ANTIDROMIC ACTION. Part II. Stimulation of the peripheral nerves of the cat's hind foot. By J. N. LANGLEY.

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CONTENTS.

THE general conclusions arrived at in Part I(1) were that antidromic nerve impulses cause dilatation of the capillaries of the foot of the cat but not of the arteries from the iliac artery down to the branches given off by the digital arteries, and probably that antidromic impulses do not directly cause dilatation in the final arterial branches. It seemed that further light on the subject might be obtained by stimulating the several peripheral nerves.

It was found that stimulating the posterior roots of the 7th lumbar nerve after section of one of the branches of the plantar nerves, commonly caused pallor in the area which did not flush. Since stimulation of a plantar nerve branch caused similar pallor in the non-flushing region, experiments on the peripheral nerves afford a convenient method of determining the cause of the pallor.

From these points of view the experiments recorded in this Paper were undertaken. The cats were anæsthetised in the manner described in Part I and lay unbound on a warmed table.

1. *The effects produced by stimulating the peripheral nerves.*

The superficial branches of the plantar nerves were stimulated a little proximally of the pad. The anatomical course of these nerves has been described in Part I. It may be recalled that they are sensory only and that the branches are distributed as in Table I.

TABLE I.

Internal plantar	Medial branch to medial side of 2nd toe
,,	Central branch to inner side pad and adjoining sides of 2nd and 3rd toes
,,	Lateral branch to mid pad and adjoining sides of 3rd and 4th toes
External plantar	Medial branch to outside pad and adjoining sides of 4th and 5th toes
,,	Lateral branch to lateral side of 5th toe

We may give first the effect on secretion of sweat, since this is usually the most local. Each branch causes secretion in the anatomical area just given. When it runs to one side only of a toe, the secretion is never on the whole surface of the cushion. Sometimes it is strictly confined to one longitudinal half, but not infrequently a few drops occur 0·5 to 1 mm. over the mid line, and more frequently in the proximal part and the tip than in the mid region. Similar unilateral secretion occurs on stimulating each plantar digital nerve. In some cats, as is known, secretion is scanty. In these, secretion occurs either in part of the longitudinal half of the cushion, or in the whole of it only after repeated stimulation. Thus there is but a trifling overlap in the peripheral distribution of the secretory fibres of the plantar digital nerves, and as secretory activity decreases no overlap is observable. The overlap of secretion from side pad to mid pad and from mid pad to side pad varies but is not more than 2 mm.

The effect on the colour of the foot of the vaso-constrictor fibres of the superficial plantar nerves is usually overpowered by antidromic vaso-dilator impulses. The first stimulation may cause either pallor or flushing, and usually a weak first stimulation—one just felt on the tongue —causes pallor, and a strong stimulus causes flushing. If pallor is caused by the first strong stimulation it gives way to flushing as the stimulus is kept on, and after a few repetitions of the stimulus there is flushing only. Occasionally there is pallor in one part of the area anatomically supplied by the nerve branch and flushing in another part, but in all cases obvious flushing, and in most cases great flushing, is obtained either with the first or with later stimulations.

Whilst stimulating any one of the superficial plantar nerve branches will at some time or other cause flushing in the area of distribution of the branch as given in Table I, the flushing may be more extensive in the cushion of the toe than the distribution there given, and it may even occur on the whole of it, although the nerve can only be traced to one side. Similarly on stimulating any one plantar digital nerve, the flushing may be fairly strictly homolateral in the cushion, or spread to a part or the whole of the opposite side. The chief condition affecting the outspread from one side to the other has been mentioned in Part I, viz. previous antidromic vaso-dilation on the opposite side, *i.e.* the state of tone of the vessels at the extreme periphery. The effect is readily seen by successive stimulation of the several plantar branches. Thus if the superficial external plantar nerve is stimulated, the flushing on the 4th toe is usually on the lateral side only, but if it is stimulated some minutes after stimulation of the internal plantar (or of its lateral branch) the flushing spreads

more or less into the medial side of the 4th toe and may include the whole of it.

Variation of tone of peripheral vessels does not however account for another variation in the degree of outspread of flushing from one side of a cushion to the opposite side. We have seen in Part I that each toe is supplied with a digital artery which runs along one side of a toe and crosses under the tendon of the flexor brevis to supply the opposite side. We may then speak of one side as the proximal artery side, and the other as the distal artery side. The two sides are innervated by the superficial plantar nerves as in Table II.

TABLE II.

Distal artery side of 2nd toe	Int. pl. medial branch
Proximal „ „ 2nd „ } Distal „ „ 3rd „ {	„ central „
Proximal „ „ 3rd „ } Proximal „ „ 4th „ {	„ lateral „
Distal „ „ 4th „ } Proximal „ „ 5th „ {	Ext. pl. medial „
Distal „ „ 5th „	„ lateral „

When no plantar nerve has been stimulated, the usual effect of stimulating a branch which supplies the distal artery side of a toe is to cause flushing of the cushion fairly strictly confined to that side, and stimulating a branch which supplies the proximal artery side is to cause flushing spreading over the mid line chiefly at the proximal part and tip, but not extending to the whole of the opposite side. The part which does not flush as seen from the plantar surface is roughly an oval area (cp. Fig 1 *B*) and this becomes paler. It will be convenient to speak of this pale area as the "oval" area, though it is not usually curved on the dorsal surface.

After other nerves have been stimulated there is a variable degree of outspread not only from one side to the other, but in different parts of the cushion, and as I have said the whole of the cushion may flush when the nerve on either side is stimulated.

The customary greater outspread of flushing from proximal artery side to distal artery side cannot be due to dilatation of the proximal artery since the whole of the distal artery side does not flush. It might be due to a few nerve fibres from the proximal artery side crossing with the artery to the opposite side but I have not been able to trace such fibres, and if there were such, one would expect the middle of the opposite side to flush as much as the ends. In some cases, nerve stimulation on the proximal artery side causes secretion farther over the mid line in the area which flushes than does stimulation of nerve on the distal artery side,

suggesting a greater crossing of nerve fibres in the cushion itself, but I have not found this constant, and the chief causes of the greater outspread from flushing we are considering is I think the position of the veins.

In each cushion a small vein (efferent vein) can be seen starting $\frac{1}{3}$ to $\frac{1}{2}$ way from the tip, generally a little on the side of the distal artery. Its course is not along the mid line of the cushion, but to the side of the digit which has the distal part of the artery as in Fig. 1*A*. Leaving the cushion it joins a plantar venous network.

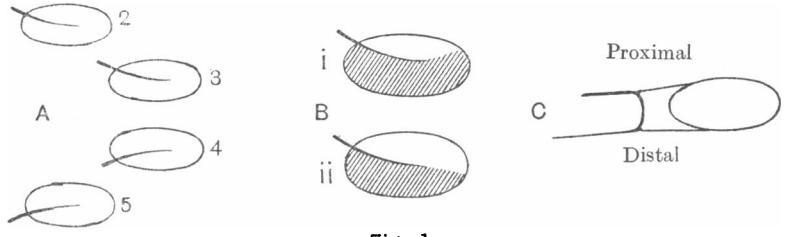


Fig 1

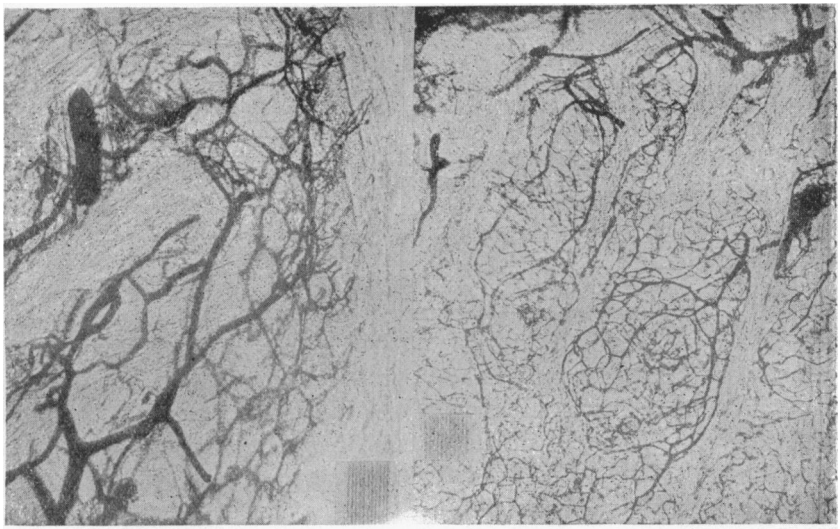
Fig. 1. *A*. Course of the plantar efferent vein from the dermal venous network in the several toes.

B. i. Common extent of flushing (shaded) from proximal artery side to distal artery side. ii. Extent occurring less commonly.

C. To illustrate a relatively greater decrease of blood on the opposite side to that which flushes, when the flushing is on the distal artery side than when it is on the proximal artery side (cp. p. 55).

On stimulating the nerve supplying the proximal artery side the flushing can as a rule be seen to be bounded by the vein as far as the vein is visible (cp. Fig. 1 *B*). Obviously if there were a network of capillaries or veins under the epidermis, flushing on the proximal artery side would cause increase of pressure in the network up to the efferent vein and the greater outspread of flushing from the proximal artery side to the distal than from the distal to the proximal would be accounted for. In order to determine whether a network of capillaries or veins exists, I had injections made by my laboratory assistant Mr Freeman. Fig. 2 *a* is a photograph of an oblique section through the epidermis and derma, so that the vessels in the derma have approximately the appearance they have in sections parallel with the surface. The capillaries of the papillæ end in a loop and there is only a slight capillary connexion beneath the epidermis. In the derma there is a close network of small veins which receive blood on the one hand from the papillæ and on the

other hand from the superficial part of the subcutaneous tissue of fat with sweat glands. In the fat lobules there is a very close network of capillaries, smaller than those of the papillæ (Fig. 2 *b*). In specimens injected with nitrate of silver and stained with hæmatoxylin I have not



(*a*) (*b*)

Fig. 2. (*a*) Oblique section of lower part of epidermis and of the derma, showing dermal venous network and capillaries of papillæ. (*b*) Two lobules of fat with sweat glands showing close network of capillaries, the superficial veins from these join the dermal venous network in the upper part of the figure. Magnification shown by the lines 10 μ apart.

found any indications of either a muscular coat in the venous plexus or of valves. The arrangement is essentially the same as that which has been described by Spalteholz(2) in the human skin. The existence of a dermal venous network with an asymmetric efferent vein accounts for the outspread of flushing being ordinarily greater from proximal artery to distal side, than in the contrary direction. Further, the more the tone of the vessels on the non-stimulated side is lessened the farther naturally the flushing will spread across, and so unilateral stimulation will cause bilateral flushing. But this I think implies that antidromic nerve impulses cause loss of tone in the dermal venous plexus as well as in the capillaries.

The histological results make it practically certain that antidromic

flushing in the foot is largely due to increased blood in the venous network. And this conclusion is in harmony with the prompt flushing produced by increased venous pressure and also with the slight flushing which (so far as I have found) occurs in the skin of the leg. In this the dermal venous plexus and the subcutaneous fat are comparatively little developed. Further, it is doubtful whether the degree of flushing which occurs can be accounted for by dilatation of the papillary capillaries plus the distension of the venous network it causes. It would seem that in the antidromic flushing of the foot there must also be either dilatation (loss of tone) of the venous network or distension of them by blood flowing from dilated capillaries of the subcutaneous tissue. In other words, that the antidromic vaso-dilation is not confined to the skin capillaries and I show in another paper that the sympathetic nerves can cause flushing in the foot by setting free metabolites in the sweat glands; thus on stimulating the plantar nerves the secretion has to be taken into account. Flushing and visible secretion are, however, independent changes. It is common to obtain flushing without secretion, and flushing is obtained, though it is usually lessened, after intravenous injection of 10–20 mgm. of atropine sulphate. Free secretion with slight flushing sometimes occurs towards the end of an experiment.

Cold causing local arterial contraction when combined with lower blood-pressure or with much loss of blood greatly reduces the effect of stimulating the plantar nerves. But flushing when established is apparently very little affected by cold, for in one experiment in which the posterior roots of the 7th lumbar nerve caused a brilliant flush, there was very little change on packing it round with ice though possibly the flush was a trace bluer. Dale and Richards(3) have pointed out that cold causes capillary congestion with arterial contraction.

Flushing in one part of the foot produced by stimulating a plantar nerve branch is accompanied normally by pallor in the rest of the foot, and the pallor is usually greater than that produced by stimulating the posterior roots of the 7th lumbar nerve after section of one of the plantar branches (cp. Part I). The pallor which occurs on the side of a toe opposite to a stimulated digital nerve has already been referred to. There are some other points to notice.

The degree of pallor varies greatly. In the course of an experiment the non-flushing toes may become dead white or there may be no certain change of tint. It is roughly proportional to the degree and area of flushing. Thus it is generally greater on stimulating the nerve branch which causes flushing of the mid pad than on stimulating either of the branches which

cause flushing of a side pad, and each of these causes more pallor than the branches which run to one side of a digit only.

On stimulating the digital nerve of one side, the pallor on the opposite side is generally greater when accompanying flushing of the distal artery side than when accompanying flushing of the proximal artery side. Taking the circulation from the point where the digital artery crosses to the opposite side of the toe (Fig. 1 *C*), dilatation on the distal artery side will take more blood from the branch to the cushion of the toe on the proximal artery side than dilatation on the proximal artery side will take from the branch to the cushion of the toe on the distal artery side. The nerve which causes flushing of the mid pad (cp. Table I) is the lateral branch of the internal plantar. Stimulation of this branch usually causes great pallor in the side pads, good pallor in the 2nd and 5th toes and appreciably less pallor in the "oval" areas of the 3rd and 4th toes.

In the 2nd and 5th toes the pallor begins and may be nearly confined to the sides facing the mid line of the foot, indicating that the other sides receive some blood from the saphenous arteries. Further, the 2nd toe not infrequently becomes paler than the 5th. Ligature of the digital artery and nerves of the 3rd or 4th toe does not prevent some blood passing to the cushion, for stimulation of the lateral plantar will then cause pallor in it.

The evidence that the pallor is a passive result of the flushing will be given in § 2, but a curious result indicating this may be mentioned here. Sometimes when the nerve on the proximal artery side is stimulated there is first flushing spreading over the mid line and leaving only an "oval" pale area, then there is free secretion on approximately the half of the cushion of the toe, and as this occurs the pale area on the opposite side becomes larger. This suggests that the fluid removed from the deep capillaries in secretion reduces the blood-pressure in the dermal venous network and that this reduction affects the vessels of the opposite side because they are passively dilated, but is insufficient to affect those of the same side which are dilated by antidromic action.

The deep external plantar nerve supplies the plantar muscles. As I have said (Part I, p. 433), its connexions with the superficial plantar nerves, and so with the pad and toes, are variable, and it commonly sends them no fibres visible on dissection. I mentioned one case in which it sent an obvious strand to the 4th digital nerve. In this case it caused free secretion, sometimes accompanied by pallor and sometimes by flushing in the half of the toe supplied by the digital nerve. In another case it caused moderate secretion also accompanied either by pallor or flushing in the medial half of the 5th toe. In the eight experiments made, it always caused distinct, and sometimes great, pallor in the medial part

of the foot and less pallor, and sometimes a doubtful pallor, in the lateral part of the foot. Usually the inner side pad and the 2nd toe were most affected.

Apart from these changes, the areas affected varied in different experiments and with successive stimuli. Sometimes the 3rd toe was markedly paler and not infrequently the anterior part of the mid pad, and posterior part of the cushions of the 3rd and 4th toes became paler than the rest of these regions.

If the stimulation is prolonged for a minute or more, the paler parts may recover some tint, and after the end of the stimulation there is generally more or less flushing of the whole foot. When flushing is produced in a part of the foot by stimulating a superficial plantar nerve, the flushed part pales much more slowly than the rest on stimulating the deep external plantar. Thus with decreased capillary tone, a considerable decrease of local blood-pressure has relatively slight effect on capillary diameter. In most of the experiments the motor nerves were not paralysed and a primary immediate pallor was caused by the contraction; except, however, for the prompt pallor, the results were the same when the cat was decerebrated and curarised.

Some pallor may be caused in a toe after section of its digital nerves, so that part of the pallor is probably due to the contraction of the deep metatarsal arteries. A part seems also to be due to dilatation of muscle vessels, but so far I have only made preliminary experiments on the question of antidromic action on muscle.

A point which deserves further investigation is that in the three experiments in which the deep external plantar was stimulated after giving ergotoxine there was no reversal of the effect on the foot. The effect was to abolish or nearly abolish the action of the nerve. The nerve still appeared to cause slight paling, but this was not quite certain and when one or two of the toes were made to flush by stimulating a superficial plantar nerve, the deep external plantar did not cause these to become pale. In one experiment, 20 mgms. of ergotoxine were injected into the jugular vein, and the effect was little if at all greater than with 3–5 mgms. Five mgms. (probably less) are sufficient to reverse the action of the sympathetic on the foot (cp. p. 60) so that the whole of the effect of the deep external plantar was in the metatarsal region. The results suggest that either there is no reversal in small arterial trunks, or that the effect of the reversal is counteracted by dilatation in the vessels of the muscles.

The *anterior tibial nerve*, as the deep external plantar, causes pallor; its effect is greatest on the 2nd toe, somewhat less on the 3rd and still

less on the 4th and 5th. I have found it to cause secretion in the medial half of the 2nd toe, possibly with more experiments slight secretion would be found over a more extensive area.

The *dorsal nerve of the foot, i.e.* the superficial peroneal and such filaments of the internal saphenous nerve as may run to it, usually has less decided and more variable effects. When first stimulated it usually causes slight pallor followed by slight flush, or pallor in the tips of the toes and in patches elsewhere on the pad and toes. After several stimulations, and sometimes on the first stimulation, it causes partial flushing or general flushing of varying degree, similar effects can be seen in the dorsal skin of the digits. On stimulating it I have observed slight secretion in the 3rd, 4th and 5th toes, and in a small part of the mid pad. The part which secretes most is not constant and secretion may occur in some parts only of the toes as in one-half, or in the middle. Repeated stimulation is required to determine the maximum area of secretion.

The internal and external saphenous nerves I have only stimulated in two experiments. In neither was there any distinct effect on the plantar surface though the internal saphenous nerve appeared to cause trifling pallor in the inner toes.

The posterior tibial and peroneal nerves. Except in two experiments, the motor nerves were not paralysed, so that the contraction caused immediate pallor. The results were however the same, apart from immediately pallor and less after-flush in two experiments in which the animals were decerebrated and curarised.

The posterior tibial nerve when first stimulated causes usually marked pallor of the pad and toes lasting 30 to 60 seconds and free secretion. The pallor then lessens and gives way to great reddening. If the stimulus is discontinued at the end of 30 to 60 seconds, reddening sets in almost at once. The flushing gradually lessens but often lasts a quarter of an hour. When the stimulus is repeated a number of times, the primary pallor decreases, and after a variable number of stimuli there is no pallor but a slow flush, very distinct but usually less than the late flush produced by the early stimuli.

The peroneal nerve causes pallor followed by flushing in the dorsal skin of the digital region. On the plantar surface it causes a variable degree of pallor. In a considerable number of cases the effect was slight and confined to the tips of the toes and to patches on the rest of the toes and the pad. In these the nerve was not stimulated at the beginning of the experiment and it is probable that the maximal effect was not obtained. Secretion was never obtained on the whole secretory surface,

but not infrequently there was a trifling secretion in isolated patches on one or more of the toes and on the pad. There was variable degree of after-flushing.

2. *The cause of the pallor accompanying antidromic flushing.*

I have so far assumed that the pallor in one part of the foot which accompanies antidromic flushing in another part is a passive pallor. This was not my first impression, for the degree of the pallor sometimes occurring strongly suggested reflex arterial contraction. Experiment, however, showed that pallor occurred when no reflex action was possible.

The most striking instance of pallor accompanying flushing is that produced by stimulating the superficial lateral internal plantar nerve a little proximally of the pad. This, besides causing intense pallor of the side pads (the most constant effect), commonly causes great pallor of the 2nd toe and as great or nearly as great pallor of the 5th toe. There is no detectable nervous connection between the stimulated nerve and the 2nd and 5th toes, so that there is no anatomical basis for supposing that it sends vaso-constrictor fibres to these digits, and as both its secretory and its antidromic fibres have a local action it is most unlikely that its vaso-constrictor fibres have a wide distribution.

Krogh(4) has recently supported the hypothesis that the nerve fibres form terminal networks—separate networks being formed by vaso-constrictor and afferent nerve fibres—and that stimulation of a small region at the periphery may cause either vaso-constriction or vaso-dilation in adjoining regions. The chief argument for this appears to be that a crystal of nitrate of silver placed on the web between two toes of a frog was found by Krogh, Harrup and Rehberg(5) sometimes to cause dilatation in the web of the adjoining toes. A crystal would for some time form a nearly saturated solution and in view of the close network of vessels in the frog's foot, a more reasonable explanation is, I think, that the solution passed either by the network or by diffusion from the veins in sufficient concentration to affect directly the vessels. Some time ago(6) I gave reasons for considering that peripheral sympathetic nerve networks if they occur at all can only be of very limited extent[1]. If a network existed and stimulation of a part of it caused impulses to spread to other regions, impulses would also spread out, and almost certainly spread farther, on stimulating any of the nerve branches

[1] The overlapping of fibres of adjoining nerve roots is of course a different matter. This is due to plexus formation either in the nerve trunks as in the sciatic or in pre-terminal branches as with the afferent fibres of the skin of the trunk.

running to and helping to form the network. Thus the overlap of the areas affected by adjoining peripheral branches would be great. In fact the overlapping of the effect of adjoining nerve branches is very small. I mentioned this in connexion with the innervation of the iris, the blood-vessels of the trunk and the hairs of the cat. It is somewhat greater in the stomach and intestine but is not extensive. It is small in the skin of the frog. We have seen in this paper how little overlapping there is in the secretory and vaso-dilator effect of adjoining digital nerves. The results do not show that small areas of networks do not exist, but they show that they must be extremely limited, and a slight outspread of stimulus on local peripheral nerve stimulation almost certainly occurs from axon reflexes, since the nerves divide at the periphery. It is then most improbable that the pallor which occurs in one part of the foot when another part flushes is due to the local dilatation of the vessels stimulating a part of a vaso-constrictor nerve network and so producing pallor elsewhere. I made, however, some direct experiments. (1) The web between the 2nd and 3rd toes was cut for two-thirds of the distance[1] from the free edge, the sciatic and internal saphenous nerves cut, and the lateral internal plantar branch stimulated. The stimulation still caused pallor of the 2nd toe. (2) 1 p.c. novocaine was injected into the lateral side of the 2nd toe; this abolished all secretory and antidromic effect on this toe (cp. p. 62). Stimulation of the lateral internal plantar nerve still caused paling of the 2nd toe with flushing in the usual regions. The change of tint in this form of experiment is however not very great since novocaine causes pallor in the injected region. Experiments were also made with ergotoxine which will be referred to later.

Section of the posterior roots of the lower lumbar and sacral nerves does not prevent the pallor, so that it is not a reflex from the central nervous system.

The pallor of the 2nd toe on stimulating the lateral internal plantar nerve is not prevented by section of its dorsal digital nerves, all the superficial plantar, the deep external plantar, the internal saphenous and the sciatic nerves.

If the pallor were an axon reflex it should be produced by electrical stimulation of the central ends of the nerves of the flushing region. But I have not found, after section of the sciatic and internal saphenous nerves, any certain pallor in the 2nd and 5th toes on stimulating the central ends of the plantar or dorsal digital nerves of the 3rd toe, or the central end of the artery supplying it.

Lastly I have made some experiments on the effect of injecting ergo-

[1] Section further than this cut the main vein of the digit.

toxine. As is well known Dale(7) has shown that ergotoxine paralyses vaso-constrictor fibres in the cat; he mentions an experiment in which after 5 mgms. of "cornutine," stimulation of the lumbar sympathetic, which previously caused marked pallor, caused slight but distinct flushing.

The results were quite decisive. Ergotoxine increases both the flushing and the pallor caused by stimulating the superficial plantar nerves. The pallor was rather less regularly increased than the flushing. In one experiment (body weight 2·5 kgs.) I injected into the jugular vein 10 mgms. of ergotoxine phosphate in four successive doses in the course of three-quarters of an hour and then 10 mgms. in one dose. Throughout, the superficial lateral internal plantar nerve caused brilliant flushing in the usual areas, great pallor of the side pads, good pallor of the 2nd toe, rather less of the 5th toe. At the end of the experiment the effect was a little slower in developing than at its best, but was more marked than it had been before ergotoxine was given.

It is then, I think, clear that the pallor accompanying antidromic vaso-dilation is passive and due to the dilated vessels withdrawing blood from the adjoining regions.

Dale found that a larger dose of ergotoxine was required to paralyse the motor nerves to the base of the bladder, and the pilomotor nerves than to paralyse the vaso-constrictor nerves. For my purpose there was no object in giving a minimal dose, but I may mention that the first dose of 1·5 mgms. increased the effect of the internal lateral plantar both on flushing and secretion, and in another experiment the same effect was obtained with a first dose of 2·7 mgms. (body weight 1·3 kgs.). Five mgms. of ergotoxine (the smallest dose tried) reversed the action of the lumbar sympathetic on the foot. The pilomotor fibres were paralysed by 20 mgms., the motor nerves to the bladder were not quite paralysed by this dose. The larger amounts were not however given at one time.

Passive pallor alone does not, however, always account for the relative pallor in different parts of the foot. Some difference of capillary tone is required for this. Since differences undoubtedly occur it is not, I think, worth while discussing the particular cases.

The maximum pallor is much greater than any that has been described as accompanying hyperæmia elsewhere. This I attribute to the comparatively long course of the deep metatarsal and digital arteries and to their comparatively few arterial anastomoses, so that copious blood flow through one branch causes a great decrease of blood flow in adjoining branches. In the skin the arterial anastomoses are many. It need hardly be mentioned that the flushing of the pad and toes has little or no affect on the blood-pressure of the large arteries since it does not appreciably reduce the total resistance.

The disappearance of blood from the superficial vessels which causes the pallor might be produced in one of two ways, or by a combination of these, (*a*) the decrease of arterial blood-pressure might lead to a decrease of capillary diameter, or (*b*) the decrease of arterial diameter might prevent the corpuscles from passing through but not prevent plasma from passing, so that the corpuscles would be driven out of the capillaries and veins—a form of pallor which was said by Lister to occur sometimes in the frog's web.

On the whole the phenomena seem to me to require a shrinking of the capillaries as the blood-pressure is reduced for the following reasons:

(*a*) Complete pallor is commonly obtained by clamping the external iliac artery, and not infrequently by stimulating the lumbar sympathetic. It is possible that on clamping the iliac artery, the peripheral arteries contract sufficiently to stop the passage of corpuscles, but until this is shown its occurrence may be doubted. Further, if an artery contracts sufficiently to stop the passage of corpuscles, the corpuscles will rapidly block the artery, and it may be doubted whether in the intervening stage, plasma could pass in sufficient quantity to drive the corpuscles out of the capillaries and dermal venous network.

(*b*) The pallor progresses smoothly without any sudden change and, as I have said, it is sometimes slow and may take a minute to reach its maximum. With progressive decrease of arterial lumen, the stoppage of the corpuscles would be sudden and one would expect a more abrupt change than actually occurs.

(*c*) In the pallor accompanying antidromic flushing the small efferent vein of the cushion of the toe usually remains distinct. It hardly seems reasonable to suppose that the washing out would so often proceed to the extent of removing blood from the dermal venous network and yet leave corpuscles in the small efferent vein. The appearance suggests the continuance of blood flow though to a greatly restricted degree.

Whilst then in certain conditions it is inevitable that there should be some washing out of the corpuscles by a plasma stream, I think that the chief cause of pallor is the shrinking of the capillaries and dermal venous plexus in consequence of decrease of internal pressure.

In any case the experiments show that the volume of blood in the cat's foot is largely dependent on the local arterial blood-pressure. This is, of course, an old theory applied to a particular case, but it is not in agreement with the results obtained by Roy and Graham Brown(8) in the frog's web and other tissues, nor with those obtained by Krogh(9)

in the frog's web and tongue, and in striated muscles. According to these the diameter of capillaries and the volume of blood in them are practically independent of arterial blood-pressure in normal conditions.

Roy and Graham Brown found that the change in capillary diameter caused by increasing the external pressure was usually too slight to admit of measurement, but sometimes was 10–15 p.c. I found(10) at times definite though slight variations of diameter accompanying variations of arterial pressure. Krogh observed practically no change in the size of the capillaries of the web and tongue of the frog with varying arterial pressure, and he found(11) that normal arterial pressure was insufficient to open many of the capillaries of striated muscle. Krogh, however, noticed that capillaries are constantly varying in size, and that a dilated capillary yields readily to pressure so that there should be a variation in the diameter of some capillaries when the arterial pressure varies. The probability is that capillary tone varies greatly in different tissues. Each stage of tone may be regarded, not as a continued contraction but as being a different physical condition, such as has been shown to exist both in unstriated and striated muscle. Roy and Graham Brown argued that the elasticity of capillaries must vary in different degrees of contraction.

3. *Notes on the action of drugs.*

Novocaine has been found to paralyse afferent nerves before the motor nerves of skeletal muscle. It seemed then possible that the antidromic vaso-dilator fibres of the plantar nerves might be paralysed before the efferent sympathetic fibres. The injection of 0·1 to 0·2 c.c. of 0·5 to 1 p.c. novocaine under the plantar surface of a digit about the level of the 2nd phalanx rapidly prevents stimulation of the plantar nerves proximally of the pad from causing flushing of the cushion of the injected toe. The rest of the innervated area flushes. The sympathetic secretory and vaso-constrictor fibres are also paralysed. To observe the effect on vaso-constrictor fibres a plantar nerve branch which does not supply the pad should be taken. The duration of the paralysis depends naturally upon the amount of novocaine injected and its concentration. With the amount given above the paralysis lasts 10 to 30 minutes. In recovery I have not found any certain difference in the time at which flushing and secretion begins. If there is any differential action it can, I think, only be slight. A similar amount of novocaine injected into the mid pad prevents the posterior roots of the 7th lumbar nerve from causing flushing in the mid pad, but not in the side pads or toes. If, however, the injection is deep in the mid pad, the underlying plantar nerve branch is affected, and the adjoining halves (approximately) of the 3rd and 4th toes do not flush on stimulating the posterior roots. The injection causes local pallor during the paralysis, apparently by arterial constriction.

Nicotine. An intravenous injection of 20 mgms. of nicotine does not prevent the posterior roots from causing flushing. The flushing is however

decreased. The decrease may be attributed to lowered blood-pressure in consequence of paralysis of the peripheral ganglia.

Curari. As found by most observers an amount of curari sufficient to paralyse the motor nerves of skeletal muscle has little or no effect on antidromic flushing. If sufficient is given to paralyse the peripheral ganglia and so cause a great fall of blood-pressure, the antidromic effect is much reduced.

Atropine. Ostroumoff found that atropine did not prevent the sciatic nerve from causing a rise of temperature in curarised dogs. As the rise of temperature is mainly due to antidromic action, the result is fair evidence that neither the atropine nor the curari given prevented antidromic action. Reid Hunt in plethysmograph experiments found that atropine did not prevent antidromic increase of volume of the hind limb. And intravenous injection of 10 mgms. atropine sulphate does not prevent the lower lumbar posterior roots from causing flushing in the cat's foot. In two experiments there appeared to be a slight decrease in effect, but as the blood-pressure was not taken, the decrease may have been due to fall of blood-pressure. Atropine, however, does affect the result of stimulating the superficial plantar nerves, favouring the occurrence of primary pallor, a result I deal with in another paper.

Acetyl-choline. Dale and Richards (3, p. 135) showed that intravenous injection of ·001 mgm. of acetyl-choline caused for a short time flushing of the pads of the cat's foot. I made one experiment, injecting into the mid pad 0·1 c.c. of a 0·1 p.c. alcoholic solution. The injection caused free secretion and considerable flushing in the mid pad. Stimulation of the 7th L.-posterior roots increased the flushing slightly but distinctly. The action of ergotoxine I have mentioned earlier (p. 60).

These results suggest that only drugs which abolish nerve excitability prevent antidromic vaso-dilation; the effect of other drugs depending on their effect on blood-pressure.

4. *Theories of antidromic action.*

The conclusions arrived at in Part I were that antidromic vaso-dilation is produced either by a special kind of afferent fibre ending in the capillaries or by metabolites set free in cells by impulses passing down afferent nerve fibres. These conclusions are, I think, strengthened by the results given in this paper, and they tend in addition to show that the capillaries affected in the foot are not confined to those of the skin but include those of the subcutaneous tissue and probably also the dermal venous network. The theory of action by metabolites is that

which appeals to me most. I have made some experiments on the local injection of blood from flushed areas and of skin extracts, but so far with varying results. Whilst the final decision must rest on further experiments, it will clear the ground to consider briefly the theories which have been put forward and the facts on which they are based.

The history begins with the early observation of Schiff that section of the nerve roots supplying a limb caused a rise of temperature in the limb. The method was that introduced by Cl. Bernard to show the presence of vaso-constrictor fibres, and Schiff argued that there were direct vaso-constrictor fibres in the anterior roots of all the spinal nerves. The facts were disputed and the theory of direct fibres gradually discredited. The discovery by Goltz (1874) that crimping the sciatic nerve caused a rise of temperature in the hind limb was the origin of numerous observations on the question of the existence of vaso-dilator fibres in the sympathetic, and of direct vaso-dilator fibres in the spinal nerves. As is well known a new turn was given to the question by Stricker (1876) who found that stimulation, chiefly mechanical, of the posterior roots of the nerves of the hind limb caused a rise of temperature in it. The main result was confirmed by Bonuzzi, Bornezzi, Morat and Werziloff, and all attributed it to the presence of vaso-dilator fibres differing only from the known vaso-dilator fibres in that they left the spinal cord in the posterior roots and ran direct in the spinal nerves. Morat(12), besides observing that visible flushing in the foot could be obtained by ordinary electrical stimulation of posterior roots, stated that flushing was obtained 8–10 and 15 days after their section. In the fuller account published a little later(13) he only mentioned dilatation on stimulating the posterior roots as being obtained after degeneration of the anterior roots, so that it was doubtful on what experiments the earlier statement was based. He considered, however, that the vaso-dilator fibres had their trophic centre in the spinal ganglia, but otherwise were like other vaso-dilator fibres. Subsequently(14) finding that the vaso-dilator effect eventually disappeared after section of the posterior roots, Morat reverted to the theory that the trophic centre was in the spinal cord.

Although Stricker's results, in their main features, received confirmation, the theory that the posterior roots contained vaso-dilator fibres was not widely accepted, partly because most observers had described certain conditions as being necessary which were not necessary in the recognised vaso-dilator fibres, but chiefly because the theory was irreconcilable with the Bell-Magendie law, and absence of degeneration

in the peripheral ends of cut posterior roots had been confirmed by several recent observers. This absence of degeneration I had also found, and in consequence in giving an account of the sympathetic system I said(15) that the effect could not be caused by fibres arising from the spinal cord, and I was inclined to believe that the effects described were not due to fibres in the spinal nerve roots. Later the way to reconcile the results occurred to me, viz. by impulses passing backwards along the afferent fibres after the manner of that in the axon reflexes which I had found in sympathetic fibres. The protracted rise of temperature which had been described in the muscles led me to believe that the effect was due to metabolites set free in muscle spindles, the metabolites causing vascular dilatation. Bayliss(16), using the plethysmograph method, showed that both electrical and mechanical stimulation of the posterior roots caused marked increase of volume of the limb of the dog and he attributed the vaso-dilator action, as previous observers had done, to efferent nerve fibres. I communicated my views to him through the Head of the Laboratory (Prof. Starling) and suggested stimulation and histological examination of the posterior roots after they had been cut and allowed to degenerate. Bayliss's subsequent experiments(17) confirmed the theory of vaso-dilation by afferent fibres and he showed that various other conceivable theories were not tenable. He found, however, that stimulation of the posterior roots caused a considerable dilatation of the foot and a very small dilatation in the leg after the skin had been removed and the foot cut off. In consequence he considered that the effect was almost entirely in the skin and that it was probably due to the endings of the afferent fibres in the arteries acting both as motor and sensory organs. The question of the degree of dilatation in muscle can hardly be considered as settled, for only one experiment was made, and removal of the skin would probably interfere with the circulation in the muscle. In the foot there is muscle, fat and gland tissue as well as skin and as mentioned above there is evidence that the dilatation is not confined to the skin.

N. Bruce(18), following up some results obtained by Spiess, observed that oil of mustard locally applied ceased to cause dilatation of the conjunctival vessels after degeneration of the conjunctival nerves. He concluded that the normal dilatation caused by oil of mustard was due to stimulation in the epithelium of the endings of nerve fibres which divided and sent one branch to an artery, *i.e.* the dilatation was held to be produced by a peripheral axon reflex. There are several possibilities as to the action of oil of mustard. It might affect the deeper tissues as

well as the epithelium, and set free metabolites partly by direct action and partly by stimulating sensory nerves. The less action after nerve degeneration might be due to the absence of nerves to stimulate or to a decrease in the responsiveness of the tissue.

Bardy(19) confirmed in the main Bruce's results, though he did not find a complete absence of hyperæmia on applying oil of mustard after degeneration of the sensory nerves. He modified Bruce's theory by interpolating a sympathetic nerve cell in the centrifugal part of the axon reflex. This theory I consider untenable. It is based on the action of nicotine. Bardy found that repeated local instillation of 2 p.c. nicotine, after partial local anæsthesia, greatly reduced the effect of the oil of mustard and paralysed the vaso-constrictor effect of the cervical sympathetic on the nictitating membrane. The repeated application of 2 p.c. nicotine would annul the conductivity of the sensory fibres, and the condition would be similar to that produced by cocaine. The paralysis of the cervical sympathetic would be caused either by the abolition of the conductivity of the vaso-constrictor fibres by nicotine directly applied, or to the absorbed nicotine paralysing the nerve cells of the superior cervical ganglion. The other result on which Bardy relied was that intravenous injection of 60 mgms. of nicotine abolished the hyperæmic effect of oil of mustard. This is the natural result of the great reduction of blood-pressure caused by a large dose of nicotine. In fact, Bardy notes that there was a similar reduction in the effect of oil of mustard on ligaturing the common carotid, a procedure which causes less local fall of blood-pressure than that caused by the injected nicotine.

Gaskell(20), who took Bayliss's experiments to show that antidromic action was solely in the skin, suggested that the sensory nerves might cause the formation of acid metabolites in the epidermis and that the vaso-dilation was due to the action of these. Ebbeke(21) investigated the effect of mechanical stimulation on the blood vessels—chiefly in the skin. The red stripe which is produced by rather strong stroking he considered was a capillary dilatation produced by metabolites of the epidermic cells, and he suggested that antidromic action might also be of the same nature.

The effect of the posterior roots on the vessels of the frog's web is still obscure, for not all observers find positive effects, and there are differences in the accounts of those who do find them. But according to Doi(22) the arteries and capillaries of the web, and according to Krogh, Harrup and Rehberg, the arteries and some of the capillaries dilate on stimulating the posterior roots. The observations are perhaps somewhat in

favour of a direct action on the arteries, but it is obvious that as the arteries are practically in the same plane as the capillaries, metabolites might affect both.

Krogh, Harrup and Rehberg from the persistence of local reactions in arteries and capillaries in the web of the frog after excision of ganglia and section of the sciatic adopt tentatively the view that a certain number of nerve fibres are kept alive after nerve section by peripheral nerve cells. In view of the histological evidence of degeneration obtained by Euglein in the ear of the rabbit and by myself in the sartorius muscle of the frog and in view of the absence of recognisable nerve cells in the periphery, it is I think more probable that the persistent reactions they found were either due to conduction from cell to cell in the vessels or to aberrant nerve cells. I once found a small group of nerve cells of the type of sympathetic cells in the upper part of a frog's sciatic nerve.

Finally I may say a word or two on the mode of reaction of the capillaries. The theory that their contraction and expansion is due to a variation of tonic contraction of branched cells (Rouget's cells) surrounding them has not, I think, at present any satisfactory basis. In the cat's foot, and in such other mammalian tissues as I have examined, the cells in connexion with the capillaries seem to me indistinguishable from the immediately adjoining connective tissue cells, and it is rare to find one which has the appearance of surrounding the capillary with its processes. It is not claimed that Rouget cells form more than a most imperfect coat to the capillary. If then, the tone resided in these cells, there would be in the more or less tonic normal state, a series of bulgings of the distensible epithelioid coat whenever the internal pressure was greater than the external. The main arguments for the theory are the improbability of the epithelioid wall having contractile power, and that in a few cases in the frog the capillaries have been found to contract earlier and more strongly in the region of an external cell. On the other hand it may be said that there is no improbability in the thin epithelioid wall shrinking or expanding with variations of surface tension such as can be caused by minute amounts of chemical bodies, nor in each change of surface tension involving a different state of distensibility and as regards the localised contraction Roy and Graham Brown (8) definitely state that the capillary tube may expand and contract as a whole.

Summary.

The effects on the colour of the pad and toes of the foot of the cat produced by stimulating the several nerves are given. The chief results as regards antidromic action are:

The superficial plantar nerves, notwithstanding the presence in them of sympathetic vaso-constrictor fibres, nearly always cause marked

flushing in the pad and toes on strong or repeated stimulation. Each plantar digital nerve causes secretion and flushing more or less confined to its own half of the cushion of the toe.

Stimulation of the digital nerve on the side of the toe having the proximal part of the artery does not cause flushing on the whole of the opposite side of the toe although this is supplied with blood from a distal branch of the artery. This confirms the view that antidromic impulses do not cause dilatation of small arterial trunks.

The secretion obtained by stimulating a plantar digital nerve never spreads more than about a millimetre into the opposite side of the cushion of the toe.

The flushing may be similarly restricted. The degree to which it spreads to the opposite side depends on two factors. The most important is the degree of tone in the vessels of the opposite side. If this has been reduced by antidromic action, the whole of the opposite side of the toe may flush.

The other factor is the position of the afferent vein of the dermal venous plexus; this is placed on the side of the toe which has the distal artery, thus the dilatation spreads farther from proximal to distal artery side than in the reverse direction.

On stimulating one of the superficial plantar nerves, all parts of the pad and toes which do not flush become paler. The pallor is not due to outspread of stimuli by a nerve network or to an axon reflex—amongst other reasons because, both flushing and pallor are more marked after paralysis of the vaso-constrictor fibres by ergotoxine; thus local arterial pressure in the foot has a great effect on capillary diameter.

The deep external plantar nerve ordinarily causes pallor of the foot by an action in the metatarsal region; this is not reversed by 20 mgms. of ergotoxine phosphate.

The successive stages of the theories of the mode of production of vaso-dilation by the lumbar nerves are reviewed and the evidence which the facts afford of the mode of production is discussed.

Conclusions.

The flushing caused by antidromic nerve impulses in the pad and toes of the cat is due to dilatation in the capillaries of the skin and in all probability to dilatation of the dermal venous network and the capillaries of the subcutaneous tissue. The three together may be spoken of as the capillary system.

Antidromic impulses do not cause dilatation of the arteries from the

aorta up to the final arterial branches and probably not directly in the final arterial branches.

Decrease of blood-pressure combined with decrease of blood supply causes this capillary system to become nearly empty of blood and the size of the vessels to decrease. The degree to which this effect is produced with a given lowering of blood supply depends on the tone of the capillary system. If the tone has been reduced by previous antidromic impulses, great decrease of local blood-pressure causes slight change only in the capillary system. This is in harmony with the observations of Krogh that in the frog a low blood-pressure is sufficient to dilate a capillary the tone of which has been reduced by mechanical stimulation.

The facts at present known are insufficient to decide whether the antidromic vaso-dilation is produced by afferent fibres ending in the capillaries or by afferent fibres setting free metabolites. The indirect evidence seems to me to be in favour of the latter theory. On the metabolic theory the varying tone of the capillaries may be regarded as produced by physical changes in the epithelioid wall leading to a change in diameter and in extensibility.

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