walls, especially the smooth muscle layers, and only in a few cases was a significant adrenaline admixture found. It is then highly probable that the noradrenaline content in the vascular walls is contained within the vasoconstrictor nerve endings. The slight possibility that noradrenaline might merely be a precursor to the definite transmitter with a methylation to form adrenaline at the moment of release, is contradicted by the fact that, on intense stimulation of the sympathetic fibres to e.g. the spleen or the liver, predominantly noradrenaline is released into the blood stream (Peart 1949, West 1950, Mann and West 1950). When given by way of the blood stream, noradrenaline induces a pure constriction in all vascular areas with the exception of the coronary vessels (see 23).

Folkow and Uvnäs (1948a) were able to show that selective activation of the sympathetic vasoconstrictor fibres always elicited a pure constrictor effect, even in the muscles, where adrenaline mostly elicits a vasodilatation. Even after sympathicolytic drugs, when adrenaline markedly dilates the muscular blood vessels, the constrictor fibre effect was never reversed but only more or less completely blocked. This it is important to stress, as it was recently suggested by Schaefer (1952) and Cannon *et al.* (1954), that after all adrenaline might be the transmitter, which sometimes should be able to induce vasoconstriction, sometimes vasodilatation. This suggestion, which was presented as an alternative to the idea of specific sympathetic vasodilator fibres, will be discussed in more detail later on (see 19). Recent investigations by Lundholm (1951, 1955) indicate that the dilator action of adrenaline is related to its glycolytic action on the skeletal muscle cells, where the released lactic acid would be the ultimate dilator agent (see also 23 and 25). If such an indirect mechanism is the entire explanation of the adrenaline dilatation, a hypothetical release of adrenaline at constrictor nerve endings with the influence strictly localised only in the vascular smooth muscle cells should induce pure vasoconstrictor effects also in the muscles. Therefore, even if noradrenaline released at the constrictor nerve endings, should be admixed with adrenaline, it in no way follows that these fibres would ever be able to induce vasodilator effects in the muscles.

Similarly, the fact that injection of noradrenaline dilates the coronary vessels does not necessarily exclude noradrenaline as the transmitter at possible coronary vasoconstrictor nerve endings. Intra-arterially injected noradrenaline will also reach and excite the heart muscle, and the increased production of vasodilator metabolites might then overpower a possible direct constrictor effect on the vascular smooth muscle cells. If then noradrenaline is released at vasomotor nerve endings in the vascular walls, when only traces of the transmitter will reach the myocardium, a pure vasoconstrictor response may be obtained. Excessively far-reaching conclusions should therefore not be drawn from comparisons of the effects of the transmitter substance when released at the nerve endings and when administered by way of the blood stream.

In this connection some papers, interpreted as indicating a different type of transmission mechanism than what is generally accepted, should be discussed. Barreda *et al.* (1948) suggest that excitation of the vasoconstrictor fibres releases a substance which has a vasoconstrictor effect only in the presence of blood plasma. The experimental evidence presented to support this modified view concerning the humoral transmission at the vasoconstrictor nerve endings is not convincing, however, and therefore does not

necessitate a re-evaluation of the experimentally well-established current ideas. Armin and Grant (1955) have shown that plasma itself acquires a vasoconstrictor substance after haemorrhage.

A somewhat similar hypothesis is proposed by Akers *et al.* (1954) from a direct study of the blood vessel responses in the rat's mesoappendix. No direct vasoconstriction could be observed on splanchnic stimulation, but it is claimed that the sensitivity to topical application of adrenaline was highly increased. It is suggested that the vasoconstrictor fibres exert their action mainly by sensitising the vascular smooth muscles to blood-borne vasoconstrictor substances. There is such an abundance of observations indicating that constrictor fibre stimulation induces a prompt and powerful vasoconstriction that it seems obvious to assume that the technique used, with due respect for its many advantages, has its limitations, as has recently been pointed out by Wiedeman and Nicoll (1953), Burton (1953), and Baden (1954). It is not impossible that in fact splanchnic stimulation evoked a vasoconstrictor response of the "classical" type, though on the analogy of observations by Webb and Nicoll (1952) mainly larger arterioles were influenced. The blood flow might then be considerably slowed down even if the radius of the smaller blood vessels in the field did not change to any extensive degree. As the stimulation rates used were high, an "overflow" of the constrictor fibre transmitter might be the explanation of the lower adrenaline threshold.

(7) The Correlation Between the Discharge Rate of the Vasoconstrictor Fibres and the Vascular Response

The quantitative importance of the vasoconstrictor fibre control of the blood vessels can hardly be fully realised until the correlation between the discharge rate of the fibres and the induced vasoconstrictor response is known. Until quite recently practically no quantitative data were available concerning their effects on the blood vessels.

There are *a priori* reasons for believing that the relatively slow reactions of the vascular smooth muscles might allow a summation of contraction up to maximal levels already at relatively few stimuli per second, and further, that the thin vasomotor fibres are probably not able to discharge at any higher rates. Kottke *et al.* (1945–46) also noted that stimulation of the renal vasoconstrictor nerves with low frequencies induced marked effects on the blood flow, while the constrictor response could not be maintained for any length of time if higher stimulation rates were used. Folkow (1952) studied the constrictor responses of the blood vessels of the muscles when their sympathetic vasoconstrictor fibres were

maximally excited at various stimulation rates. A small but definite constrictor response was obtained when the nerve fibres were stimulated with only thirty impulses per minute, with an approximately linear increase of the vasoconstriction when the stimulation frequency was increased up to about eight impulses per second. Still higher stimulation rates added relatively little to the constrictor response, with definite maximal effects at fifteen to twenty impulses per second, when the peripheral resistance was increased about ten times. Variations of the discharge rate up to a maximum of, say, six to ten impulses per second should therefore be able to cover practically the full range of obtainable vascular constriction. At still higher rates signs of transmission failure occurred after only a few minutes of continuous stimulation. This failure at higher stimulation frequencies seemed to be predominantly due to an exhaustion of the transmitter release mechanism at the preganglionic nerve endings, though probably other factors were also involved. As regards the sympathetic control of the suprarenal medulla, Celander (1954) arrived at similar conclusions and Cannon *et al.* (1954) observed that the spikes recorded from a bundle of sympathetic fibres soon decreased in magnitude at higher stimulation rates, indicating a progressive failure of the fibres. The existence of such a transmission failure at stimulation rates above, say, ten impulses per second may indicate that normally the sympathetic nerve fibres only exceptionally exceed this discharge limit, the more so as the effector responses are then almost maximal. More direct evidence for such an assumption will be given later on (see 8).

In a similar investigation, Girling (1952a) studied the relationship between the stimulation frequency and the vasoconstrictor response in the ear of the rabbit when the cervical sympathetic chain was excited. A definitely maximal vasoconstrictor effect was obtained at a stimulation frequency of around twenty impulses per second, but there seemed to be little tendency to relatively more intense vasoconstrictor responses at the lower range of stimulation rates, as was observed by Folkow (1952). This might possibly be due to the fact that only a fraction of the constrictor fibres to the ear vessels are contained in the cervical sympathetic trunk, to judge from the findings of Feldberg (1926) and Douglas (1954). Owing to the convergence principle in the arrangement of the constrictor fibres, stimulation of only a fraction of the fibres will, at any given rate, expose the effector cells to a proportionally lower concentration of the mediator. The hyperbolic curve correlating the effector response to the stimulation rate might therefore be depressed and flattened to the right, as was illustrated in experiments on the nictitating membrane by Rosenblueth and Rioch