

Resumido por el autor, Swale Vincent.

Contribución al estudio de los reflejos vasomotores.

La estimulación de los nervios sensoriales en perros anestesiados con éter o cloroformo produce generalmente un aumento en los movimientos respiratorios, cuando la narcosis no es muy fuerte o cuando no se emplea el curare. Este aumento de movimientos respiratorios produce una disminución de la presión sanguínea y cuando son pronunciados no se puede obtener ningún reflejo presor, aun estimulando fuertemente. Con narcosis fuerte o compresión del cerebro no se produce la disminución de la presión sanguínea debida a esta causa. La interferencia mecánica con la circulación es la causa de esta disminución, puesto que se elimina abriendo el tórax. Este fenómeno complica seriamente los experimentos sobre los reflejos vasomotores. En los perros anestesiados con éter o cloroformo o con el cerebro comprimido, una débil estimulación de los nervios produce generalmente una disminución, y una fuerte estimulación un aumento en la presión sanguínea. La frecuencia de la estimulación ejerce efectos sobre el reflejo; cuando es rápida se obtiene un aumento, y con menor rapidez una disminución. Los nervios más voluminosos responden de un modo más marcado al estímulo que los menores. La estimulación de la piel, músculos e intestino origina generalmente una disminución en la presión sanguínea, pero si se estimula la piel de un modo violento y extenso se produce un aumento en dicha presión. Bajo la acción de la morfina y el curare, por el contrario, un aumento en la presión tiene lugar generalmente, aunque con la morfina la estimulación débil puede producir una disminución de la misma. La influencia de las glándulas endocrinas sobre los reflejos vasomotores no es clara (véase sin embargo Pearlman and Vincent "Endocrinology," en prensa). El cambio de reflejo en la estimulación de los nervios somáticos se produce principalmente por los efectos sobre los vasos sanguíneos del área esplácnica.

A CONTRIBUTION TO THE STUDY OF VASOMOTOR REFLEXES

D. OGATA AND SWALE VINCENT

Physiological Laboratory, University of Manitoba, Winnipeg, Canada

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I. INTRODUCTION

General blood-pressure is affected reflexly by central stimulation of various sensory nerves (reflex vasomotor action). This subject has been studied already by a number of authors. A complete list of the older investigations may be found in Tigerstedt's *Lehrbuch der Physiologie des Kreislaufs*,⁴¹ papers by Asher¹ and Bayliss² in *Ergebnisse der Physiologie*, and in Nagel's *Handbuch der Physiologie* (Hofmann¹¹). The history up to November, 1914, is given by Vincent and Cameron.⁴³ As to more recent important investigators of this problem, we may refer to Porter,²⁹⁻³⁴ Martin,²²⁻²⁶ Ranson,³⁵⁻³⁶ Gruber,^{8,9} and their respective co-workers, also to Domitrenko⁶ and Hunt.^{15,16}

Even among these recent investigators there seems to be considerable difference of opinion as to what may be regarded as the usual or normal response to afferent impulses. Thus Porter

and Quinby³⁴ say: "It is sometimes urged that in shock the blood-pressure falls instead of rising on stimulation of afferent nerves. This abnormal reaction was observed in several of our experiments." This statement clearly involves the assumption that a rise is the normal effect, though it is recognized that the fall is a not very unusual occurrence. Vincent and Cameron⁴³ seem to be of opinion that the usual effect of stimulating the central end of the cut sciatic nerve is a rise, and the fall due to a pure vasomotor reflex is rather rare. So also Hunt. On the other hand, Martin and Lacey²³ having observed regularly a definite drop in blood-pressure by weak stimulation and a rise by far more strong stimulation, became doubtful of the truth of the generally accepted doctrine that pressor responses are the normal results of sensory stimulation.

These differences of opinion must be due to some factor or factors other than the strength of stimulus. Besides the factors most usually considered, such as different modes of stimulation, different nerves, different conditions of the same nerve, different narcotics, drugs, etc., there are two important considerations recently brought forward which unmistakably affect the vasomotor reflexes or complicate the problem of their elucidation.

In 1915 Vincent and Cameron⁴³ called attention for the first time to a fall of blood-pressure caused by increased respiratory movements. They write: "While anaesthesia is fairly complete the effect of stimulating the central end of the cut sciatic nerve is a pure and distinct rise. As the effect of the anaesthetic begins to pass off, the effect of stimulation will be a rise of blood-pressure followed by a more or less pronounced fall. Respiratory movements will now be found to have been markedly increased, and the extent of the fall of pressure appears to be at any rate proportional to the violence of the respiratory activity."

Martin and Lacey²³ investigated the influence of the interruption of the primary current at widely varying rates, but failed to notice any effect, as also did Hunt¹⁴ in his earlier work. Only quite recently it was clearly pointed out by Gruber⁸ that with the same strength of stimulus, pressor and depressor results

were obtainable by varying the rate of stimulation from 1 to 20 stimuli per second. This was later incidentally confirmed by Hunt.¹⁶

Thus, for the investigation of the complicated problem of vasomotor reflexes, it became very necessary to investigate each possible factor separately. In this way only would one be able to answer correctly for the normal vasomotor response.

The present investigation was undertaken for the purpose of studying some of the factors separately, of confirming previous investigations, and of trying, if possible, to reconcile contradictory views as to the conditions which determine any particular vasomotor response.

We beg to acknowledge our indebtedness to Mr. John Carmichael for his valuable assistance in all our experiments.

2. THE INFLUENCE OF RESPIRATORY MOVEMENTS UPON BLOOD-PRESSURES

It is well known that the respiratory center can easily be affected by central stimulation of sensory nerves. Thus Howell¹³ writes in his Textbook of Physiology that "stimulation of any of the sensory nerves of the body may affect the rate or the amplitude of the respiratory movements." But no mention is made of the influence of these movements upon blood-pressure. The same applies to other text-books, except Starling's,³⁸ in which we find, "The increased respiratory movements will also aid the venous circulation and have a similar effect in increasing the systolic output," which would necessarily bring about a *rise* of blood-pressure. But, "A constant and immediate result of exaggerated respiratory movements is a fall of blood-pressure," and not a rise, as Vincent and Cameron pointed out. They found that "the extent of the fall of pressure appeared to be at any rate largely proportional to the violence of the respiratory activity," that the fall of blood-pressure was "brought about by performing rapid artificial respiration by compression of the thorax," that "deep voluntary breathing in the case of the human subject produced a regular and pronounced lowering of the blood-pressure," that "the more widely the thorax is opened

the more the fall of pressure tended to become replaced by a rise," and that the effect of artificial respiration was "a rise, and not a fall, when the animal was under curare," i.e., when a stop was put to the spontaneous respiratory movements. Thus the fall of blood-pressure as a result of increased respiratory movements seems to have been sufficiently established.

By the majority of previous observers curare was thought to be an indispensable drug in the study of the problem of vasomotor reflexes, with or without any consideration of its action on the vasomotor center itself. But we know that narcotics and other drugs are not always free from influence upon these reflexes, as pointed out by various previous investigators,^{14,29,3} and, therefore, in experimental work they should be reduced to as few as possible or altogether eliminated (Vincent and Cameron). The change in character of the respiratory movements, especially their increase, becomes thus an almost unavoidable complication in the study of vasomotor reflexes when curare is not used and the narcosis is not deep enough. If this complication be left out of consideration, erroneous conclusions may be reached.

Since the appearance of Vincent and Cameron's paper several writers have referred to the influence of the increased respiratory movements. Unfortunately, they are not in complete harmony with one another. Ranson and Billingsley^{35,36} say, "With stronger stimulation the greatly increased respiratory movements may no doubt play an important part in the drops in blood-pressure," but Gruber and Kretschmer⁹ write that their "experiments do not support Vincent and Cameron's theory that the fall in blood-pressure is brought about by movements of respiration which interfere with the heart's activity." This latter statement seems to deny definitely the respiratory rôle upon blood-pressure. Vincent and Cameron did not positively deny that there is a true vasomotor fall of blood-pressure under certain conditions as a result of central stimulation of afferent fibers. But they insisted, and rightly, too, that many apparent vasomotor falls are really due to increased respiratory movements. We shall see later that the fall of blood-pressure with weak stimuli is a commoner occurrence than Vincent and

Cameron were inclined to believe. At any rate, the matter is so important that we have repeated the experiments to test the effects of respiration on blood-pressure.

We have stimulated electrically the central stump of several cut nerve trunks (saphenous, tibial, peroneal, sciatic, ulnar, and median) with various strengths of stimulus.

When the narcosis (with ether or chloroform) was not deep enough, the respiratory movements were always increased by strong stimulation. The most frequent response of the blood-pressure to stimulation, e.g., of the sciatic nerve, may be illustrated by figure 1.

With weak stimulation there is practically no increase of respiratory movements either in amplitude or in frequency, and the blood-pressure is either a fall or a fall followed by a more or less marked rise. When stronger stimuli are applied, the respiratory movements increase either in amplitude or in frequency, or in both, and the blood-pressure rises, instead of falling, and is followed by a marked fall. The rise of blood-pressure increases usually in proportion to the development of the strength of stimulation.

In figure 2 the anesthesia was made much deeper with the same animal as in figure 1, and stimuli of several strengths were applied to the same nerve.

There is very little increase of respiratory movements on each stimulation, and the response of blood-pressure is also small in degree. The latter, as seen from the figure, is either a fall or a rise according to the strength of stimulation, and the marked fall after the rise which is observed in figure 1 simultaneously with the increased respiration cannot be seen. This suggests at once that the marked fall accompanied by remarkably increased respiratory movements might be ascribed, at any rate, mainly, to the influence of the latter movements caused by sensory stimulation. Moreover, under brain compression it is not very difficult to stop the respiratory movements entirely, and in this case only very strong stimulation will initiate spontaneous respiratory movements. Under these conditions a fall of blood-pressure of the same character as that observed with an in-

creased respiration never occurs. Thus it would not be unreasonable to assume that figure 2 shows real vasomotor reflexes, even though weak, not complicated by the increased respiratory movements, while figure 1 represents the vasomotor reflex masked by the effects of increased respiration.

It is often very difficult or almost impossible to obtain any rise of blood-pressure when the respiratory movements are very violent. In those cases a marked fall is the only result of central stimulation of afferent fibers.

How these increased respiratory movements affect the blood-pressure was very carefully investigated by Vincent and Cameron. After pointing out several possible causes, they came to the conclusion that this fall is due to direct mechanical interference with the heart's action and with the return of the blood to the heart.

In order to confirm this theory, we opened the thorax in the middle line as did Vincent and Cameron, and found that the falls disappeared. The contrast is clearly shown in figures 3 and 4.

In these two cases the same nerve of the same animal was stimulated with the same strength of stimulus, in figure 3 in the intact animal and in figure 4 with thorax open.

In addition to opening the thorax we cut both vagi, both phrenici, and as many intercostals as possible on both sides, without obtaining very different results from those obtained by merely opening the thorax.

In a very few cases a marked fall of a similar character to that due to the increased respiratory movements, was observed in animals with thorax wide open. It was, however, soon discovered that this fall was produced by compression of the inferior vena cava by the heart which became more freely movable than before through opening the thorax. The heart fell back upon the soft-walled vein, and thus diminished the flow of blood to the right heart.

But it is certainly true that by means of almost pure vasomotor reflex, i.e., without any or with very little increase of respiratory movements one can obtain a marked fall preceded by a rise, as shown in figure 5.

Therefore we do not conclude that such a fall of blood-pressure is always produced by increased respiratory movements. But the important point for us at present is the undoubted fact that increased respiratory movements can and do cause a fall of blood-pressure, and that this fall can be easily eliminated by opening the thorax sufficiently wide.

These observations, along with various others quoted above from the paper by Vincent and Cameron both on animals and on human subjects, confirm fully their statement as to the occurrence of a fall of blood-pressure brought about by increased respiratory movements, and probably explain the nature of this fall. We believe that the increased respiratory movements caused by sensory stimulation form a very important complication which has often led to misunderstanding of the true vasomotor reflexes.

Gruber and Kretschmer, as mentioned before, deny this respiratory effect upon blood-pressure. They used a slow rate of stimulation and the fall of blood-pressure was the usual effect. But the fall is generally thought to be a result of weaker stimulation, and they do not deny that the increased respiratory movements to a certain degree cause a fall of blood-pressure when the stimulus is strong enough as to produce them.

Our experiments were made on thirty-three dogs.

3. THE EFFECT OF THE STRENGTH OF THE STIMULUS UPON VASOMOTOR REFLEXES

After repeated experiments by numerous investigators, the generally accepted view as to the effect upon the vasomotor reflexes of different strengths of stimulus seems to coincide with Knoll's¹⁹ original statement, i.e., that a depressor effect is usually the result of a weak stimulation, while a pressor effect follows, as a rule, a stronger stimulation. Reid Hunt¹⁴ pointed out that weak stimulation was one of the methods of obtaining a reflex fall of blood-pressure, and Vincent and Cameron noticed the same fact.

Among more exhaustive investigations on this point we should refer to those by Porter,²⁹⁻³⁴ Martin,^{22-26,40} and their respective

co-workers. The former writer seems to regard a rise of blood-pressure as the normal vasomotor response, while the latter holds a different view. Martin and Lacey's²³ experiments were conducted on cats either under brain pithing, decerebration or brain compression, or under ether or urethane. The nerves stimulated were the sciatic, radial, median, ulnar, and saphenous. The results of their experiments were very definite. "In every one of the experiments the stimulation was repeated many times over a range of stimuli from the threshold value to three or four times the threshold. Well-marked drops of pressure followed all such stimulations," save in one exceptional case. Thresholds for pressor reflexes were much higher than those for depressor reflexes. Thus the experiments of these workers support Knoll's statement.

Our own experiments consisted in stimulating various nerves (sciatic, tibial, peroneal, saphenous, median, ulnar, and vagus) with induction shocks on dogs under ether, chloroform, and brain compression. As to the method, we have to mention that the different effects of weak and strong currents, respectively, were satisfactorily attained by means of sliding the secondary coil up to or away from the primary, but that on many occasions more than one battery was used to obtain a stronger stimulus. The rate of stimulation was 38 to 54 in a second.

The fall of blood-pressure due to the increased respiratory movements being taken into consideration, the main results of our experiments may be summarized as in the following table:

ANAESTHETICS	FALL WITH WEAK STIMULATION. RISE WITH STRONG STIMULATION	FALL WITH WEAK AND STRONG STIMULATION	RISE WAS ONLY RESULT OF STIMULATION
Ether.....	20	2	4
Chloroform.....	14	4	4
Brain compression.....	12	2	0
Total.....	46	8	8

The term 'fall' in the table comprises also a fall followed by a rise and 'rise' also a rise followed by a fall.

In forty-six cases out of sixty-two in total, weak stimulation produced a fall or a fall followed by a rise, and strong stimulation caused a rise or a rise followed by a fall. A typical response is shown in figure 6.

The animal was under ether and the thorax was very wide open in the middle line in order to eliminate the disturbance from increased respiratory movements. Figure 7 shows a similar response under chloroform.

In the remaining sixteen cases the response was either a fall or a rise through all strengths of stimulation which we used, and the different effects with weak and strong stimulation were not observable.

Thus it does not seem to us unreasonable to conclude that weak stimulation of the central stump of the cut nerve produces usually a fall of blood-pressure and a strong stimulation produces usually a rise.

From these conclusions it may naturally be understood that from the threshold of stimulation up to a certain point the fall of blood-pressure increases with the development of the strength of stimulus, and then the fall gradually decreases until a neutral point is reached, where the vasoconstriction and dilatation just counterbalance each other, and finally the rise appears, which increases usually with the increase of the strength of stimulus, but cannot continue very long, since powerful stimuli would elicit vigorous reflex movements of the animal and obscure the true vasomotor reactions unless indeed the animals were deeply under curare. As we have been unable so far to find any attempt by previous investigators except Stiles and Martin⁴⁰ to describe this rather peculiar course of vasomotor responses, we thought it worth while to emphasize it in this place (fig. 8).

In our experiments we have employed also stimuli of other kinds than electric induction shocks, namely, mechanical, thermal, and chemical. In this series thirty-eight out of sixty-seven stimulations were effective, and of these thirty-five caused a fall of blood-pressure and only three produced a rise. As the calibration of these stimuli was not so practicable as with induction shocks, we cannot draw any very positive conclusions, but we

are inclined to believe that a greater number of pressor responses could be obtained if we could improve the method of stimulation so that the sensory fibers might be stimulated more strongly.

It thus appears from our experiments that the depressor effect of weak stimuli is much more common than Vincent and Cameron thought, though these observers were careful not to deny its occurrence. Reid Hunt,¹⁶ in a recent paper, seems to have had the same difficulty that Vincent and Cameron encountered in obtaining the depressor effect of weak stimulation, which he ascribed to the different frequency of stimulation they employed.

The fact that a weak stimulation of a sensory nerve causes, as a rule, a reflex fall of blood-pressure and a strong stimulation a reflex rise, together with the statement of Bayliss³ that the orthodox effect due to the stimulation of the depressor nerve (nerve of Cyon⁵) can be converted into a rise by the action of strychnine, led us to inquire whether a pressor response could be obtained by strong stimulation of the depressor nerve. So far as our results inform us, neither such a strong current as would injure the nerve nor induction shocks up to eighty per second frequency could reverse the depressor response. The response to the stimulation after injection of strychnine was sometimes increased and sometimes decreased, but the reversal of the response did not appear in our experiments even with a dose which caused general convulsions on weak stimulation.

4. THE INFLUENCE OF THE FREQUENCY OF STIMULATION UPON VASOMOTOR REFLEXES

That the frequency of stimulation has a certain effect upon vasomotor reactions seems to have been known to the older investigators. In 1883 Kronecker and Nicolaides²⁰ noticed that the vasomotor centers could more easily be affected by changing the frequency of stimulation than by changing its strength. They write: "One can never attain such a strong vasoconstriction by increasing the intensity of the stimulating current as by increasing the frequency of the current of moderate intensity." We have not been able to consult the original paper of these writers.

From a reference in *Ergebnisse der Physiologie* by Asher,¹ it is not clear whether the stimulation was directly upon the nerve centers or reflexly through afferent nerves.

But the credit of pointing out clearly that the frequency of stimulation has an effect upon vasomotor reflexes must be ascribed to Gruber.⁸ This writer remarks: "That summation takes place with rapid rates of stimulation is undisputable, but it does not seem probable where the strength is more than 400 times threshold that the phenomenon of summation can explain the different effect obtained with these rates of 1 per two seconds and 20 per second interruptions." The similar effect of frequency of stimulation was afterward proved incidentally by Reid Hunt,¹⁶ who considers it convenient to use the infrequent rate of stimulus to obtain a reflex fall of blood-pressure.

Our experiments on this subject have been carried out on dogs with rates of stimuli of 1, 2, 5, 10, 20, 40, and 80 per second upon various nerves, under chloroform and curare or under brain compression. Though our results were not so conclusive as those obtained by Gruber (in fifteen out of forty stimulations similar results to his were obtained), still we do not hesitate to ascribe an important rôle to the frequency of stimulation. According to Martin's²² investigations, the intensity of stimulation in Z-units is directly proportional to that of the current in the primary circuit. We arranged the apparatus in such a way as to get a current of a certain strength and one ten times stronger as we desired. With the former current we obtained a fall by stimulating five times per second, and a distinct rise by stimulating ten times per second, while with the latter current we observed a fall with the rate of stimulus one per second and a rise with five per second stimulations. A selected record is shown in figure 9, where one and the same nerve was stimulated with the same intensity but with different frequency.

Much more remarkable were the rates of stimulation at which the maximum pressor response was reached.

	RATE OF STIMULI PER SECOND						
	1	2	5	10	20	40	80
Number of experiments whose maximum pressor response was reached at the rate of stimuli mentioned above.....	0	0	0	4	18	12	4

As is seen from the table, in 78.9 per cent the maximum response is reached between twenty to forty per second stimulation, and in one-third at the rate of forty per second. Beyond these points the effect increased only in four cases. This phenomenon may be seen also in figure 9.

Kronecker and Nicolaidēs²⁰ observed the fact that the effect of stimulation of the vasomotor centers increased with the frequency of stimuli up to twenty to thirty per second, but not beyond this point. Tur⁴² also pointed out that the effect of stimulation of the lingual nerve increased until the stimuli reached forty per second, beyond which, however, the effect diminished. These observations coincide fairly well with our own.

5. EFFECTS UPON VASOMOTOR REFLEXES OF STIMULATING NERVE TRUNKS OF DIFFERENT CATEGORIES (SENSORY, MOTOR, AND MIXED NERVES) AND OF DIFFERENT SIZES

According to the investigations of some authors, different nerves, apart altogether from the depressor nerve, respond differently to central stimulation. Hofmann,¹¹ in Nagel's Handbuch, says: "There are single nerves, which for the most part (glossopharyngeal) are depressor, and others which are exclusively (splanchnic) or preponderatingly (sciatic, facial, infra-orbital, cervical nerves) pressor." Vincent and Cameron studied the effect of stimulating the main trunk of the sciatic, as well as its common peroneal, lateral cutaneous, and purely muscular branches, the saphenous, median of axilla, the hypoglossal, the glossopharyngeal, the superior laryngeal, and the vagus. But the different nerves all produced similar or comparable results on the blood-pressure. They were strongly tempted to the hypothesis that an equivalent stimulation of a roughly equal number of afferent fibers will yield similar reflexes.

Our experiments also have led to the conclusion that there is no essential qualitative difference between the various nerves subjected to stimulation (sciatic, tibial, peroneal, median, ulnar). A possible exception may be made in the case of the saphenous. It may be that there is a greater tendency to a fall on stimulating this nerve than in the case of others. Whatever the nerve may be, whether a purely sensory nerve, as the saphenous; a mixed nerve, as the sciatic, peroneal, tibial, ulnar, or median, or a purely motor nerve, such as a muscular branch of the femoral, the course of response to weak and strong stimulation was in most cases a fall and a rise as already described in section 3.

A few examples are quoted in tabular form where a selected purely sensory nerve and a purely motor or a mixed nerve apparently of the same size were stimulated in turn under entirely similar conditions.

Sensory and motor nerves compared

ARRANGEMENTS OF STIMULATION	RIGHT SAPHEOUS	BRANCH OF RIGHT FEMORALIS
1 battery coil at 30 cm. 15 seconds...	-4 mm. Hg.	0, mm. Hg.
1 battery coil at 25 cm. 15 seconds...	-10 mm. Hg.	-1, +2 mm. Hg.
1 battery coil at 20 cm. 15 seconds...	-10, +2 mm. Hg.	-4, +2 mm. Hg.
1 battery coil at 15 cm. 15 seconds...	+4, -12 mm. Hg.	+4, 0 mm. Hg.
1 battery coil at 10 cm. 15 seconds...	+6, -14 mm. Hg.	+8, -2 mm. Hg.
1 battery coil at 5 cm. 15 seconds...	+16, -18 mm. Hg.	+14, -12 mm. Hg.
1 battery coil at 0 cm. 15 seconds...	+22, -14 mm. Hg.	+26, -14 mm. Hg.

(From experiment 47. Under brain compression.)

The sign '-' means a pure fall of blood-pressure, '+' a pure rise, and '-, +' or '+, -' a mixed response, namely, a fall followed by a rise or a rise followed by a fall, respectively.

Sensory and mixed nerves compared

ARRANGEMENTS OF STIMULATION	RIGHT SAPHEOUS	RIGHT PERONEAL
1 battery coil at 30 cm. 15 seconds...	0 mm. Hg.	0 mm. Hg.
1 battery coil at 25 cm. 15 seconds...	-6, 0 mm. Hg.	-1, 0 mm. Hg.
1 battery coil at 20 cm. 15 seconds...	+2, -10 mm. Hg.	-4, +4 mm. Hg.
1 battery coil at 15 cm. 15 seconds...	+6, -12 mm. Hg.	+2, -6 mm. Hg.
1 battery coil at 10 cm. 15 seconds...	+8, -12 mm. Hg.	+14, -10 mm. Hg.
1 battery coil at 5 cm. 15 seconds...	+22, -10 mm. Hg.	+20, -14 mm. Hg.
1 battery coil at 0 cm. 15 seconds...	+22, -12 mm. Hg.	+22, -20 mm. Hg.

(From experiment 47. Under brain compression.)

With the increase of the strength of stimulus the respiratory movements also increased, though not very markedly, and therefore some of the falls following the rise on stronger stimulation might have been more or less due to this complication. But in the main it seems that the purely sensory nerves have somewhat lower threshold than other kinds of nerves (fig. 10).

Whether this is due to a large number of afferent fibers contained in the sensory nerve than in those of the other kinds of the same size could only be decided by more numerous experiments and more elaborate methods than those we have employed, as, for example, the measurement of resistance of each nerve and more satisfactory methods of controlling the intensity of stimulation in each case.

In connection with the problem as to different kinds of nerves we have studied the influence of the size of the nerve upon vasomotor reflexes. The hypothesis of Vincent and Cameron is quoted at the beginning of this section. A similar problem was taken up also by Stiles and Martin,⁴⁰ who compared the effect of stimulating two nerve paths at the same time with that of exciting each by itself. They found that "stimulation of two afferent paths at the same time has often a more marked vasomotor effect than the stimulation of either path alone with an equivalent strength of current. The degree of summation was only moderate." This shows that the stimulation of a larger number of afferent fibers will produce often a more marked effect than that of few fibers.

We stimulated two nerves of the same category but of different sizes separately one after another under conditions as similar as possible, a different number of afferent fibers being assumed to be present in the nerves of different sizes.

The results may be represented as follows, page 369.

These few examples show that the results were not very conclusive. We can say only so far with some confidence that when the responses were in the same sense, i.e., when the fall or the rise was the result of corresponding equivalent stimulations, the reflex change of blood-pressure was on the whole more marked with the nerve of larger size than with those of smaller size (fig. 11).

Mixed nerves compared with each other

ARRANGEMENTS OF STIMULATION	RIGHT SCIATIC	RIGHT PERONEAL
1 battery coil at 30 cm. 15 seconds...	0 mm. Hg.	0 mm. Hg.
1 battery coil at 25 cm. 15 seconds...	-6, 4 mm. Hg.	-10, 0 mm. Hg.
1 battery coil at 20 cm. 15 seconds...	-14, 0 mm. Hg.	-8, 4 mm. Hg.
1 battery coil at 15 cm. 15 seconds...	12, -22 mm. Hg.	8, -6 mm. Hg.
1 battery coil at 10 cm. 15 seconds...	18, -16 mm. Hg.	12, -10 mm. Hg.
	RIGHT SCIATIC	RIGHT TIBIAL
1 battery coil at 25 cm. 15 seconds...	-2, 2 mm. Hg.	-2, 2 mm. Hg.
1 battery coil at 30 cm. 15 seconds...	-6, 4 mm. Hg.	-2, 0 mm. Hg.
1 battery coil at 15 cm. 15 seconds...	16, -18 mm. Hg.	10, -8 mm. Hg.
1 battery coil at 10 cm. 15 seconds...	22, -22 mm. Hg.	20, -16 mm. Hg.

(From experiment 47. Under brain compression.)

Sensory nerves compared with each other

ARRANGEMENTS OF STIMULATION	RIGHT SAPHENOUS	A BRANCH OF THE RIGHT SAPHENOUS
1 battery coil at 25 cm. 10 seconds...	0 mm. Hg.	0 mm. Hg.
1 battery coil at 20 cm. 10 seconds...	-6, 0 mm. Hg.	0 mm. Hg.
1 battery coil at 15 cm. 10 seconds...	-18, 0 mm. Hg.	-2, 0 mm. Hg.
1 battery coil at 10 cm. 10 seconds...	-22, 0 mm. Hg.	-8, 0 mm. Hg.
1 battery coil at 5 cm. 10 seconds...	-18, 0 mm. Hg.	+2, 0 mm. Hg.
1 battery coil at 0 cm. 10 seconds...	+4, 0 mm. Hg.	-4, 0 mm. Hg.
	RIGHT SAPHENOUS	A BRANCH OF THE RIGHT SAPHENOUS
1 battery coil at 25 cm. 10 seconds...	0 mm. Hg.	0 mm. Hg.
1 battery coil at 20 cm. 10 seconds...	-4, 0 mm. Hg.	0 mm. Hg.
1 battery coil at 15 cm. 10 seconds...	-8, 0 mm. Hg.	0 mm. Hg.
1 battery coil at 10 cm. 10 seconds...	-4, 0 mm. Hg.	-4, 0 mm. Hg.
1 battery coil at 5 cm. 10 seconds...	+4, 0 mm. Hg.	-4, 0 mm. Hg.
1 battery coil at 0 cm. 10 seconds...	+2, 0 mm. Hg.	-6, 0 mm. Hg.

(From experiment 48. Under brain compression.)

These conclusions coincide with the experience of Stiles and Martin and lend some support to the hypothesis of Vincent and Cameron.

It may not be amiss to add to these conclusions that in few cases when the stimuli were very strong the smaller nerve reacted more vigorously than the larger one, which phenomenon may perhaps be explained partly by different resistances of different-sized nerves to currents of similar strength.

Thus, so far as our experiments go, we are inclined to conclude provisionally that among nerves of different categories there are no essential qualitative differences of response, and the greater the number of afferent fibers stimulated, the more marked is the response of blood-pressure within a limited range of strength of stimulation.

6. VASOMOTOR REFLEXES FROM NERVE TERMINATIONS

Several investigators have stimulated the nerve terminals instead of the nerve trunk itself.

When we apply a stimulus to a surface such as the skin we should bear in mind that we may actually be stimulating either the end-organs alone or these structures as well as the nerve fibers, according to the mode of stimulation. Any physiologically appropriate stimulus, though mild, applied to the end-organs would give rise to more highly effective impulses than inappropriate ones. Thus the study of vasomotor reflexes in response to stimulation of the sense organ with its most appropriate stimulus is highly desirable. But even with other kinds of stimulation we may learn much that is valuable, because any stimulus which plays a part in our normal daily life comes usually through the end-organs on the outer or inner surface of the body, and not by way of exposed nerve trunks, as in the foregoing experiments.

The skin, the mucous membrane of the nose, muscles, the intestine, and other abdominal organs were employed frequently by previous investigators. We have selected the skin, muscles, and the intestine as representative of regions containing different modes of nerve endings. The stimuli used were mechanical (incision, scratching, pinching, kneading), thermal (hot or boiling water and cold water or lumps of ice), chemical (10 per cent solution of sulphuric acid), and electrical (induction shocks of various strengths). The animals (dogs) were under ether, chloroform, or brain compression.

The results of a first series are presented in the following tables:

Mechanical stimulation of the skin

ANESTHESIA	STIMULATED PORTION	MODE OF STIMULATION	REFLEX RESPONSE OF BLOOD-PRESSURE		
			No effect	Fall	Rise
Ether.....	L. inn. thigh	Pinching	0	2	0
	R. inn. thigh	Scratching	2	5	0
	R. inn. thigh	Incision	0	6	0
Chloroform.....	L. inn. thigh	Pinching	1	1	0
	R. inn. thigh	Scratching	2	3	0
	Abdomen				
	Over saphenous, ulnar, and sciatic nerves	Incision	3	4	0
Brain compression.....	L. inn. thigh	Scratching	0	2	0
	R. inn. thigh	Incision	0	3	0
Total.....			8	26	0

Thermal stimulation of the skin

Ether.....	L. inn. thigh	65°C.—boiling water	0	5	0
	L. inn. thigh	Ice—15°C. water	3	0	0
Chloroform.....	L. inn. thigh	Boiling water	2	3	0
	L. inn. thigh	Ice	0	1	0
Brain compression.....	L. inn. thigh	Boiling water	0	1	1
	L. inn. thigh	Ice	2	0	0
Total.....			7	10	1

Electrical stimulation of the skin

Ether.....	L. inn. thigh	Strong induction shocks	8	5	0
Chloroform.....	L. inn. thigh	Strong induction shocks	4	2	0
Brain compression..	L. inn. thigh	Strong induction shocks	4	2	0
Total.....			16	9	0

As is clear from the tables, almost every stimulation in this series, produced a reflex fall of blood-pressure, and no significant qualitative difference is observable either with different modes of stimulation or with different methods of anaesthesia or with different portions of the skin.

That this statement is applicable almost without any modification to the results of stimulation of muscles and intestine will immediately be understood from the tables on page 373.

Thus it is fairly clear that the stimulation of nerve terminals in the skin, muscles, and the intestine produces usually a reflex fall of blood-pressure, as was reported by Vincent and Cameron.

But the threshold of stimulation for the nerve-terminals in the skin is very much higher than that for the exposed nerve-trunks. Thus a stimulus which is to be reckoned a strong one for the exposed nerve-trunk is to be considered a weak one for the surface of this skin. This fact explains the previously described results. So far the effects have all been those of a weak stimulation, namely, a fall of the blood-pressure.

If, now, we take steps to secure a considerably greater amount of stimulation by simultaneous scratching of large areas in different regions, it is not difficult to satisfy oneself that the same general law applies for the nerve-terminals as for one exposed nerve-trunk. Thus, if we scratch a limited area with a moderate degree of vigor, we get a fall, while more violent application of the instruments to a large area, will give a rise (fig. 19).

In the last section we compared the effects of stimulating two nerves of the same category but of different sizes, and showed that the nerves of greater size usually surpass those of smaller size in their power of evoking vasomotor reflexes, and referred to Vincent and Cameron's hypothesis that the number of afferent nerve fibers is an important factor. In our stimulation of nerve endings, as a rule, we could only apply the stimulations to a small portion of the surface. Now the nerve fibers spread widely from the nerve trunk, and the stimulation of a nerve would be equivalent to the stimulation of the entire surface to which the nerve is distributed. In other words, the stimulation of a small portion, e.g., of the skin, corresponds to that of a

Mechanical stimulation of muscles

ANESTHESIA	STIMULATED MUSCLE	MODE OF STIMULATION	REFLEX CHANGE OF BLOOD-PRESSURE		
			No effect	Fall	Rise
Ether.....	R. add. mag.	Scratching	0	1	0
	R. sartor.	Scratching	0	2	0
	R. sartor.	Kneading	0	3	0
	L. semitend.	Scratching	3	0	0
Chloroform.....	R. add. mag. or 1 semitend.	Scratching	4	0	0
Total.....			7	15	0

Stimulation of the intestine

Ether.....	Small intestine	Kneading	0	3	0
	Interior surface of small intestine	Induction shocks	1	1	0
	Interior surface of small intestine	Pinching	0	1	0
	Interior surface of small intestine	Boiling water applied	1	1	0
	Small intestine	Distension	0	4	0
Chloroform.....	Small intestine	Kneading	0	2	1
Brain compression.....	Small intestine	Kneading	0	4	0
	Interior surface of small intestine	Induction shocks	0	1	2
	Interior surface of small intestine	Scratching	0	1	0
	Interior surface of small intestine	Boiling water applied	0	1	0
	Interior surface of small intestine	Ice piece applied	0	1	0
Total.....			2	20	3

small number of sensory nerve fibers. If the stimulation of a few fibers be the equivalent of a weak current, the fall of blood-pressure caused by stimulating the nerve terminals may be ascribed to the fact that we are stimulating only a few fibers.

Under morphia and curare a rise of blood-pressure is more easily obtained than a fall on stimulation of nerve-endings. But under morphia at any rate it is not difficult to obtain a rise with a strong stimulus and a fall with a weak one (fig. 19). Gaskell's⁷ discovery that in mammals "A large dose of curare will remove both the contraction of the muscle and the dilatation of its blood-vessels upon stimulation of the nerve," may possibly account for the greater tendency towards a rise when the animal is under this drug.

The paralysis of the vasodilator nerves by curare seems to necessitate the taking of certain precautions in interpretation of the results of experiments.

It seems probable that if it were found possible to increase very considerably the energy and extent of the stimulation in the cases of kneading of muscle and of the intestine, we should have to record a rise of pressure instead of the fall with which we are familiar.

7. THE INFLUENCE OF THE DUCTLESS GLANDS UPON VASOMOTOR REFLEXES

The extracts of some of the ductless glands (adrenal body, thyroid, and pituitary) have been alleged to affect the vasomotor irritability on one way or another.^{17, 43, 12, 27, 28} Since the results of the previous investigations are not conclusive, we thought it might be worth while to investigate the matter again. It is to be feared that our experiments are not much more convincing than those of previous workers on this subject.

The change of blood-pressure (augmentation or diminution) due to the injection of the extracts of these glands is an undesirable complication. In cases where an augmented blood-pressure is the result, as with adrenin and pituitrin, the decreased pressor reaction to the stimulation of a nerve may most properly be ascribed to the diminished response of the already more or

less contracted blood-vessels, or possibly to the additional contraction of the blood-vessels of the small areas other than those previously affected by the drug.

But the comparison of the vasomotor reflexes before and after the injection of adrenin ("adrenalin" Parke, Davis & Co.) seems to show that the pressor reflex is slightly decreased in the latter case. The results of Hoskins and Rowley were similar and more definite. The elimination of the function of the suprarenal glands by tying them off gave no clear results.*

The injection of thyroïdin (Parke, Davis & Co.) and the extirpation of both thyroid glands do not appear to have any distinct influence upon vasomotor reflexes.

Pituitrin (Parke, Davis & Co., surgical) showed scarcely any significant results.

All these experiments were performed on dogs under brain compression for the purpose of excluding any influences from the increased respiratory movements and those of anaesthetics and other drugs.

8. THE QUESTION AS TO WHICH VASCULAR AREAS ARE CONSTRICTED OR DILATED ON CENTRAL STIMULATION OF SOMATIC NERVES

The fall of blood-pressure produced by stimulation of the depressor nerve is effected chiefly by dilatation of the splanchnic area,²¹ though, as Bayliss has shown, the vessels of the limbs, head, and neck also partake in the relaxation. The latter writer showed also that the rise of blood-pressure on stimulation of the central stump of the splanchnic (?) nerve was, for the most part, due to the constriction in the splanchnic area. The reflex rise of blood-pressure due to the stimulation of the

*That is to say, when the nerves to the limb are intact. In the denervated limb there is a very important difference according to whether or no the adrenal bodies are eliminated. Mr. Pearlman and myself have recently found that when the central end of the sciatic is stimulated in such a way as to give a pressor response the intact limb follows passively the blood-pressure while the denervated limb constricts. After removal of the adrenal bodies the denervated limb also dilates. These results are explained more fully in a paper about to be published in 'Endocrinology.'—S. V.

sensory nerves of the skin, too, depends mainly on the constriction of the blood-vessels in the same area,³⁸ and Hofmann¹¹ writes: "The rise of blood-pressure on stimulation of sensory nerves is produced by the constriction of the blood-vessels of abdominal organs as in asphyxia. At the same time the blood-vessels of the brain, skin, and muscles dilate, as a rule, and an increase of the volume of limbs takes place." Thus the splanchnic area plays a principal part in the reflex changes of blood-pressure on stimulation of the somatic as well as the splanchnic nerves.

We have made some experiments on this point, and can confirm the above statements. The dogs had both vagi cut and were under morphia and curare or brain compression, and the sciatic or saphenous nerve was stimulated with induction shocks. The volume changes of the limbs (hind and fore) and of the abdominal organs (small intestine, kidney, and spleen) were recorded.

The rise of blood-pressure, when sufficiently high, was always accompanied by a remarkable diminution of the volumes of abdominal organs and a pronounced dilatation of limbs (fig. 18).

The pronounced fall of blood-pressure with weak stimulation when the animal was under brain compression was seen to be accompanied by a distinct increase of the volume of the intestine. Thus it appears clear that a reflex rise and fall of blood-pressure on stimulation of a somatic nerve (sciatic, saphenous) is brought about chiefly by constriction and dilatation of the blood-vessels in the splanchnic area.

9. SUMMARY

1. In dogs under ether or chloroform, stimulation of sensory nerves (saphenous, tibial, peroneal, sciatic, ulnar, and median) causes usually increased respiratory movements when narcosis is not profound or curare is not employed. These increased movements produce a fall of blood-pressure, and when they are very violent, one cannot obtain any pressor reflex even with a strong stimulation. When much increased respiratory movements are prevented by very deep narcosis or brain compression, fall of

blood-pressure due to this cause does not occur. Mechanical interference with the circulation as a result of the increased movements of the thoracic walls seems to be the main cause of this fall, since it can be eliminated by opening the thorax. When this complication is not taken into careful consideration the results of vasomotor experiments are liable to be misinterpreted.

2. In dogs under ether, chloroform, or brain compression, a weak stimulation of the central end of the cut nerves (sciatic, saphenous, tibial, peroneal, median, ulnar, and vagus) produces usually a fall and a strong stimulation, a rise of blood-pressure. With a gradual increase of the strength of stimulus up from the threshold, the reflex fall of blood-pressure first increases, then decreases, and gradually becomes converted into a rise, passing through a neutral point. We have failed to obtain a pressor effect by the strongest stimulation of the depressor nerve of Cyon.

3. The frequency of stimulation has an effect upon vasomotor reflexes. With a rapid rate of stimulation a rise is obtained and with a slow rate of stimulation in many cases a fall of blood-pressure. Of the different rates of stimulation we employed (one to eighty per second), the maximum pressor response is reached at twenty to forty per second.

4. No essential qualitative difference was found among various nerves (sciatic, tibial, peroneal, median, ulnar, branch of femoral nerve) subjected to stimulation. The saphenous nerve has a greater tendency to give a fall than those above mentioned. A purely sensory nerve seems to have a somewhat lower threshold than other kinds of nerves. Between nerves of the same category but of different sizes, the larger one produces usually a more marked response within a limited range of the strength of stimulation.

5. When the animal is under ether, chloroform, or brain compression, stimulation (mechanical, thermal, chemical, and electrical) of nerve terminations, such as those in the skin, muscles, and the intestine, causes a fall of blood-pressure in the great majority of cases, but violent or extensive stimulations of the

skin produce a rise. Under morphia and curare, on the contrary, a rise is a usual response, due clearly to a specific pharmacodynamical influence of these drugs. But under morphia a weak stimulus will produce a fall.

6. The influence of the ductless glands (adrenal, thyroid, and pituitary) upon vasomotor reflexes is not clear.* The injection of adrenin, thyroïdin, and pituitrin and tying off or extirpation of the glands produced in our experiments no distinct effect.

7. The reflex change (fall or rise) of blood-pressure on stimulation of the somatic nerves (sciatic, saphenous) is produced chiefly by the dilatation or constriction of the blood-vessels in the splanchnic area, as in the cases of the stimulation of the splanchnic and the depressor nerve.

*See footnote, page 375.

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PLATES

PLATE 1

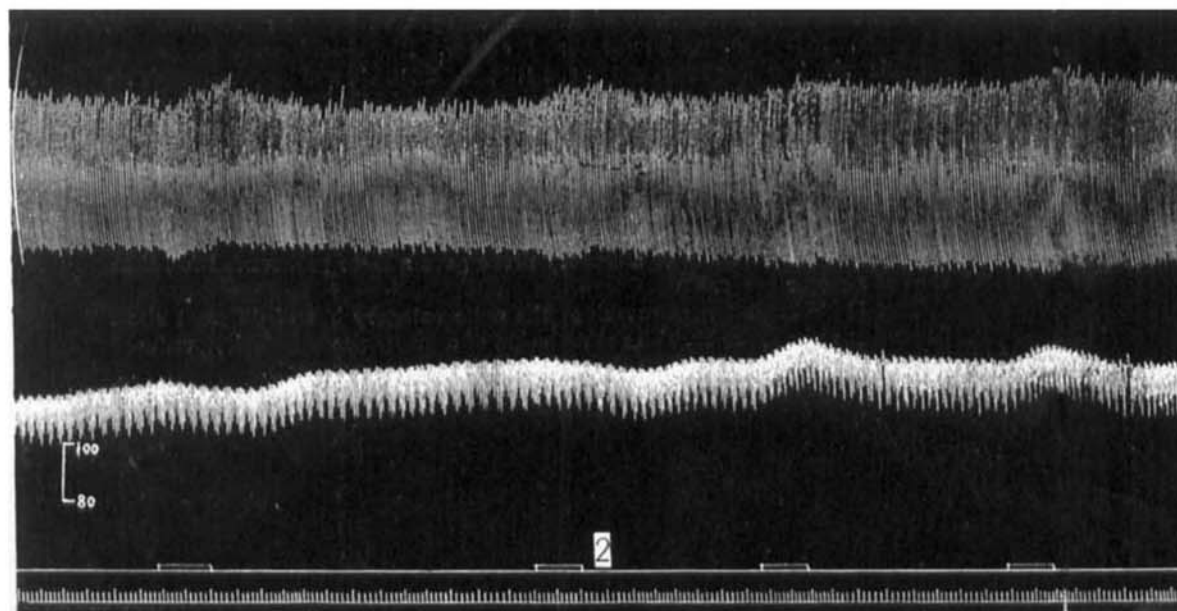
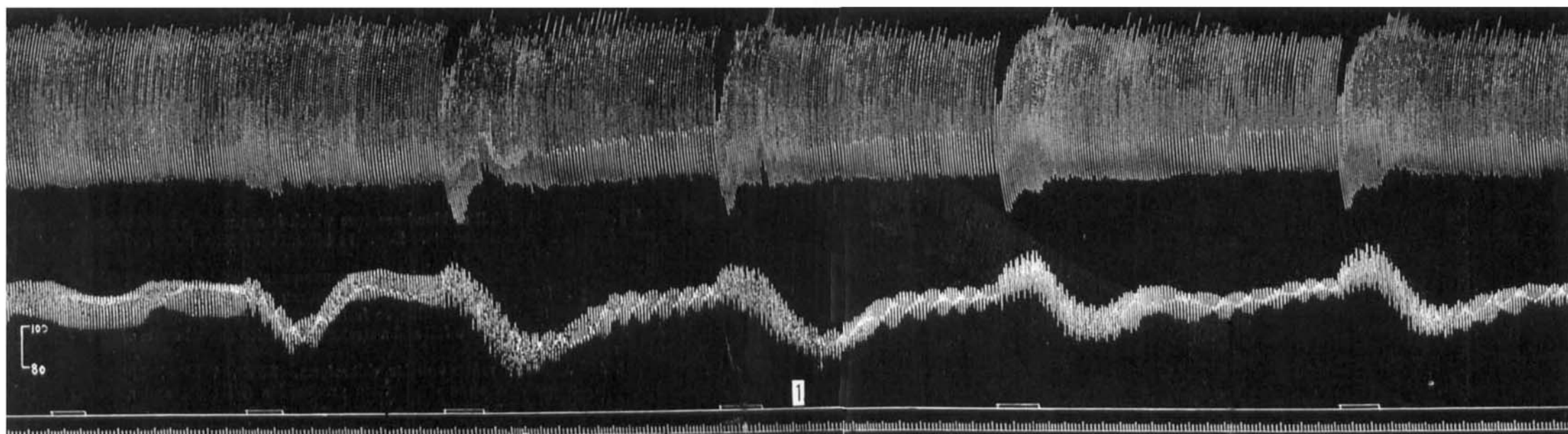
EXPLANATION OF FIGURES

Fig. 1 The effect of increased respiratory movements upon vasomotor reflexes. Bitch. 9 kilos. 10/5/1918. Ether. The left sciatic nerve was stimulated at intervals, the stimulus increasing from left to right. Upper curve, respiratory movements. Lower curve, blood-pressure. Base line is that of zero pressure, with periods of stimulation. The height of the blood-pressure in mm. Hg. is indicated by the cm. measured out and numbered. Time in seconds. For further explanation see text.

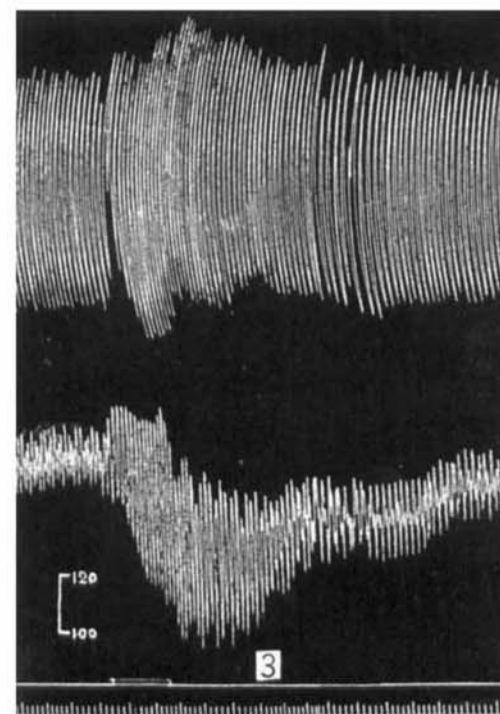
Fig. 2 Increased respiratory movements prevented by very deep narcosis. Same bitch as in figure 1. For explanation see text.

Fig. 3 Effect of increased respiratory movements upon blood-pressure. Bitch. 14 kilos. 30/5/1918. Ether. Thorax intact. The left sciatic nerve was stimulated. The result is a marked fall of blood-pressure.

Fig. 4 Effect of increased respiratory movements upon blood-pressure prevented by opening the thorax. Same bitch as in figure 3. Thorax wide open in the middle line. The same nerve was stimulated with the same strength of stimulus as in figure 3. The result is a marked rise of blood-pressure.



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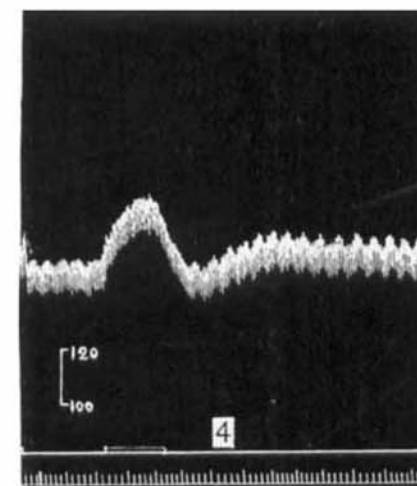


PLATE 2

EXPLANATION OF FIGURES

Fig. 5 A marked fall of blood-pressure which is apparently not due to increased respiratory movements. Dog. 12 kilos. 9/5/1918. Ether. The left sciatic nerve was stimulated.

Fig. 6 An example of vasomotor reflexes upon weak (left) and strong (right) stimulations. Same bitch as in figure 3. Thorax was very wide open in the middle line to eliminate the influence from increased respiratory movements. A weak stimulation caused a fall and a strong stimulation caused a rise of blood-pressure.

Fig. 7 Vasomotor reflexes under chloroform. Bitch. 7 kilos. 28/5/1918. Thorax wide open. A weak stimulation produced a fall (left) and a strong stimulation produced a rise (right) of blood-pressure.

Fig. 8 Effects of weak and strong stimuli, respectively, under brain compression. Dog. 18 kilos. 15/8/1918. Brain compression and artificial respiration. Right ulnar nerve stimulated. The fall of blood-pressure increased at first with the development of the strength of stimulus and then passed over to a rise crossing a neutral point.

Fig. 9 Effect of frequency of stimulation upon vasomotor reflexes. Bitch. 13 kilos. 18/7/1918. Chloroform and curare. Right saphenous nerve was stimulated. The frequency employed 1, 2, 5, 10, 20, 40, and 80 per second, respectively, from left to right. The one per second stimulation caused a fall, the two per second stimulation showed practically no effect, and the other stimulations produced a rise. The maximum pressor response was reached at forty per second stimulation in this case.

Fig. 10 Stimulation of a sensory (saphenous) and a motor (a branch of the femoral) nerve. Dog. 9 kilos. 10/10/1918. Brain compression and artificial respiration. Stimulation of a sensory nerve gave a more pronounced fall than that of a motor nerve.

Fig. 11 Stimulation of nerves of the same category but of different sizes. Same dog as in figure 10. The stimulation of a larger nerve (sciatic) produced a more marked response than that of a smaller nerve (peroneal).

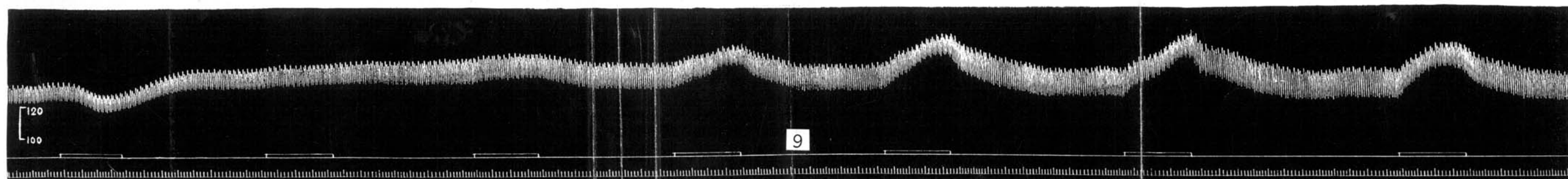
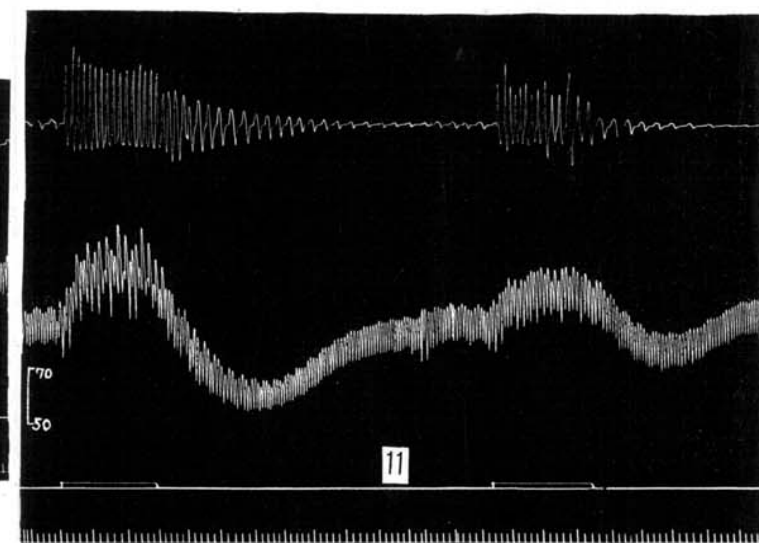
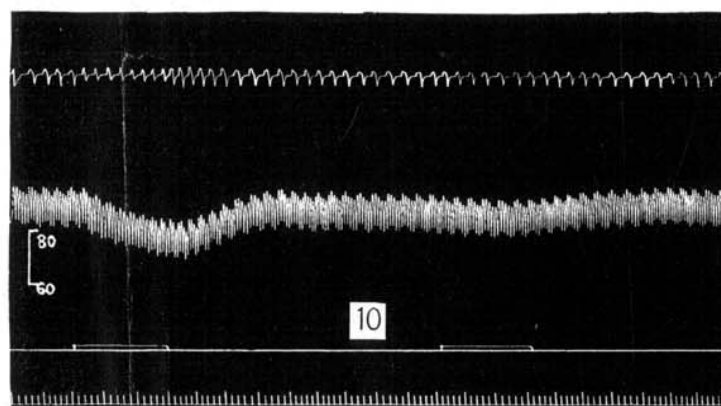
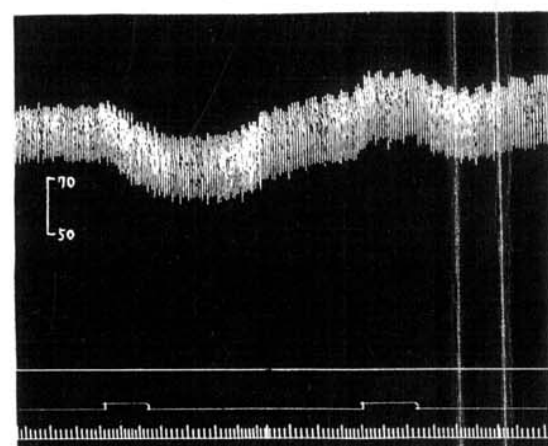
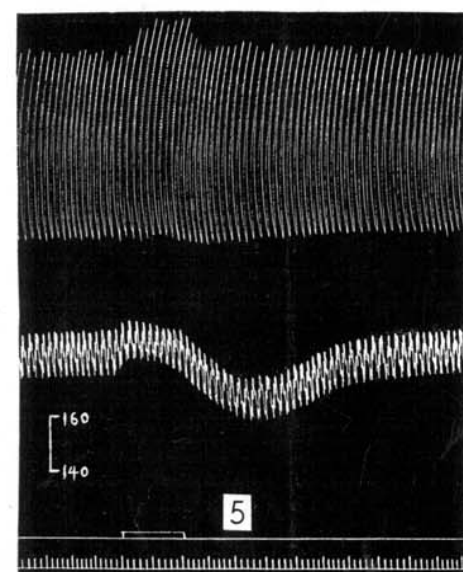
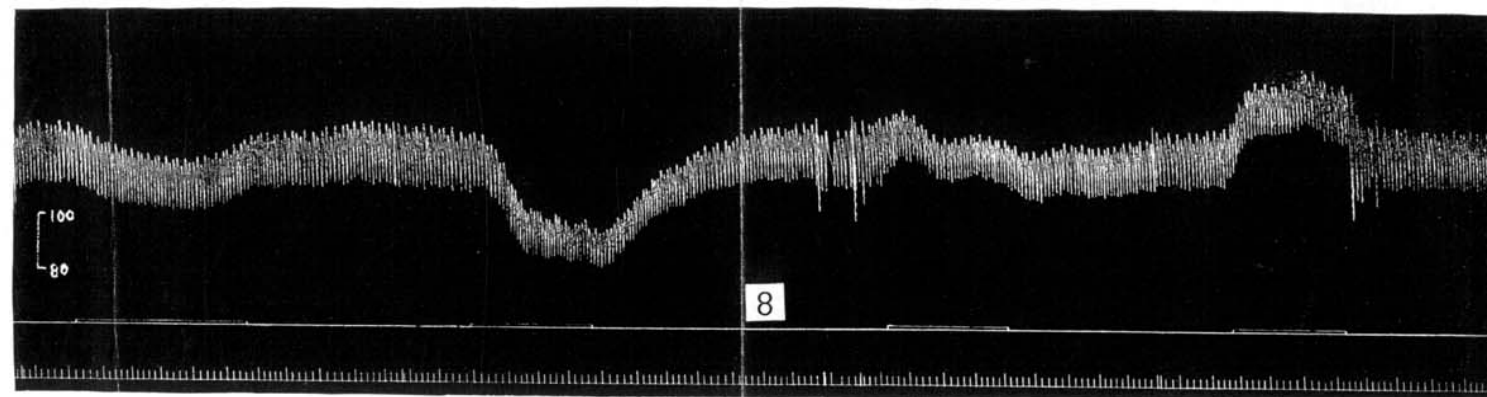
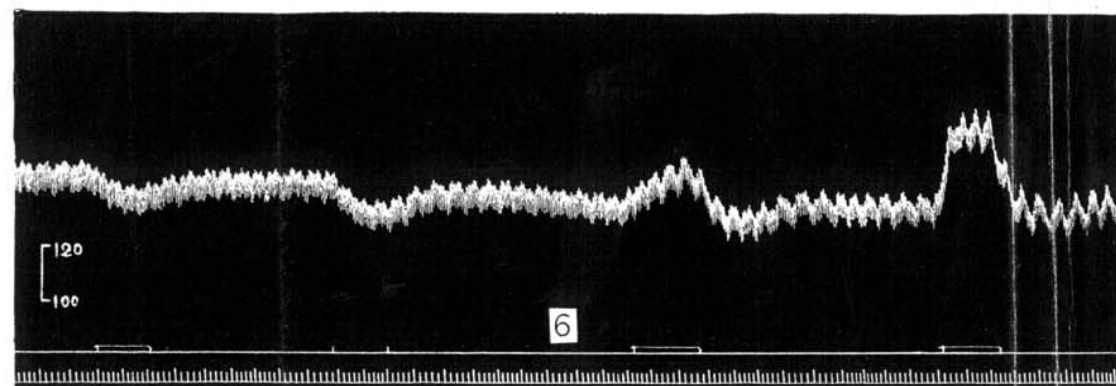


PLATE 3

EXPLANATION OF FIGURES

Fig. 12 Scratching of the skin. Dog. 12 kilos. 9/5/1918. Ether. A marked fall of blood-pressure. Respiratory movements practically unaffected.

Fig. 13 Application of heat (boiling water) on the skin. Dog. 10 kilos. 25/10/1918. Brain compression and artificial respiration. A fairly marked fall of blood-pressure.

Fig. 14 Electrical (strong) stimulation of the skin. Dog. 11 kilos. 14/5/1918. Ether. A very marked fall of blood-pressure. Respiratory movements affected very slightly.

Fig. 15 Scratching of muscle (right sartorius). Bitch. 10 kilos. 22/10/1918. Ether. A fairly marked fall of blood-pressure. Respiratory movements show no increase.

Fig. 16 Kneading of muscles (lateral muscles of the right thigh). Dog. 10 kilos. 25/10/1918. Brain compression and artificial respiration. Gentle kneading produced a pure fall (left) and violent kneading a fall followed by a rise (right). Artificial respiratory movements affected mechanically by the manipulation.

Fig. 17 Kneading of the small intestine. Same dog as in figure 16. A fairly marked fall of blood-pressure. Artificial respiratory movements slightly affected mechanically by the manipulation.

Fig. 18 Simultaneous tracings of the carotid blood-pressure and the volumes of kidney and hind limb. Dog. 10 kilos. 13/12/1918. Morphine and curare. Artificial respiration. Strong stimulation of the right sciatic nerve caused vascular constriction of the kidney, dilatation of the limb, and a rise of blood-pressure.

Fig. 19 Dog. 10 kilos. Ether. Effects of weak, moderate, and very strong stimulation of the skin. The weak stimulation gives a pure fall, the moderate stimulation a rise followed by a fall, while one very strong stimulation gives a pure rise.

