

FURTHER OBSERVATIONS ON THE VASO-MOTOR REFLEXES AND ASSOCIATED PHENOMENA.

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INTRODUCTION.

THE text-books give a meagre and, in our opinion, an unsatisfactory account of the vaso-motor reflexes. It is usually assumed that sensory nerves are pressor nerves, and that, when, for any reason, they act as depressor nerves, this is to be regarded as an exceptional "reversal" of their true and proper action. This, we consider, is an unjustifiable attitude to adopt. The older workers usually employed two or three different kinds of anæsthetics, and very commonly administered curare and even atropine in addition. It is now recognised by many investigators that the results obtained from experiments on animals under anæsthetics may differ in many respects from those on the unanæsthetised (pithed or decerebrate) subjects. Thus, Macdonald and Schlapp⁽¹⁾ have shown that the depressor effect of small doses of adrenaline is due to a pharmacodynamical influence of the anæsthetic. This has recently been confirmed by Vincent and Curtis⁽²⁾ who find also that the shape of the splanchnic blood-pressure curve depends on the presence or absence of certain anæsthetics. These considerations have prompted us to a re-investigation of the vaso-motor reflexes in the decerebrate animal.

Very little attention has been paid to blood-pressure reflexes brought about by stimulation of the terminals of sensory nerves. Previous to the work of Vincent and Cameron⁽³⁾, and Ogata and Vincent⁽⁴⁾ we can find no records of experiments bearing upon this point.

It is shown that in the normal animal the reflexes under discussion occur as a result of stimulation of the skin and other sensory surfaces, or from muscles, somatic or splanchnic. We have so far confined our investigations to large and small nerve trunks, the intestine, the skin, and skeletal muscles.

LITERATURE.

The literature of the subject up to 1919 will be found in the papers of Vincent and Cameron⁽³⁾, and of Ogata and Vincent⁽⁴⁾. These observers paid special attention to the effects of various anæsthetics when given singly or in combination. They found as others had found that in the usual laboratory animals when every allowance is made for the effect of anæsthetics, a general law can be enunciated to the effect that a strong stimulus will produce a reflex rise of blood-pressure while a weak one will give a fall. The frequency of stimulations has also an effect. With a frequent rate of stimulation a rise is obtained, and with an infrequent rate a fall (Gruber⁽⁵⁾). Cooling the nerve tends to produce vaso-dilator effects (Howell⁽⁶⁾ and others). Stimulations of a recently regenerated nerve tends to produce a reflex fall of pressure (Reid Hunt⁽⁷⁾). Vincent and Cameron were the first, it would appear, to investigate the result of stimulating nerve terminations, such as those in the skin, muscle and the intestine. They found that stimulation of the skin, kneading of muscle, and manipulation of the intestine all cause a fall of blood-pressure under certain conditions and a rise under other conditions. Ogata and Vincent thought that violent or extensive stimulations of the skin produce a rise while weaker stimulation causes a fall. As will be seen, we cannot confirm this.

METHODS.

(a) General.

All the experiments have been performed upon decerebrate cats. After the preliminary operations of inserting a tracheal tube and tying both carotid arteries (the animal being under ether anæsthesia) decerebration was performed by means of a small trephine hole in the side of the skull. This was enlarged by bone forceps. By this method less bleeding results than by a large trephine hole in the top of the skull and, moreover, a clear view of the plane of transection can be obtained when the fore part of the brain is removed. The brain stem was transected usually between the anterior and posterior corpora quadrigemina and the cranial cavity carefully packed with small swabs of cotton wool soaked in warm normal saline.

The blood-pressure was recorded in the usual way by means of a mercurial manometer connected with one of the carotid arteries.

In all cases at least one hour was allowed to elapse after decerebration before any stimulation in order to obviate the effects of ether anæsthesia.

In the majority of cases normal respiration was continued and a record taken.

(b) *Special.*

Nerve. Small skin nerves in the region of the thigh were dissected out and stimulated by an induced current at an approximately constant frequency. Small bundles of the sciatic nerve were also separated carefully from the main trunk and stimulated in a similar manner.

Intestine. Stimulation took the form of a kneading manipulation by the hands, care being taken to avoid sustained pressure and pulling on the mesentery.

Skin. Scratching of the skin was performed with blunt scalpels, and the stimulation was varied by gradation of the intensity and extensiveness of the stimulus. The intensity of the stimulus was increased by more vigorous scratching over the same area but was never sufficient to draw blood, and the extensiveness of the stimulus was varied by the employment of several scalpels over different areas at the same time. Various parts of the body surface were used, including arms, legs, thorax, abdomen and ears.

Muscle. The experiments were performed upon the gastrocnemii muscles. The tendo achillis was cut close to its insertion, and the muscle separated from the leg as far as its origin. The popliteal vein and the sciatic nerve were exposed in the popliteal space. It was thus possible to knead the muscle without stimulating adjacent structures. Kneading was performed in a manner comparable to that applied to the intestine.

RESULTS.

The nerves.

Variations in the strength and frequency of the current. Using the decerebrate animal we find that strong stimulation of the main trunk of the sciatic nerve gives a rise of blood-pressure, while a weak one will give a fall. These results are independent of alterations in the respiratory rhythm or depth, as was shown by a simultaneous record of the respiratory movements. We have also stimulated the sciatic nerve with the same strength of current, but with different rates of interruption of the primary circuit, and find that a rise is obtained with the rapidly interrupted stimuli, and a fall with interruptions of less frequency (Fig. 1). This result was first obtained by Gruber⁽⁵⁾ and confirmed by Vincent and Cameron⁽³⁾ and Ogata and Vincent⁽⁴⁾.

These experiments show then that the "strong and weak" and the

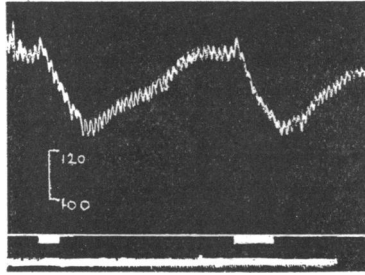


Fig. 1.

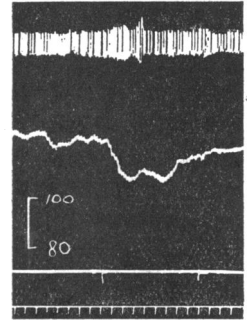


Fig. 2.

Fig. 1. Stimulation of main trunk of sciatic nerve. Strong stimulus. Frequency 4 per second. There are marked falls of pressure.

Fig. 2. Stimulation of small skin nerve. Secondary coil 7 cm. from the primary coil. The effect is a pure fall. Contrast Fig. 4.

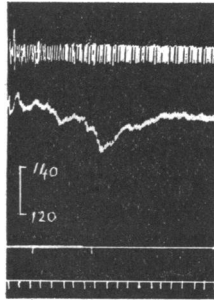


Fig. 3.

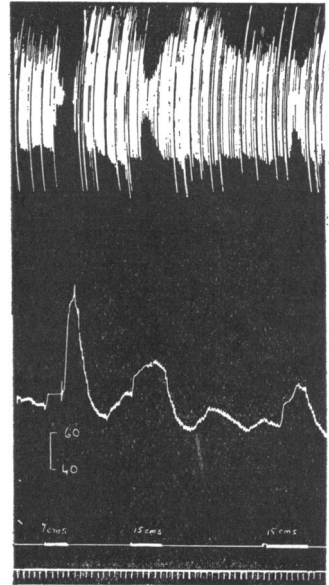


Fig. 4.

Fig. 3. Stimulation of small skin nerve. Secondary coil 15 cm. from the primary coil. Again a pure fall. Contrast Fig. 4.

Fig. 4. Stimulation of main trunk of the sciatic. Secondary coil at 7 cm., 15 cm., 15 cm. respectively from the primary coil. Same rapid frequency as in Figs. 2 and 3. Marked rises of pressure are now obtained instead of falls.

“frequent and infrequent” laws hold good even in an animal without any anæsthetic.

Variations in the size of the nerves stimulated. On several occasions falls of blood-pressure were obtained upon stimulating small skin nerves or small bundles of the sciatic nerve (Figs. 2 and 3), and when the same stimuli were applied to the sciatic nerve, rises of blood-pressure were produced (Fig. 4). Such results have not been obtained invariably, and this we attribute to the difficulty of securing such small nerves undamaged and of maintaining a constant E.M.F. in the secondary circuit of the apparatus used.

The intestine.

(A) *Stimulation of the intestines by kneading for 10 sec. with all the nerves intact.* In every case an initial rise of blood-pressure was recorded and the remainder of the results of each stimulation (consisting of either a secondary rise or a fall or both) depended upon (1) the amount of the exposure of the gut, (2) the period of exposure, and (3) the number of successively repeated stimulations.

1. We kneaded the gut whilst it was still in the abdominal cavity, and found that a marked secondary rise occurred invariably. The

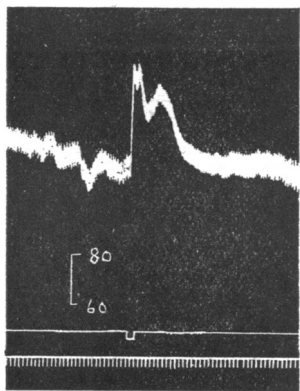


Fig. 5.

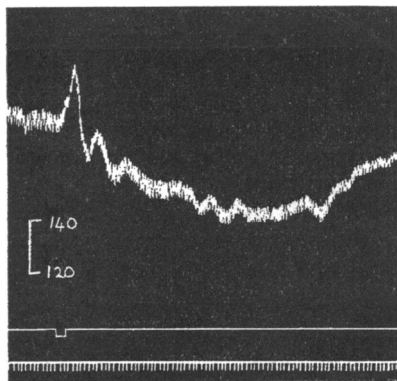


Fig. 6.

Fig. 5. Kneading intestine (whilst still in the abdominal cavity) through mid-line incision gives a rise without any fall. Note the marked secondary rise.

Fig. 6. Artificial respiration. Kneading of intestine applied after prolonged exposure. Marked after fall of pressure.

secondary rise took place shortly after the initial rise had begun to pass off (Fig. 5).

After the intestines had been taken out of the abdominal cavity and freely exposed, similar stimulations caused, in the great majority of cases, an after fall in addition to the initial rise and secondary rise.

2. Moreover, this after fall shows a definite increase in depth below the original level as the period of exposure lengthens (confirmatory of Vincent and Cameron) (Fig. 6). We found this to be so in all our experiments. Often the first stimulation after general exposure of the gut—provided it was applied *immediately* after general exposure—revealed only a small fall, and on a few occasions failed to produce any fall at all. But each successive stimulation thereafter increased the fall, and it was initiated by the second stimulation when the first failed to produce it (Fig. 7). We shall show that this apparent “failure to fall”

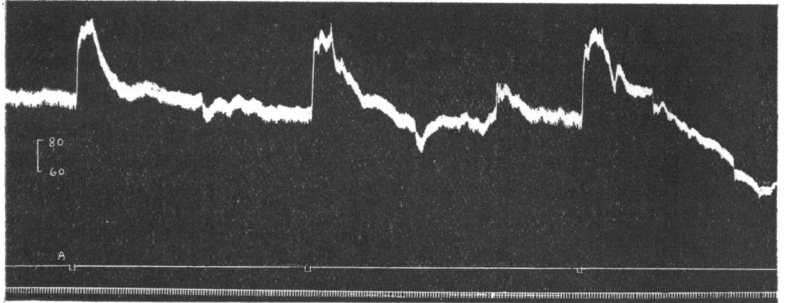


Fig. 7. Effects of successive kneadings of intestine. The first stimulus (A) was applied immediately after displacement of the intestines from the abdomen. Note the gradual production of an after fall and the descent of the position of the secondary rise on the decline of the initial rise.

in these instances is quite compatible with the conclusions we have reached.

Another effect was observed upon the secondary rise after general exposure of the gut. Just as the fall deepened with the length of exposure, so did the secondary rise appear lower and smaller on the decline following the initial rise, until finally it disappeared in the fall.

3. A further factor influencing the results was the effect of successive stimulations at short intervals. In all such series of experiments the initial rise was gradually diminished and the secondary rise disappeared, in a manner corresponding to that indicated above, and eventually was replaced by a distinct fall.

(B) *Stimulation of the intestines by the insertion of cotton wool plugs and balloons, all the nerves remaining intact.* We performed several

experiments in which we used as a stimulus a plug of cotton wool, which was passed backwards and forwards within a loop of small intestine at a rate of 2 excursions per sec. (approx.); we also incised a portion of gut longitudinally and rubbed the mucous membrane with a similar plug. A small balloon was passed into the lumen and inflated for periods of 10 sec. and 20 sec., and other experiments were performed in which the balloon was inflated at intervals of 1 per sec. Results obtained by these methods of stimulation were comparable with those obtained by kneading the gut, the only difference being quantitative.

(C) *Stimulation of the intestines by kneading for 10 sec. with the semi-lunar ganglia extirpated and the vagi cut.* Careful dissection having revealed a lesser splanchnic nerve in the cat, we took the precaution of removing the semi-lunar ganglia in order to eliminate all nervous influence. The vagi were cut in the neck.

As in previous experiments we found an initial rise a constant factor. The secondary rise was present in 83 p.c., and relatively to the initial rise was greater than in experiments under (A) and (B) (Fig. 8).

We also found that no after fall was produced, and that the secondary rise was increased by prolonged stimulation. A series of stimulations at short intervals resulted in the gradual disappearance of the secondary rise, but no fall could be obtained at the end of the series as in (A) 3.

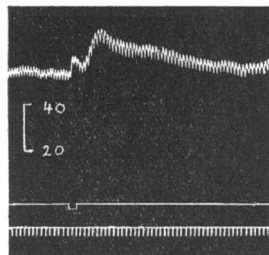


Fig. 8. Semi-lunar ganglia extirpated. Vagi cut. Abolition of the fall and production of very large secondary rise.

The skin.

The results we have obtained may be divided into two main categories:

- (a) Those in which a pressor response was elicited.
- (b) Those in which a depressor response was elicited.

(A) *The "pressor" group.* The rise of blood-pressure resulting from scratching the skin, although varying quantitatively in proportion to the extent of the area scratched and the intensity of the stimulus, showed a similar curve in all cases. The curve consisted of a moderately sharp rise whose maximum height persisted until the end of stimulation, and a decline to the original level composed of two parts, (1) a short quick fall commencing at the end of stimulation, and (2) a distinct—and sometimes pronounced—step inaugurating a slow and gradual return to

the mean blood-pressure (Fig. 9). The sharp rise and fall were either diminished or abolished by avoiding pressure and stimulation of the underlying and adjacent structures, and a delayed and gradual rise with rounded peak and slow decline was produced (Fig. 10).

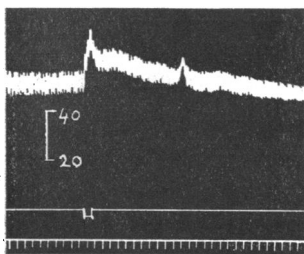


Fig. 9.

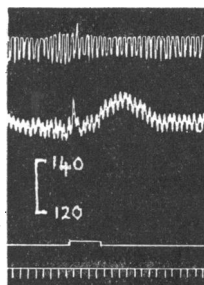


Fig. 10.

Fig. 9. Scratching of skin over abdomen. Note the prolonged decline to the mean level.

Fig. 10. Stimulation of skin of leg by scratching with blunt scalpel. Slight initial rise followed large secondary.

By repeatedly stimulating one area of skin the rise of blood-pressure was gradually diminished and finally abolished.

(B) *The "depressor" group.* The fall of blood-pressure was uncomplicated by any secondary effects shown on the curve. A rapid fall began at the beginning of stimulation, and continued until the end of it. The return to the original level began as soon as stimulation ceased, and the gradient was somewhat less than that of the decline (Fig. 11).

In several experiments in which a rise of blood-pressure was obtained, we noted an obvious tendency for a fall to take the place of the rise in the later stages of the experiments.

This was especially noticeable after repeated stimulation. After a period of rest the rise returned.

In one animal no effects upon the blood-pressure could be produced during the period of stimulation. Immediately following the cessation of stimulation, however, a considerable rise of blood-pressure occurred. Later in the experiment similar stimulation caused an initial fall of

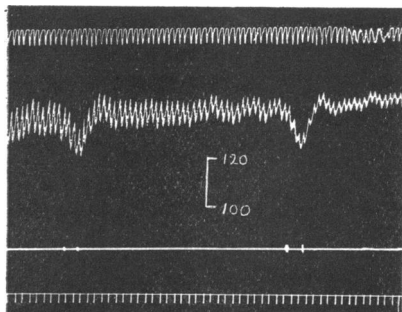


Fig. 11. Effect of scratching skin of right leg. Initial fall. No increase of respiration.

pressure, which commenced at the *beginning* of stimulation and was followed by a secondary rise. Still later, falls were registered without secondary rises. Administration of chloralose markedly increased the depth of the fall (Fig. 12).

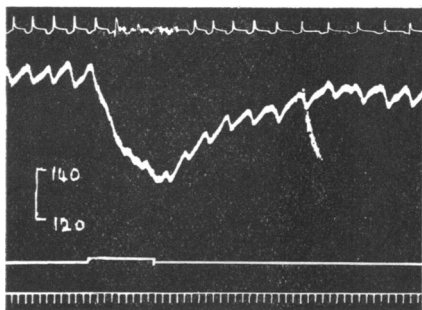


Fig. 12.

Fig. 12. 10 c.c. chloralose saturated at 40° C. administered intravenously 5 min. before application of stimulus. Extensive stimulation over both arms and legs. Very marked fall.

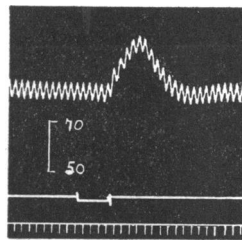


Fig. 13.

Fig. 13. Kneading of left gastrocnemius muscle. A pure rise.

The Muscles.

As in the case of the results obtained by stimulation of the skin, so with the kneading of the muscles two sets of responses have been observed.

(A) *The "pressor" group.* (1) *Stimulation of the intact muscle.* There was a noticeable tendency for the initial rise to be omitted in the curve, and in such instances the secondary rise was delayed, and the gradient was much smaller than that obtained in the intestine (Fig. 13). Also, the whole rise had a configuration similar to a secondary rise, *i.e.* a gradual incline and decline with a rounded apex. With very large muscles or groups of muscles the curve corresponded to the curve resulting from scratching a skin area with pressure.

(2) *Stimulation of the denervated muscle.* The sciatic, anterior crural, and obturator (anterior and posterior divisions) nerves were divided. The rise of blood-pressure due to stimulation of the muscle was increased.

(3) *Stimulation of the muscle with veins clamped.* The popliteal and femoral veins were clamped by means of artery clips. The rise was completely obliterated (Fig. 14), and returned when the clips were

removed. A similar experiment was performed on the denervated muscle with identical results.

(4) *Repeated stimulation of the intact muscle* resulted in a rapid decrease in the height of the rise and ultimate failure to give any response. Similar stimulation of the denervated muscle in the same animal required a much longer period of stimulation before the rise could be eliminated.

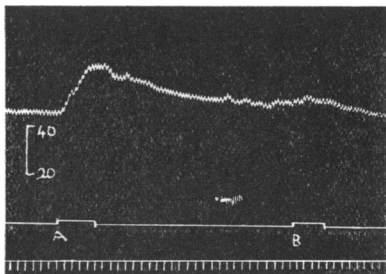


Fig. 14.

Fig. 14. Kneading of left gastrocnemius. *A*, with veins open. Note prolonged decline. *B*, with veins clamped. Blocking the venous return abolishes the rise.

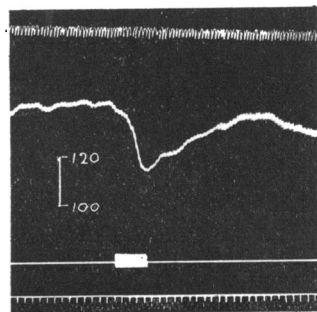


Fig. 15.

Fig. 15. Kneading of left gastrocnemius. A pure fall.

(B) *The "depressor" group.* (1) *Stimulation of the intact muscle.* The fall was rapid and recovery equally so (Fig. 15).

(2) *Stimulation of the denervated muscle.* This resulted in the abolition of the depressor response. In the same animal it was possible to obtain a marked fall with the left gastrocnemius intact, and no response with the right gastrocnemius denervated (Fig. 16).

(3) *Stimulation of the intact muscle with the veins clamped.* No change was effected beyond an exaggeration of the depth of the fall.

In two animals rises were obtained early in the experiment and falls later.

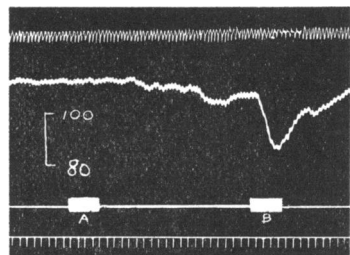


Fig. 16. First stimulation (*A*) applied to denervated right gastrocnemius muscle. Result, nil. Second stimulation (*B*) applied to intact left gastrocnemius muscle. Result, a fall.

Concomitant phenomena.

Respiration. We found that similar results were obtained under artificial respiration, as with normal respiration. Most of the results were obtained with animals breathing naturally. In some cases falls were accompanied by increased respiration and were probably augmented indirectly thereby (Vincent and Cameron⁽³⁾). This chiefly applied to the intestine and the skin; abnormal respiratory effects were rarely recorded in the series of muscle experiments. All experiments, in which increased respiration took place coincident with falls of blood-pressure, have been discarded.

Peristalsis. Kneading of the gut produced no increase of peristalsis, and no detectable alteration in the blood-pressure tracings was caused by peristaltic action. We thought that the passage of the plug of cotton wool in an antiperistaltic direction slightly exaggerated the effects of the stimulation upon the blood-pressure.

DISCUSSION OF THE RESULTS ON NERVE TERMINALS.

Examination of the results shows that three distinct effects upon the blood-pressure may be produced: an initial rise, a secondary rise, and a fall, and that these three effects may be in evidence in any one animal upon stimulation of either the intestine, or the skin, or the muscle.

We consider the initial rise to be due solely to the mechanical effect of the stimulation. The absolute constancy and similarity of its appearance under all conditions in the case of the gut (a very vascular area), combined with the facts that it is only present in the skin stimulation when pressure is exerted upon underlying structures, and in the muscle stimulation when large muscles or groups of muscles are used, warrant this assumption. However deftly the kneading of the gut is done, it is impossible to avoid exerting a little pressure, and the consequent expulsion of blood will be sufficient to explain the form of the initial rise and its constant presence. Herein the decerebrate animal appears to differ from the anæsthetised. Vincent and Cameron found that a marked fall of blood-pressure without an initial rise was almost invariably obtained after the intestines were completely exposed in the anæsthetised animal. Probably the mechanical effect was neutralised by the cause of the fall.

In the case of the fall of blood-pressure, the fact that it could never be obtained in any tissue after all nervous influence had been removed

has led us to the inevitable conclusion that it is due to a true vaso-motor reflex. Such cancellation cannot be effected by interference with the vascular system of the tissue, which, contrariwise, increases the fall. Moreover, where results are not masked by a mechanical effect (skin and muscle), the fall is seen to be a steep one which commences without any delay, and recovery is quick, thus typifying a nervous response rather than a chemical. Repeated stimulation never caused the fall to be abolished. This fall of blood-pressure cannot be ascribed to a reflex causing increased respiration, and hence a fall of blood-pressure due to a mechanical action upon the heart, since all the falls included in the results quoted above occurred without any change in respiration.

The secondary rise cannot be nervous in origin because it still persists after section of all the nerves. In fact, it is present under all conditions except three: (a) after prolonged exposure and manipulation (intestine, muscle), (b) after frequently repeated stimulations (intestine, skin, muscle) and (c) after clamping or ligation of the venous return (muscle). It is important to notice that after frequently repeated stimulations a period of rest results in the reappearance of the secondary rise upon stimulation, and that after removal of the clamps upon the veins a rise of blood-pressure is often to be observed. Obviously, this implies in the former case an exhaustion and a restoration of some influence, and, in the latter, a damming back and subsequent liberation of a similar influence. Series of similar experiments with denervated intestine and muscle gave identical results. We infer from this that the secondary rise is due to the liberation of some chemical substance having a pressor effect, in fact, an autacid pressor substance.

This inference is further corroborated by the form and incidence of the secondary rise in all the experiments. It is most in evidence at the beginning of an experiment when the tissues are fresh. Again, there is always a well-marked delay after stimulation before it appears. Its form is in marked contrast to the fall, the gradient of the incline being small and the return to the mean pressure being very slow and gradual, such as would be expected from the liberation of an autacid substance into the blood stream.

It therefore becomes clear that two mutually antagonistic influences are at work—the vaso-motor reflex causing a fall of blood-pressure, and an autacid substance having a pressor effect. Further examination of the results confirms this. Thus, in the case of the gut when the secondary rise is very marked—as before general exposure of the gut—no fall is recorded; when the secondary rise becomes smaller the fall appears and

increases proportionately to the decrease of the secondary rise. The first stimulation after exposure thus becomes the critical one, and we found that when the secondary rises prior to general exposure were extra large, there was no fall on application of the first stimulus, and when the secondary rises were small prior to general exposure, that there were falls afterwards. Our conclusion that the influence causing the secondary rise antagonised the vaso-motor reflex was also confirmed by the series of experiments when repeated stimulation of the intestine and skin caused the secondary rise to give place to a fall.

Thus, the vaso-motor effect and the chemical effect are mutually antagonistic, and the presence or absence of the secondary rise and the fall, or variation in their relative proportions, is determined by the factors affecting the condition of the tissue. Thus, when the precursor of the autacoid substance is exhausted by frequent stimulation the vaso-motor reflex is manifested; when the vaso-motor reflex is eliminated by removing all nervous control the autacoid substance has unhindered action, and, therefore, we should expect a larger secondary rise under such circumstances. This is what occurs; similarly, denervation of muscle causes the rise of blood-pressure to be greater because it removes the antagonism of the vaso-motor reflex.

Either of these influences may predominate, or, in rare instances, may exactly neutralise each other. Consequently, the individual cat responds to stimulation according to whichever influence is in the ascendancy. As our results demonstrate, there are two main groups of animals—those giving a pressor response, and those showing a depressor reaction.

The fact that the stimulation of nerve terminals causes a vaso-motor reflex of a depressor character is quite in harmony with our results obtained by stimulation of nerve trunk. The weak electrical stimulation of the main nerve producing a fall of blood-pressure is possibly equivalent to the most intensive stimulus we have applied to the terminals. Possibly in some instances there is a parallel between stimulation of the terminals and stimulation of a small nerve, which, we strongly suspect, gives a fall of blood-pressure because of the small number of fibres it contains. An adequate conception of the blood-pressure reflexes in the body cannot be obtained by simply stimulating the sciatic nerve with strong induced currents.

SUMMARY OF RESULTS.

Experiments have been performed upon decerebrate cats after all traces of anæsthetic have disappeared. Stimuli corresponding as nearly as possible to those occurring normally have been applied to the nerves, intestine, skin and muscles under varying conditions. We have found in the case of the nerve that the "strong and weak" and the "frequent and infrequent" laws hold good, and that there is a possibility of the size of the nerve affecting the nature of the response. The results of kneading the intestine show that the amount and period of exposure, the amount of stimulation, and denervation have well-defined effects.

Our conclusions are: that in intestinal, muscular and skin stimulation, two important and antagonistic factors are requisitioned to influence the general blood-pressure; a vaso-motor reflex of a depressor nature, and the liberation of an autacoid substance having a pressor action¹: that either may predominate, or that the two may neutralise each other: that after exposure, and after prolonged or repeated stimulation, the vaso-motor reflex is in the ascendancy owing to exhaustion of the autacoid pressor substance, and that where very vascular areas are concerned a mechanical effect may be superimposed: that the response to stimulation of various tissues in any one individual may be pressor or depressor according to the general condition and nutrition of the part stimulated and other factors not determined, and that the vaso-motor depressor effect is in harmony with the results obtained by stimulation of nerve trunks.

We beg to acknowledge our indebtedness to Mr M. Kremer for his assistance in conducting some of the preliminary experiments, and to the Ductless Gland Committee of the British Association for a grant to one of us (S. V.).

¹ *Note added in proof.* It is of some interest to recall that in 1903 Vincent and Sheen⁽⁸⁾ found very definite evidence of the presence of a pressor substance in fresh tissue extracts. It was not found in saline decoctions. We have recently repeated the experiments of Vincent and Sheen and are convinced that such pressor material is undoubtedly present in many fresh tissue extracts, and that it is frequently destroyed by moderate elevation of temperature. Whether this is identical with the autacoid substance described above we cannot yet be certain.

REFERENCES.

1. Macdonald and Schlapp. *This Journ.* 62. p. xii. 1926.
2. Vincent and Curtis. *Ibid.* 63. p. 151. 1927.
3. Vincent and Cameron. *Quart. Journ. of Exp. Physiol.* 11. p. 75. 1915.
4. Ogata and Vincent. *Journ. Comp. Neurol.* 30. p. 355. 1919.
5. Gruber. *Amer. Journ. Physiol.* 42. p. 214. 1907.
6. Howell, Budgett and Leonard. *This Journ.* 16. p. 298. 1894.
7. Reid Hunt. *Ibid.* 18. p. 381. 1895.
8. Vincent and Sheen. *Ibid.* 29. p. 242. 1903.