List of Papers referring to
Original Work submitted in
support of M.D. Thesis by
R.J.S. McDowall.


"A Vago-Pressor Reflex" Journ. Physiol. 59, 1924.

"On the Nature and Significance of Vagus Escape" Journ. Physiol. 61 (1926).


"Spontaneous movements of blood-vessels" Journ. Physiol. 60 Proc.

"The influence of the depressor fibres of the vagus on the capillaries". Journ. Physiol. 61 Proc.


"A small combined air and animal warmer for use on ordinary tables". Journ. Physiol. 57 Proc. 1923.


"Class experiments in leucocytosis" Journ. Physiol. 65 Proc. 1928.


"A central chemical control of the heart rate" Journ. Physiol. 67 Proc. 1929.


"On a cortical flexor tone in the fore-limb of the cat, with observations on the hemiplegic attitude in man" Brain 56, 1933 (Jointly with D.M.Blair)


"The reactions of the pupil in the chloralosed animal" Quart. Journ. Exper. Physiol. 15, 1925.


"The water supply of the Egyptian Expeditionary Force, with special reference to the efficiency of mechanical rapid filtration with chlorination". J. of Hygiene, Jan. 1921.

"The action of alcohol on the circulation" J. of Pharm. & Exper. Therapeutics 25, 1925.

ON THE NATURE OF HISTAMINE ACTION.
BY R. J. S. McDOWALL.

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ON THE NATURE OF HISTAMINE ACTION.
BY R. J. S. McDOWALL.
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The object of the experiments with which this investigation deals is to study in some detail the cause of the fall in systemic blood-pressure, which occurs when a small dose (01 mg.) of histamine is injected intravenously.

In 1918, Dale and Richards(1) showed most conclusively that the action of histamine is on the capillaries, and later Dale and Laidlaw showed that the condition of histamine shock was due to increased capacity of the vascular system and lessened output of the heart. The early part of the fall in systemic blood-pressure produced by large doses of histamine they considered to be accelerated by pulmonary constriction which greatly diminished the flow of blood to the left side of the heart. With regard to the fall of blood-pressure which follows small doses, Dale and Richards (1, p. 163) state that "it is not a volume effect due simply to increased capacity of the system, but to a diminished peripheral resistance." This conclusion they based on a careful and elaborate series of perfusion experiments in which they found that there was a diminished peripheral resistance if histamine was added to the perfusion fluid (Ringer-Locke solution containing blood corpuscles and a trace of adrenalin). This evidence was supported by the result found by Dale and Laidlaw(2) that histamine produced larger excursions of the lever in cardiometer tracings; this was interpreted as indicating an increased output of the heart. From these experiments therefore it was assumed that more blood-pressure reached the heart during the action of histamine, a result which would be expected if the peripheral resistance was diminished.

The immediate impulse which led to the commencement of the present investigation came from finding that the venous pressure did not always rise as would be expected if there was a diminution of peripheral resistance and if more blood passed through to the veins. Moreover, when it rose, neither its onset nor its magnitude bore any constant relation to the systemic change, as might with reason be expected if they were due to the same cause.
**HISTAMINE ACTION.**

**Method.** All experiments were made on cats anesthetised in the first instance with ether; when deeper anaesthesia was required a chloroform-ether mixture, or chloroform alone, was used. Venous pressure was recorded by a method described elsewhere.

The question of dose was first considered. If under light anaesthesia a small dose such as 0.01 mg. was given, there was a rise of venous pressure; as the dose was increased the rise became less and when the shock dose was approached there was usually a fall in venous pressure. These results appeared to support the conclusions of Dale and Richards and the results of Connett who obtained a fall of venous pressure with relatively large doses (5 mg.). But in view of the fact that Dale had called attention to the action of anesthetic in making carnivora sensitive to the histamine, the depth of anaesthesia was varied. It was found that the venous response was markedly altered. Under light anaesthesia with a dose of 0.01 mg. there was a rise of venous pressure as stated above, but under deep and prolonged anaesthesia there was a venous fall, although the systemic fall was about the same in both instances (Fig. 1). An explanation for this venous alteration was sought for. It might be said that the general sensitivity had increased and that the small dose was now having the effect of a large dose. This may readily be dismissed as the fall in arterial pressure does not necessarily change in magnitude although the venous response alters completely. An alteration in venous response without modification of the arterial suggests in itself that they are due to different causes.

It might also be said that deep and prolonged anaesthesia weakened the heart and that the histamine would then stimulate it, causing it to empty itself more effectively and so lower the venous pressure. While such anesthesia is liable to cause high venous pressure through cardiac weakening, the same fall of venous pressure occurred in some cases when the venous pressure was not abnormally high (Fig. 2). Even if histamine stimulates the isolated heart, it does not follow that it stimulates the heart in the body. Dale and Laidlaw in their earlier paper came to the conclusion that the heart was weakened, and the occurrence of obvious cardiac failure on the injection of a small dose of histamine in an animal whose heart is already weak shows that the total effect of the histamine in the heart is to reduce rather than to improve cardiac efficiency. Further, when the pulmonary circulation is impaired or paralysed there is no evidence that the heart is benefited by histamine. Such benefit would show itself by a rise in pulmonary pressure, but at the stage just mentioned lessened efficiency of the heart may be evidenced.
by irregularity of the heart's action and a fall in the pulmonary pressure (Fig. 2D). It is therefore concluded that cardiac effects following the

![Fig. 1. Cat 3. 1 kg. c.e. mixture. Effect of varying anaesthesia on the change of venous blood-pressure caused by injecting .01 mg. histamine. The upper tracing is the venous pressure in mm. H2O; the lower tracing is the carotid pressure in mm. Hg. Natural respiration. Time in minutes. At each arrow .01 mg. of histamine was injected.

A. Ordinary sufficient anaesthesia. Rise of venous pressure.
B. Later, anaesthesia throughout, corneal reflex still present, only slight rise of venous pressure. The primary venous fall is due to an inspiratory gasep seen in respiration tracing.
C. Anaesthesia increased. Venous pressure large fall.
D. Anaesthesia lessened. Venous pressure fall decreased.
E. A few minutes later, rise of venous pressure.

injection of histamine are insufficient to explain the change in the venous pressure response under deep anaesthesia.

The most satisfactory explanation appears to be that the rise of venous pressure which occurs under light anaesthesia is one due to backward pressure or obstruction in the pulmonary circulation, and that the anaesthetic removes the pulmonary obstruction. Histamine as first shown by Dale and Laidlaw(2) using the method of Bradford and Dean(5), constricts the pulmonary vessels to a marked degree (cp. Fig. 2A). They have shown in relation to large doses that the sharp initial fall in systemic arterial pressure is due to this cause, and it will be seen below that even with small doses this factor may make itself manifest. When it is remembered that the right ventricle is
already impaired by the lowered and falling aortic and coronary pressures, it is not difficult to imagine that it is no longer able to empty itself against the increased resistance in the pulmonary vessels.

Now it has been shown by Brodie and Dixon that the action of the vagus on the bronchial muscles may be greatly reduced or may be obliterated by deep anaesthesia. I have found that the action of adrenaline on the bronchioles may be similarly reduced and have brought forward evidence(8) that the action of amyl nitrite on the pulmonary vessels may be prevented by deep chloroform anaesthesia. This is presumed to be due to the local action of the anaesthetic on the lungs themselves. When the effects of anaesthetics on living tissue generally are considered it is indeed difficult to see how the lung tissues can escape serious impairment when exposed to anaesthetic vapour for prolonged periods.

As has been said above, the rise of venous pressure following a small dose of histamine disappears under deep and prolonged anaesthesia, and I have suggested that the rise is due to backward pressure from the lungs. Demonstration that the pulmonary constriction is reduced or abolished by such anaesthesia would be strong circumstantial evidence in favour of the suggestion. Experiments were therefore made to test this point. Pulmonary pressure was recorded by the method of Sharpey Schafer(9) and it was found that on varying the depth of anaesthesia a series of changes parallel to those in the venous pressure could be obtained when histamine was injected. At first under light anaesthesia there was the typical rise in pulmonary pressure (Fig. 2A), but as the anaesthetic was deepened there was a delay in the pulmonary rise (this point was first noted by my colleague Mr Winfield who witnessed the experiment) and later it lessened (Fig. 2B) and then it disappeared entirely (Fig. 2C). If the experiment be prolonged there may be an actual fall of pulmonary pressure (Fig. 2D) which may be considered to be due partly to cardiac weakness and partly to less blood reaching the right side of the heart.

The results just given lead me to consider that the fall of systemic blood-pressure caused by a small dose of histamine in an animal under light anaesthesia is due mainly, if not entirely, to pulmonary constriction causing decreased output of the left ventricle and not to decreased capillary resistance. Thus the histamine effect does not indicate that variation in capillary resistance plays an important part in the circulation as Dale and Richards suggest it does. Any increased flow into the veins is probably annulled by increased capillary capacity. The
experiments of Dale and Richards mentioned above were made on tissues removed or isolated from the body and the results are not necessarily applicable to the normal circulation. It is true the evidence is deficient on two points. (1) That the rise of venous pressure never occurs unless there is pulmonary constriction and (2) that the pulmonary constriction is always sufficient to prevent the heart emptying itself normally. Owing to other factors which arise these points do not seem to be capable of absolute experimental proof.

The increased pulmonary resistance caused by histamine accounts for some of the other effects which it produces or may produce.

(a) It was noted by Bayliss in some unpublished experiments privately communicated to me that the venous rise caused by a small dose of histamine sometimes did not occur until the systemic blood pressure was beginning to return to its normal level. This delay can, I find, be brought about by the anaesthetic and it is the natural result of the decreasing excitability of the pulmonary tissue to histamine.
(b) Dale and Laidlaw noted that on the injection of a large dose of histamine, the systemic fall frequently took place in two stages. The first stage they considered was due to pulmonary constriction cutting off the blood from the left side of the heart, the second to increased capacity of the system. In one experiment I obtained a similar fall in two stages on injecting a small dose of histamine (Fig. 3). If the first stage in one case is due to pulmonary constriction, it may be assumed to be so in the other. In this experiment there was a fall in venous pressure (Fig. 3) so that in this experiment the effect of the pulmonary constriction was more than counterbalanced by the increased capacity of the capillaries just as ordinarily occurs on injecting a large dose of histamine.

(c) I have also found that in shock when the capillaries are already dilated, there is still a rise in venous pressure. Such a rise could not be due to more blood passing through to the veins as there was evidence of increased peripheral resistance, indicated by a rise of the systemic pressure from arteriole constriction. Investigation of the pulmonary circulation at this stage showed that the pulmonary rise could still be obtained, although the usual systemic arterial fall did not occur. It is
assumed then that the venous rise was due to the pulmonary constriction.

SUMMARY.

The parallelism between the disappearance under deep anaesthesia of the rise of pressure in the pulmonary artery and the rise of venous pressure which occurs as the result of the injection of a small dose of histamine suggests that they are both due to the same cause, namely, pulmonary constriction which is affected by the anaesthetic. Other results are given which support this view.

If the anaesthetic is increased so as to abolish the pulmonary effect, there is a fall of venous pressure although the systemic arterial fall may not have altered, nor the heart have been weakened.

The results indicate that the fall of arterial pressure which occurs on the injection of a small dose of histamine is the result of diminished output of the heart, due partly to pulmonary constriction, and partly to less blood reaching the heart as a result of increased capacity of the capillaries, and not, as Dale and Richards hold, to decreased capillary resistance.

REFERENCES.

(1) Dale and Richards. This Journal, 52. p. 110. 1918.
(5) Bradford and Dean. This Journ. 16. p. 34. 1874.
(6) Dixon and Brodie. This Journ. 29. p. 77. 1908.
THE EFFECT OF THE CIRCULATION ON THE ELECTRICAL RESISTANCE OF THE SKIN.

BY F. AVELING AND R. J. S. McDOWALL.

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THE EFFECT OF THE CIRCULATION ON THE ELECTRICAL RESISTANCE OF THE SKIN.
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Of recent years, especially among psychologists, considerable attention has been drawn to the fact first noticed by Féré, that under conditions of emotion the electrical resistance of the skin of man may undergo considerable reduction, and this has given rise to a large number of observations in man on what is called the psycho-galvanic reflex. The efferent nervous impulses of the reflex are generally held to pass to the skin by way of the sympathetic nerve fibres, i.e. either by vascular or sweat fibres. The vascularity of the skin can be modified in a number of ways and it seemed desirable to determine how far the skin resistance varied with its vascularity.

Only very few investigators appear to have succeeded, for reasons indicated below, in bringing about any change in resistance in anesthetised animals, and those have confined themselves to a study of the nature of the sensory stimuli which produce the fall or to the study of the relation of the fall of resistance to the possible action of the sweat glands. Attention to the latter has been rather emphasised by the fact that some observers have found that the fall of resistance was abolished by atropine (Schiff and Schubert Fauville). It appears however to have been completely overlooked that the effect of atropine is not confined to its action on glands and that it has a profound effect on blood vessels. Similarly it has been considered that the persistence of the fall of resistance after temporary occlusion of the blood supply to the heart is not due to vascular changes. As we now know that the capillaries are largely independent of the arteries it will be clear that such evidence can no longer be taken as conclusive.

Advantage was taken of the fact that the vasomotor system of animals under chloralose is appreciably more sensitive than if ether is used, especially if the experiment is prolonged. The experiments were made on cats. Ordinary zinc wash-leather electrodes were lightly bandaged on to the skin, the fur being clipped off if necessary with scissors and the whole soaked in saline. The electrodes were connected with Wheatstone bridge and a galvanometer in the ordinary way used for observing resistances. In different animals the resistance varied from 30,000 to 60,000 ohms, but subsequently it was found could be change
as desired by the experimental procedures. Changes in resistance varied up to 2000 ohms. That these changes were really due to the skin could readily be demonstrated by removing it when it was found that the resistance of the circuit was less than 2000 ohms and the changes in this resistance were of such a small order as to be negligible. The results obtained were extremely definite provided fresh animals not suffering from shock were used. It was found from time to time that the reactions given before the preliminary ether anaesthesia had worn off were absent or were appreciably less than those given later under the chloralose. This is important and no doubt accounts for the completely negative results which have been recorded by other workers.

Direct vaso-constriction. This was brought about by the intravenous injection of adrenaline (1/50 mg.), which was found to bring about a marked fall in the resistance of the skin of the limbs and the pads of the feet. The fall of resistance corresponded with the usual rise of blood-pressure when the drug is injected. The return of the skin resistance to its previous height synchronised with the return of the blood-pressure. The change in the skin resistance like the rise of blood-pressure was best seen when the vagi were cut.

Indirect vaso-constriction. It is well known that in hæmorrhage there is constriction of the skin vessels as a result of increased action of the vasomotor centre. This is indicated by the pallor. When the animal was bled from the carotid artery there occurred a marked fall of skin resistance.

Of interest in this respect was the effect of small doses of histamine (1/10 mg.), which have been shown by Dale and Richards to bring about capillary dilatation. The recovery from such small doses is extremely rapid and this has been shown by McDowall and Worsnop to be due to reflex arterial constriction through the operation of the vago-pressor reflex, and they have drawn attention to the similarity in the effect of the circulation of the arteries of such small doses to the effect of small hæmorrhages. The similarity between large hæmorrhages and large doses of histamine from which the blood-pressure does not recover was pointed out by Dale and Laidlaw. It was found that on the injection of a small dose of histamine there was a decided fall in the skin resistance which persisted after recovery of the blood-pressure. In this we have further evidence of the similarity referred to above between the action of hæmorrhage and histamine. It is of interest to note in this respect that clinically in conditions of shock due to toxin absorption from wounds, there is a marked pallor of the skin and a sensation of coldness to the touch.
A similar fall in skin resistance was brought about by the action of cold which we know brings about a constriction of the skin vessels in order to prevent heat loss. Cold was applied to the limb above the electrodes and to the carotid artery; and cold fluid was injected into the cephalic end of the carotid all with the same result.

*Vaso-dilatation.* This was brought about mechanically by compressing the inferior vena cava, when the electrodes were applied to the lower limbs. The procedure brought about a momentary fall of resistance but this was after half to one minute succeeded by a marked rise in skin resistance which persisted. This we may presume was brought about by the congestion of the part.

Dilatation of blood vessels was also brought about by the administration of amyl nitrite, which also caused a marked rise in the skin resistance.

Irritation of the part by plucking out the hairs previous to the application of the electrodes brought about a steady rise in skin resistance. When the electrodes were removed it was observed that the skin, previously pale, had become reddened as a result of the local dilatation of vessels.

A rise of resistance was also obtained by the injection of hot saline into the blood stream but the results, although definite, were not very marked.

It is then clearly evident that a vaso-constriction is associated with a fall in skin resistance and vaso-dilatation with a rise in skin resistance. A continuation of these experiments gave further results which could readily be interpreted from what has been said above.

*Asphyxia.* This was almost identical with the effect of clamping the inferior vena cava. There was a preliminary fall of resistance apparently due to the immediately stimulating effect of applying the clamp to the trachea, but thereafter there was a rise of resistance which continued to rise rapidly till the death of the animal. The procedure can readily be shown to result in an enormous raising of the pressure in the veins which we may infer brings about local dilatation of blood vessels in the region act of the electrodes. No doubt the effect of CO₂ also plays a part.

*Acetyl-choline.* If this drug is given in small doses insufficient to affect the heart its intravenous injection is associated with a rise in skin resistance. With larger doses, however, which brought about marked cardiac inhibitions there resulted a fall in skin resistance. Here we may understand that in the case of small doses there was the well-known vaso-dilator action of the drug, but with the larger doses when the
cardiac output was diminished as in haemorrhage the compensatory vaso-constriction counteracted the vaso-dilatation and brought about the fall in the skin resistance. This explanation is supported by the fact that a similar fall of resistance occurs if the output of the heart is reduced by impeding its action mechanically with the fingers.

**Pilocarpine.** The effect of this drug was specially interesting in view of its action on the sweat glands and in view of the controversy which had taken place in regard to the possibility of the secretion of sweat being responsible for changes in the skin resistance of man. Two distinct stages were usually seen. In the first there was a short but distinct fall of skin resistance, in the second a distinct and prolonged rise. The fall accompanied the evanescent pallor stage and the rise the flushed stage during which secretion takes place. The changes in skin resistance were obtained on the skin of the limbs which does not sweat. They were then clearly independent of sweating. This evidence, together with that given above, especially that in relation to cold, indicates clearly that sweating per se is not responsible for the fall in resistance. These results support those of Waller, who found that atropine given subcutaneously in sufficient doses to produce its well-known inhibition of the sweat glands did not interfere with the changes of skin resistance which occur in certain emotional states in man.

**Atropine.** As indicated in the first paragraph the result of the injection of this drug is of special significance. The effect of the injection (1 to 2 mgm.) was clearly to bring about a steady rise in resistance of 10 or 15 minutes without recovery. This confirms the work of Markbeiffer. In the early stages of such doses or if smaller doses were administered, it was possible to interrupt the rise by procedures such as the injection of adrenaline or sensory stimulation which we have seen above bring about a fall of resistance, although even at this stage it might be evident from the dilatation of the pupil and the acceleration of the heart that the parasympathetic had been paralysed (confirmation of Waller). These results are readily explained by the vaso-dilator action of atropine. This action is often overlooked, though it is referred to in most of the pharmacological text-books and is well known in man.

When injected, the vaso-dilator effect of the drug tends in the first instance to be masked by the accelerator effect on the heart which brings about a rise in blood-pressure. If, however, the vagi have been cut and the heart is already freed from vagus tone, or if the animal is suffering from shock, the same dose of atropine will be found to bring about a
profound fall of arterial pressure, which, indeed, may result in the death of the animal.

Sensory stimulation. The common stimulus adopted was pinching the skin of the fore limb with a pair of pliers. The stimulus resulted in a marked fall of skin resistance in the limbs or the pads of the feet. Repetition of the same stimulus did not always, however, bring about the repetition of the result which was normally of the same order as that obtained with a moderate dose of adrenaline (1/5 mg.). This change in reaction quite clearly did not depend on the higher centres as it was brought about in decerebrate cats.

Remarks. From what has been said it seems reasonable to believe that the fall of skin resistance which occurs on sensory stimulation is due to constriction of the skin vessels. The sensory stimulation is, as well known, accompanied by a rise of blood-pressure as would be expected from sympathetic stimulation. That the sympathetic is stimulated is seen by evidence elsewhere than from the circulation, e.g. the dilatation of the pupil, which occurs at the same time. We have seen the similarity of result to the effect of adrenaline which is known to constrict the skin vessels. Further, under conditions, e.g. haemorrhage, in which adrenaline no longer brings about a fall, there is no response to sensory stimulation although at the beginning of the experiment this could be readily obtained. The blood vessels may be presumed to be already constricted as the result of the effect of the haemorrhage and cannot be made to constrict further by sensory stimulation. This presumption is supported by the fact that often in such circumstances the vessels may be dilated and the skin resistance made to rise by the administration of a powerful vasodilator, such as acetyl-choline and especially by asphyxia or clamping the vein.

This conception is also supported by Müllers's results. He found in monkeys that section of the nerves supplying the heart only very temporarily reduced the fall of resistance obtained on sensory stimulation, although this was abolished by the local injection of 5 p.c. novocaine and adrenaline. It may be considered that the nerves concerned lie along the blood vessels, which, as we know, recover their tone fairly rapidly in spite of nerve section.

Thus procedures which are known to bring about the constriction of vessels cause a fall in the electrical resistance of the skin and a dilatation of vessels is associated with a rise in the resistance. All other procedures which affect the skin resistance of the chloralosed animal can readily be explained as being due to changes in the vascularity of the part. This
utility of such a relation is evident in the prevention of loss of blood and the throwing of a maximum amount of blood into the circulation. This will, of course, be prior to the requirements of skin dilatation for the purpose of increasing the heat loss once the exercise is begun. We have seen that the higher cerebral centres are not required and that the reaction is apparently of a reflex nature.

The reflex, however, does not appear to be limited strictly to the skin. A similar diminution is found to occur in muscles although in the latter instance the circuit has so little resistance that the changes which occur are very small compared with those of the skin.

Quite apart from the results obtained, it will be evident that we have in the investigation of the resistance of the skin, a method by which the circulation through it may be studied with accuracy, and it will be obvious that this may be of considerable value in the investigation of the location of the action of drugs especially in relation to the distribution of vasoconstriction and vaso-dilator effects. It may also prove useful in relation to the study of sweat secretion.

**SUMMARY.**

It is shown that in the cat a fall of the electrical resistance of the skin is associated with the constriction of vessels and that a rise is associated with a dilatation.

Reasons are put forward why the fall of skin resistance which occurs on sensory stimulation may be considered to be due to similar vasoconstriction.

The resistance of the skin may apparently be used as an indication of its vascularity.

In carrying out these experiments we are indebted for the assistance of Dr H. M. Wells and Dr R. C. McCarthy.

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**REFERENCES.**

Dale and Laidlaw. This Journ. 52, p. 335. 1919.

Fauville. Arch. Internat. de Physiol. 16, p. 58. 1921.

McDowall and Worsnop. This Journ. 50. 1925; Proc. Physiol. Soc. p. xxxvi.


Schiff and Schubert. Pfüger's Arch. 195, p. 75. 1922.


In the above paper all reference to similar experiments in man have been omitted in view of the very voluminous and controversial nature of the literature and the fact that in man it is not yet clear that the changes in skin resistance may not be affected by other factors.
THE CHEMICAL REGULATION OF CAPILLARY TONE.
BY A. HEMINGWAY AND R. J. S. McDOWALL.

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THE CHEMICAL REGULATION OF CAPILLARY TONE.

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ONE of the earliest observations on the activity of capillaries was made by Severini(1) to the effect that these vessels were dilated by carbon dioxide and constricted by oxygen. Subsequently, however, this was denied by Roy and Brown(2), but the more recent work of Krogh(3) has confirmed the observations of Severini and additional evidence is presented by Hooker(4) regarding the dilatation of the capillaries by venous blood.

It is now realised, especially from the work of Krogh, both by histological examination as well as by study of function, that the tone of the capillaries is quite independent of that of the arteries and several suggestions have been made as to the means whereby this tone is maintained. Dale and Richards suggested that adrenaline in the circulating blood was responsible, but, on the other hand, Krogh(5) has put forward evidence that a pituitary hormone is concerned in the maintenance of tone.

In an endeavour to assign capillary tone to the existence of a particular hormone whose presence is far from proven, the simpler explanation that the capillaries are under an acid-base control appears to have been somewhat neglected. In the present paper, evidence is put forward that any theory of capillary tone maintenance must take into account the existence of such a simple regulating mechanism.

Attempts have been made to elucidate the nature of the tone regulation by perfusion experiments on isolated organs and limbs where various principles have been added to the perfusing fluid and their effect noted. Dale and Richards(6) pointed out, and later Dale and Burn(7), that in a limb perfused with defibrinated blood it was sometimes possible at the commencement of an experiment to obtain a dilator effect with histamine (presumably due to capillary dilatation) which later disappeared and an investigation of this phenomenon was the starting-point of the present work.
The loss of tone they encountered may be considered under three headings:

1. That the perfusion fluid suggested by Dale and Richards did not contain the constituents suitable for the maintenance of capillary tone.

2. That there were present in the perfused tissues themselves substances which acted as capillary dilators.

3. A constriction of arterioles might be so great that the dilator action of histamine was not able to show itself on a more peripheral resistance.

The first possibility regarding the nature of the perfusing fluid was fully dealt with by Dale and Richards, who emphasised the necessity for an efficient oxygen supply and for adding a trace of adrenaline to the fluid, on which fact they based their suggestion that the tone of the capillaries might be due to adrenaline. Further work by Dale and Burn(7) has shown, however, that vessels perfused with defibrinated oxygenated blood exhibit a gradually developing tone over the initial period of an experiment, during which time histamine shows its dilator action. Later this disappears and then no further dilatation of capillaries can be obtained unless tone is produced by the addition of adrenaline. But using oxygenated Ringer's solution as the perfusing agent they were unable to show with any regularity the onset of capillary tone.

The second possibility, the main thesis of this paper, that the loss of capillary tone might be due to the production of dilator substances which were not removed was suggested by the fact, demonstrated by Hemingway and McDowall(8), that narcotised and alkaline muscles lived appreciably longer than ordinary muscle when removed from the body, presumably as a result of the slowing down of the processes responsible for death.

It is well known that for some considerable time after death the capillaries and the arteries are tightly constricted and this observation led the ancients to imagine, as Aristotle states, that the arteries were full of air, since they had become constricted after death, and the blood so driven out of their interior. John Hunter, too, speaks of "the stimulus of death" referring to the contraction of the vessels, which undergo "contraction by death, less in the aorta than in the more distant vessels." Later evidence in support of this is given by MacWilliam(9) in an exhaustive study of post-mortem changes in vessels; and Hooker(10) has shown the closing down of the capillaries immediately after death. It is therefore certain that there is a definite
tone in these vessels at death. But during a perfusion experiment it gradually disappears, and it is essentially with the prevention of this loss of tone that we are concerned. It may be that changes in the tissues are sufficient to account for it. Investigation showed that Ringer's fluid perfused through the hind limbs of the cat would not maintain this tone, and, even if a response to histamine could be obtained when the preparation was first set up, it disappeared in a minute or two. It was found that the fluid passing through the tissues underwent considerable change, a solution which entered with pH 7·4 showing a reaction of pH 7·0 or even less on emerging from the veins. Since the presence of lactic acid in the perfusate was demonstrated by Hopkins' test, the formation of lactic acid and other metabolites with a considerable change in the hydrogen-ion concentration was regarded as a possible factor concerned in the loss of tone.

Having regard to this, perfusions were performed using alkaline Ringer's solution to counteract the effect of the acids produced. Their formation was further retarded, as mentioned above, by preliminary narcotisation of the animal and the injection of 1–2 c.c. of N/100 NaOH or saturated NaHCO₃, spread over two or three hours to ensure the taking up of the alkali by the tissues. The perfusing fluid had the composition NaCl, 0·9 p.c.; KCl, 0·042 p.c., CaCl₂, 0·024 p.c. and the reaction was adjusted by adding M/5 Na₂HPO₄ solution in the proportion of 40 c.c. to a litre of Ringer's solution and then bringing to the required reaction by M/5 NaH₂PO₄ solution, the quantities of which had previously been determined. The method of perfusion is described elsewhere. If these precautions were taken, then no difficulty was experienced in demonstrating the dilator action of histamine several hours after the beginning of an experiment where the perfusing fluid has consisted merely of aerated Ringer's solution. Fluid adjusted to pH 7·6–7·7 has been found to give the best results, and with this reaction the emerging fluid showed a reaction of pH 7·0–7·2, so that the reaction of solution through the capillaries must have been in the region of 7·4, that is, close to what we may imagine the normal value. Fig. 1 shows the response to histamine in a perfusion which had continued for more than an hour. Here the increase in outflow also is shown by connecting the outflow cannula from the inferior vena cava by means of a T-tube to a manometer and piston recorder.

A slight change in the perfusing fluid towards acidity is sufficient to cause the disappearance of the response, and this is clearly shown in Fig. 2 where histamine was dilating when the perfusing fluid was at
Fig. 1. Showing the dilator action of histamine one hour and a half after the commencement of perfusion. Upper tracing shows pressure of fluid entering aorta. Lower tracing indicates rate of flow from inferior vena cava pressure in cm. H₂O. Initial rise in the curve is due to the injection.

Fig. 2. Dilator action of histamine, perfusing fluid pH 7.6. At A the solution is changed for one of pH 7.4. There is diminution in peripheral resistance due to loss of capillary tone and disappearance of dilator action. Original fluid restored at B with increase of tone and reappearance of histamine reaction.
pH 7.6; when this was changed to pH 7.4 there was evidence of dilatation and the response could not be obtained, the capillaries having lost their tone. When the original fluid was restored tone was recovered and histamine again gave its reaction. If during the course of an experiment the capillary tone has disappeared then it may be restored by small additions of N/100 NaOH, or NaHCO₃ solution to the perfusing fluid, by injection through the tubing near the cannula, when an increasing peripheral resistance is built up by the alkali and then the dilator effect of histamine is able to show itself. This is illustrated in Fig. 3.

![Graph](image-url)

**Fig. 3.** Increased tone built up by the addition of alkali. Partially relaxed by histamine but an increased action remaining.

This restoration of tone is, however, usually of the most temporary and evanescent character, a fact which may be taken to indicate that alkali supplied in this way is very rapidly neutralised by the acid substances produced by the tissues and washed away in the perfusing fluid. We shall see below that continuous perfusion with strong alkali, on the other hand, although possibly causing capillary tone brings about such arterial change that capillary dilatation, if present, cannot show itself.
CAPILLARY TONE.

Herein appears to lie the importance of previous treatment of the animal so as to delay post-mortem changes, since it makes it possible to perfuse the capillaries with a solution which will just bring back this tone without causing any appreciable effect on the arteries.

The difference in this method and the precautions previously found necessary may then be briefly emphasised. No hormonal substances have been introduced, neither has the viscosity nor the oxygenation of the perfusing fluid been specially considered. The results may be explained as due to the prevention or hindering of the action of lactic and possibly carbonic acid.

It is interesting to observe that the capillaries of an animal which has died of acapnic shock retain their sensitivity to histamine if perfused with an alkaline Ringer’s solution of pH 7.6. This may readily be considered to be due to the alkalosis which results from the over-ventilation and the general slowing of metabolic processes caused by the shock. That such slowing does occur is suggested by the fact that in persons dying from haemorrhage the onset of rigor mortis is delayed.

The third possibility, that the capillaries in some circumstances may not be able to show this response because of intense arterial constriction has a certain amount of evidence in its support. It has been noted that immediately after death there is intense constriction of vessels. If arteries be isolated this constriction may, according to McWilliam last for several days.

![Image](Fig. 4. Histamine action increased after arterial dilatation with acetyl choline. At 0.005 mgm. histamine. Later at C the reaction has been increased following dilatation due to acetyl choline at B.)

In the present experiments it has been noticed not infrequently at the beginning of a perfusion experiment or later, if a very alkaline
solution is being perfused, that no dilator effect of histamine can be obtained unless an arterial dilator has been previously injected. The arterial dilator may simply cause the histamine response to be greater (Fig. 4). The dilators used have been acetyl choline, small amounts of lactic acid and sodium nitrite. The effect of these arterio-dilators has not been to reduce the peripheral resistance permanently but only temporarily. The capillaries have then been more readily dilated by histamine, a result which we may presume has been brought about by a more adequate neutralisation and flushing of these vessels during the temporary arterial dilatation.

Discussion. The above results show clearly that it is possible by simply paying attention to the acid-base equilibrium of the tissues and the perfusion fluids, to maintain, in isolated tissues, a condition of tone which is relaxed by histamine. In view of the known action of this drug it may be presumed that the tone concerned is that of the capillaries. It is, however, significant to observe that the point at which tone is maintained is appreciably on the alkaline side of absolute neutrality. This point we purpose describing as the point of “functional neutrality” and is, we believe, approximately at the hydrogen-ion concentration of the blood.

It has also been seen that in studying the reactions of isolated vessels it is important to consider not only the reaction of the perfusion fluid but also the rate at which acid products are formed by the tissues concerned. We believe that many of the diverse results which have been obtained in relation to the investigation of drugs have been complicated by this factor and it seems most probable that the selective action of certain drugs may be ultimately dependent on these facts. Since we know from the work of Hoskins, Gunning and Berry(12), Hartman and Fraser(13), that adrenaline in a given concentration may dilate the vessels of muscles and constrict those of the skin, and since we may presume that acid is more rapidly produced in muscles than in the skin, it seems reasonable to suppose that this apparently differential action of adrenaline is due to differences in the hydrogen-ion concentration of the regions concerned.

It is obvious, too, that where a closed system has been used in perfusion experiments or in the heart-lung preparation there must be a considerable alteration in the condition of the experiments as they proceed unless adequate steps are taken to buffer the fluids concerned.

An appreciation of these points throws considerable light on the results of Dale and his co-workers on this subject. It is evident that
the importance of adequate oxygenation lies not only in the supply of oxygen to maintain life, but is also closely related to the oxidation of lactic acid as it is formed. It is possible, too, that the addition of blood corpuscles to the perfusion fluid, which was emphasised by Dale and Richards, not only increases the viscosity of the fluid but also increases its buffering.

To what extent the general results given in this paper are related to the nervous and hormonal control of the capillaries will be made the subject of further investigation but meantime it appears evident that there exists in the variability of the acid-base equilibrium of the capillaries a mechanism which can regulate the blood supply of the tissue concerned according to their activity.

SUMMARY.

Experiments are described which show that the maintenance of capillary tone as demonstrated by the response of these vessels to histamine is under the control of a simple acid-base equilibrium.

The expenses of this investigation were in part defrayed from a grant from the Government Grants Committee of the Royal Society.

REFERENCES.

(2) Roy and Brown. This Journ. 2. p. 323. 1879.
(3) Krogh. Ibid. 52. p. 457. 1919.
(5) Krogh and Harrop. This Journ. 54; Proc. Physiol. Soc.
(6) Dale and Richards. Ibid. 52. p. 110. 1918.
(7) Dale and Burn. Ibid. 61. p. 185. 1926.
(11) Hemingway. This Journ. 61. 1926. (In the Press.)
(13) Hartman and Fraser. Ibid. 44. p. 353. 1917.
AN ANALYSIS OF THE PRODUCTION OF HEAT IN CERTAIN MUSCLES OF THE HEDGEHOG.

By W. HARTREE and R. J. S. McDOWALL.

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AN ANALYSIS OF THE PRODUCTION OF HEAT IN CERTAIN MUSCLES OF THE HEDGEHOG.

BY W. HARTREE and R. J. S. McDOWALL.

(From the Physiological Laboratory, Cambridge.)

In a previous paper (1) by one of us, it was shown that certain isolated muscles of the hedgehog were capable of surviving for a considerable time and of working at lower temperatures than that of the body; records were given proving that the processes of contraction and relaxation were much slower than in frog's muscle. It was suggested to us by Prof. A. V. Hill that an investigation of the heat-production in these muscles would be of value, partly because the hedgehog is a warm-blooded animal and all previous experiments on the heat-production of muscles have been made on cold-blooded animals, partly because the slowness of action of these muscles of the hedgehog would make it difficult to analyse and to follow the true course of the heat-production in its initial stages. A series of experiments was made employing the usual arrangement of muscle chamber, thermopile and galvanometer.

The muscles used were (according to Huxley's (3) nomenclature) (A) the coccygeo-orbicularis, and (B) the humero-dorsalis. Preparation (A) has the advantage that it can be dissected out and the bone left attached to one end of each of the pair of muscles, and the bone can then be held in the clamp, in a manner similar to that in which the pelvic bone is held when using a pair of sartorius muscles. Preparation (B) was generally used as a single muscle turned round the end of the thermopile so that it lay on both faces of the latter. The cervico-orbicularis was also tried and did not give good results.

A certain amount of damage was inevitably done in tying a thread directly on to the muscle substance, as had to be done at one end of each of the pair of muscles in case (A) and at both ends of the single muscle in case (B); during the tying a violent contraction was always produced. The damage so caused may account for the early failure of many of the muscles. It was usual to find that the muscle continued to give a mechanical response, on stimulation, for many hours after dissection; the tension and heat-production however, were often so small...
HEAT PRODUCTION OF MUSCLE.

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The stimulus required so great, that often a considerable portion of the heat observed was due to the direct heating effect of the stimulating current. This direct heating effect of the stimulus was always determined when a muscle was dead (on the supposition that the resistances, etc., were the same both before and after death) and allowed for, but when the allowance was large it naturally diminished the effective size and accuracy of the galvanometer deflection obtained, on which the analysis of the heat depends. The muscles used were generally four or five times the weight of a pair of frog’s sartorii, but this has little effect on the size of the galvanometer deflection which more nearly represents a given change of temperature than the production of a given quantity of heat.

It was thought at first that the exposed portions of the muscle, specially those portions exposed to the thermopile itself, might be dying more rapidly than the internal portions of the muscle, and so might affect the apparent time course of the production of heat. It is obvious that if the muscle fibres directly in contact with the thermopile were dead and the fibres inside the muscle were still alive, the heat would always be delayed in its appearance at the thermopile. The records show however that if a higher proportion of the initial heat than is usual with a frog’s muscle, is produced immediately on stimulation, so that no possible injury of the surface of the muscle by dissection or exposure in account for the actual phenomena observed, as they necessitate an effect in the opposite direction. It was found that the best results were obtained by keeping the muscle in ordinary mammalian Ringer’s solution until the temperature in the chamber had practically settled down, in which case readings could be taken comparatively soon after the solution had been removed.

The size of the tension and heat readings with a given strength of stimulus varied considerably in different experiments, presumably in consequence of a difference in the condition of the muscles. In a few, if sized readings were obtained with a strength of stimulus no greater than would have to be used to obtain similar readings with frog’s muscle. Most of the experiments were carried out in air. Substitution of oxygen or air did not cause any marked difference, except in the recovery heat. Various temperatures between 0° C. and 30° C. were tried. The temperature of the animal during life is high; in the abdomen soon after death it was 33° C. and we had expected that the muscle would survive better at 30° C. than at a lower temperature. On the other hand it seemed important to use as low a temperature as possible, so as to slow down the course of the initial heat production to enable its analysis to
be made the more accurately. We found, however, after many attempts that good results could not be obtained either at 30° C. or at 0° C. In every case in which the muscle survived long enough to give any readings at all, the tension or heat in the first observations was small, even with a large stimulus. In such cases reliable heat observations were out of the question, although tension records could still be made. We cannot explain the failure at 30° C., though the failure at 0° C. is perhaps hardly surprising in the case of a warm-blooded animal. Experiments at 20°, 15° and 10° C. were fairly successful, and the results are given in the abstract below. Since, however, the processes in hedgehog's muscle at 10° C. are no slower (as one of us has since ascertained) than those in toad's muscle at 0° C., one of the reasons for the present investigation, namely that of slowing down the process taking place in the muscles as to follow the course of the initial heat-production, is of no importance as we thought at first. The action of toad's muscle is considerably slower than that of frog's muscle so that a considerable increase in the analysis of the heat will be possible with toad's muscle, which survives well at 0° C. We consider, however, that the results we have obtained with hedgehog's muscle, do give decisive evidence on the other and equally important point, namely the similarity of the process taking place during the contraction of muscles of very different animals. Further, this is the first time that an investigation of the heat-production of isolated mammalian cross-striated muscle has been made.

**Results.** In each case only a single shock or a short tetanus of not longer than 0.25 sec. (at 90 periods per sec.) was given. It was found that there was always a large outburst of heat immediately after the stimulus, which was rarely less than 60 p.c., and often as large as 70 p.c. of the total initial heat-production. Following this initial outburst was an interval, during which the tension of the muscle rises, and in which the heat-production is very small or nothing, the duration of this period being longer at a lower temperature. Following this there is a considerable evolution of heat, more or less following the process of relaxation, amounting altogether to some 30 to 40 p.c. of the total initial heat. The time relations of this heat-production associated with relaxation is shown in Fig. 1. There is no doubt whatever of its existence, or of the general type of curve governing its appearance. The rate of heat-production after the interval rises so quickly that it is impossible to assume that it does not start at its maximum value. The maximum rate of heat production during relaxation is distinctly higher at a higher temperature.
HEAT PRODUCTION OF MUSCLE.

The rate of heat-production falls off much more rapidly at high temperatures as is shown in the following table.

<table>
<thead>
<tr>
<th>Temperature in degrees C.</th>
<th>Maximum rate of subsequent H.P. in terms of total initial heat per second</th>
<th>Approximate time to maximum rate, in secs.</th>
<th>Approximate time of rate falling from maximum to 1/2 maximum, in secs.</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>0.12</td>
<td>1/2</td>
<td>3</td>
</tr>
<tr>
<td>15</td>
<td>0.20</td>
<td>1/4</td>
<td>1/2</td>
</tr>
<tr>
<td>20</td>
<td>0.30</td>
<td>1</td>
<td>1/2</td>
</tr>
</tbody>
</table>

Fig. 1. The tension (broken curve) and heat rate (full curve) for single shock at 10° C.

The initial outburst of heat occurs very suddenly and is not shown in the figure; it represents about 0.67 of the total initial heat. Following this initial outburst is an interval of rather more than a second, after which the heat rate rises again; the total area of the heat rate curve, if continued till it touches the base line, being about 0.33 of the total initial heat.

The figure gives a good idea of the slowness at 10° C. of the process involved. Unfortunately tension records were not taken in every case. Two experiments at 10° C. gave a curve similar to that shown, but it must be observed that in most of the other cases in which tension records were taken, the tension fell off in relaxation rather more rapidly compared with the fall of the rate of heat-production. It will be seen therefore that, in general character, the hedgehog’s muscle behaves in a manner exactly similar to the muscle of the frog. There is a large initial outburst of heat followed by an interval during which the tension rises, or continues to rise, and then there is a considerable heat-production during relaxation amounting to 30 or 40 p.c. of the total initial heat. This relaxation heat represents presumably, at any rate in part, the potential energy dissipated in the muscle during the process of relaxation.

It was possible to carry the analysis of the heat-production beyond the initial stages, and to determine the heat-production during the longer intervals in which recovery occurs. Some difficulty was found in obtaining reliable results, on account of the time which had to be given
after the Ringer's solution was removed and before the galvanometer was steady enough to take long records. Frequently the muscle had failed before sufficiently reliable records were possible. Three experiments, however, at 20° C. in air (from which the oxygen had been partly used during earlier contractions) gave very similar results, the total delayed heat being between 0.6 and 0.7 of the total initial heat, with a maximum relative rate of 0.004 per sec., at about 50 seconds after a tetanus of 0.25 sec. One experiment only was successful in oxygen, which at 10° C. gave a total delayed heat about 1.5 times the initial heat, with a maximum relative rate of 0.0025 per sec. at about 120 secs. after a tetanus of 0.2 sec. In this latter case a fairly large allowance had to be made for the heat appearing after 5 minutes, recovery being very slow on account of the lower temperature. It is seen however that in general the delayed heat during the recovery phase is similar, both in amount and in character to that occurring under the same conditions in a frog's muscle.

**Summary.**

An analysis of the heat-production during and after the contractile movements of the slow-moving isolated muscles of the hedgehog has shown that qualitatively and quantitatively, the same phenomena occur as in frog muscle. There is an initial outburst of heat on stimulation, continued as the stimulus be prolonged: an interval at the cessation of stimulation followed by a large and characteristic outburst of heat during relaxation and finally there is a slow, prolonged and considerable evolution of heat during recovery.

The expenses of this research have been borne in part by a grant from the Royal Society.

**REFERENCES.**

(2) Hartree and Hill. This Journal, 54. p. 84. 1920.
A VAGO-PRESSOR REFLEX. By R. J. S. McDOWALL.

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A VAGO-PRESSOR REFLEX. By R. J. S. McDOWALL.

(From the Department of Physiology, King's College, London.)

1915 Bainbridge(1) described a nervous relation between the venous pressure and the pulse rate. He showed that a rise in venous pressure used a diminution of vagal and an increase in accelerator tone, and hinted out the importance of this factor in the regulation of the cardiac output during muscular exercise. In the course of experiments made another purpose the possibility arose as to whether the vagus was also an important factor in the maintenance of blood-pressure under conditions of poor inflow. I am indebted to Dr G. V. Anrep for the formation that Pavlov in 1879 had observed that the alterations in arterial pressure which occur as the result of bleeding or of the injection of defibrinated blood were both increased if the vagi were cut. For example, he noted that in dogs the withdrawal of blood to the extent of 5 p.c. of their body weight only caused a small or temporary fall of blood-pressure when the vagi were intact but that there was a large fall if the vagi were cut.

It is well known that in haemorrhage there is constriction of arterioles and this is usually alleged to be due to increased action of the vaso-motor nerve. There is also a fall of venous pressure but no one appears to have suggested that this fall is responsible for keeping up of the vaso-motor tone. A series of experiments have been carried out to investigate this point. In all experiments cats anaesthetised with chloralose, and under artificial respiration, were used. Various methods have been adopted to reduce venous pressure.

Alcohol. I have shown elsewhere that a certain amount of alcohol produces a profound fall of venous pressure, although the arterial pressure may be unchanged. The latter observation is well known. If after the administration of alcohol (say 5 to 10 c.c. of a 50 p.c. solution) the vagi are cut there is a marked fall in arterial pressure. This fall may be permanent or may to some extent be recovered from for reasons which will be put forward below.

Histamine. In partial shock caused by the injection of one or two milligrams of histamine there is a fall of venous pressure(3), and inadequate supply of the heart(4). If sufficient histamine is given to reduce
the arterial pressure to 60 or 80 mm. Hg then the cutting of the vagi causes a further fall in arterial pressure.

**Fig. 1.** Effect of alcohol. 8 c.c. of 50 p.c. alcohol had been injected. Tracings of pressure in pulmonary artery, superior vena cava and carotid artery. Section of the vagi causes a large fall of arterial pressure without a corresponding large rise of venous pressure. In A there is no change of pulmonary pressure. In B there is a fall.

**Haemorrhage.** If blood is withdrawn from the animal to lower the arterial pressure to 60 or 80 mm. Hg and, as stated above, also the venous pressure, section of the vagi causes a further fall of arterial pressure (Fig. 2).

**Mechanical.** A loop of thin twine was placed round the thoracic vena cava and attached to a screw arrangement by which the tension on the loop could be increased and the vena cava compressed. In this way the venous pressure close to the heart could be lowered to any required extent. When the vena cava was sufficiently compressed the arterial pressure fell to 60 mm. Hg, but rose slightly as the compression was maintained. On section of the vagi the arterial pressure at once fell (Fig. 3).

It will be seen from these experiments that under a variety of conditions section of the vagi causes a fall of arterial pressure, whereas normally such section causes, as is well known, a rise in pressure. For
the alcohol experiments it is seen that the effect of the vagal section is not necessarily dependent on a previous fall of arterial pressure. From

Fig. 2. Effect of haemorrhage. After a reduction of blood-pressure from 140 mm. Hg to 60 mm. by haemorrhage, section of the vagi causes a further fall.

Fig. 3. Effect of lowering the venous pressure near the heart. Compression of infra. vena cava at V.C.C. On section of the vagi the pressure falls nearly to zero. V.C.R., vena cava released.

the histamine experiments it is seen that the effect is not due to any specific action of the alcohol, while the haemorrhage and mechanical experiments exclude any effect of capillary dilation or a fall of peripheral venous pressure. All the experiments have in common a fall in pressure close to the heart. How then can a fall of venous pressure influence the result of vagal section on arterial pressure?

It cannot be considered that the depressor nerve, or what corresponds to it in the cat, is concerned. In those experiments in which the aortic pressure was reduced the diminution would tend to increase the tone of the vaso-motor centre, but section of the vagi in the cat would still further cause an increase in vaso-motor tone.
That the nerve section itself was not responsible for the results was shown by the fact that a similar fall occurred when the vagus path were interrupted by the application of cocaine to the nerve trunk in the neck.

There appear to be only two possibilities. (1) The increased rate of the heart consequent on the section of the vagi may result in a diminished output when the venous pressure is low. (2) The vaso-motor centre may be under pressor influences which are removed when the vagi are cut.

**Changes in cardiac rate.** When the venous pressure is low an increased rate of the heart might cause diminished output as a result of diminished filling and this possibility has received special attention. Records of the rate were made by making the heart activate a system of two tambours by means of a hook attached to the anterior surface of the organ. Changes in rate were brought about by the application of hot and cold fluids to the region of the pacemaker. As the peripheral resistance is not affected and may be presumed constant, the blood-pressure may be considered to be an indication of the output of the heart. In this way it is comparatively easy to demonstrate, as pointed out by Henderson, that when the venous pressure is normal or high, an increased rate of the heart increases the output since the organ is still completely filled during the shortened diastole. When the venous pressure is low the rate of the heart within physiological limits makes no difference to the blood-pressure, as would be inferred from Starling’s *Law of the Heart*. Of course, if the cooling is excessive, say with iced saline, and the heart rate enormously reduced, the blood-pressure may fall whatever the venous pressure, but in no instance has it been found possible wi
intact vagi so to increase the rate of the heart as to diminish the diastolic filling and the output. The effect of changes in rate are seen in Fig. 4.

To return to the effect of section of the vagus, were the fall of arterial pressure due to the increased rate and a diminished output of the heart it would be possible by again slowing the heart to recover the pressure by peripheral stimulation of the cut vagus (suggested to me by Dr Hewitt) by pilocarpine or direct applications to the pacemaker as above. This has not been found to occur, a fact which is in accordance with the results in relation to the heart rate stated above. When the venous pressure is low it is possible to slow the heart appreciably without affecting the blood-pressure as the increased diastolic filling increases the output per beat and makes up for the diminution in rate (Fig. 5).

Fig. 5. Carotid blood-pressure after haemorrhage. From A to B, peripheral end of vagus stimulated; slowing of the heart but no fall of blood-pressure. Time ½ sec.

Were the effect of the section due to diminished output it would certainly give the characteristic abrupt rise of venous pressure. This does not occur. Rather there is the equally characteristic slow rise (since smooth and not cardiac muscle is concerned) which I find to be typical of diminished resistance in the arterioles. Fig. 1 also shows that the pressure in the pulmonary artery is not necessarily affected as it certainly would be if the diastolic filling were reduced. In this experiment there was an increased venous inflow to the heart which counterbalanced any fall of pulmonary pressure which may have occurred from pulmonary vaso-dilatation.

The effect of the rate of the heart may further be excluded by increasing the rate by hot applications to the pacemaker prior to the section of the vagi. Then there is the same fall of arterial pressure while the change in the heart rate is negligible (Fig. 6).

The second possibility that the vagi carry pressor influences remains for consideration. That the vaso-motor centre is concerned is shown by the fact that if the centre is cut off by section of the spinal cord in the upper dorsal region, section of the vagi under conditions of low venous inflow does not cause a further fall of arterial pressure. Tone of the peripheral arteries is then, as would be expected, an essential part of the
reflex. For complete confirmation of this and the participation of the peripheral arteries it may be shown that on section of the vagi there is

Fig. 6. Upper tracing heart rate, lower tracing carotid blood-pressure after the blood pressures have been reduced by haemorrhage. In (B) the typical effect of vagal section is seen. A and C, taken in the same animal immediately before and after the section, show that much larger changes in rate can occur without affecting the arterial pressure. Were the change in the vagal section (B) due to slowing of the heart, a similar change would be expected on slowing in (A), while if the fall in (B) were due to quickening, a recovery would be expected on slowing in (C). Time in plethysmographic experiments a distinct increase in the volume of the limb and, as is seen in Fig. 7, the increased volume of the limb is main

Fig. 7. After haemorrhage. Section of the vagi causes a fall in arterial pressure accompanied by an increase in the volume of the hind limb.

tained although the arterial pressure may return to normal for restated above. It can therefore be considered that under condition low venous pressure in the region of the right auricle, impulses pass the vagi to the vaso-motor centre which is thereby stimulated and tone of the arterioles and arteries is increased. An attempt has
made to differentiate between the effect of a diminution in venous and a fall of pulmonary arterial pressure which necessarily occurs at the same time but the experimental difficulties have so far prevented any satisfactory conclusion being arrived at.

It is evident that the existence of such a reflex will be of considerable value in conditions of loss of blood actual or relative (i.e. when the vascular bed has been increased as in certain varieties of shock). By its means the arterial pressure and especially the pressure in the coronary and vertebral arteries will be kept as high as possible when the output of the heart is reduced. In this respect the vago-pressor reflex will supplement the well-known depressor reflex, but with this difference that it will continue to act when the arterial pressure has returned to normal if the venous pressure has not—as after haemorrhage. Thus is explained a phenomenon which was difficult to understand, namely, how the vaso-motor centre is so stimulated as to maintain the arterial pressure when the normal has been reached again soon after haemorrhage, i.e. when the depressor reflex is no longer active.

The possibility of the operation of the reflex in plethysmographic experiments has also to be remembered. Thus a drug which causes a fall in venous pressure may cause diminution in the volume of a limb and variations in the reflex may account for the many admittedly anomalous results which occur in relation to limb volume, with a drug such as histamine.

**Summary.**

When the venous pressure in the large veins is low, section of the vagus causes a fall of arterial blood-pressure.

Reasons are put forward why this is to be considered a vago-pressor reflex, and not due to changes in the heart rate.

The evidence indicates that when the venous pressure is low impulses pass up by way of the vagus and stimulate the vaso-motor centre and so increase the arterial tone.

The importance of this reflex in supplementing the depressor reflex in conditions of blood loss is pointed out, and an explanation of the marked arterial constriction of secondary wound shock is afforded.

The expenses of the investigation were in part defrayed by a grant from the Government Grants Committee of the Royal Society.

**References.**

(1) Bainbridge. This Journ. 50. p. 65. 1915.
(3) —— Ibid. 57. p. 146. 1923.
(4) Dale and Laidlaw. Ibid. 52. p. 335. 1918.
ON THE NATURE AND SIGNIFICANCE OF VAGUS ESCAPE. By R. J. S. McDOWALL.


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ON THE NATURE AND SIGNIFICANCE OF VAGUS ESCAPE. BY R. J. S. McDOWALL.

(From the Department of Physiology, King's College, London.)

The escape of the heart from vagus inhibition has generally been attributed either to an outburst of energy stored during rest or to a fatigue of the nerve endings. Hill and Barnard(1), however, showed that compressing the abdomen when the heart was stopped, and thus producing a rise of pressure on the right side of the heart, might cause escape, and more recently Bainbridge(2) found that increase in the pressure in the right heart by venous injection increased the rate of the heart beat. Since this did not occur after section of the vagus he considered that the effect was a reflex one by way of the vagus, although he did not exclude entirely increased sympathetic action. It seemed then possible that increased blood pressure in the right side of the heart, caused by increased venous pressure, might play an important part in vagus escape, and this question I have investigated. All the experiments were made on cats, anæsthetised in the first instance with ether and later with choralose, and in order to make the conditions as near as possible to those occurring ordinarily in life nearly all my experiments have been made of escape from partial, not complete, inhibition. Further I have discarded all experiments in which there was indication of shock.

The effect of venous pressure on vagus escape.

In these experiments venous pressure was recorded by a method which I have described elsewhere(3). The heart rate was recorded by an ordinary mercurial manometer. It was realised, however, that strictly speaking this may not always be correct, but with high blood-pressures it has been found on checking that the waves were reasonably accurate records of left ventricular beats.

Raised venous pressure. The rise of venous pressure which occurs on stimulation of the vagus in an animal with good circulation is as striking as the fall of arterial pressure (Fig. 1), and this fact together with the observation that after a brief period of vagal stimulation the heart is markedly accelerated was really the starting point of this investigation. Such a rise can also be simply produced by injecting fluid,
such as gum-saline, into the veins. When the strength of stimulus increased to an extent which just prevented the escape, the escape

readily brought about on the injection of fluid. This occurred even when the fluid injected was at ordinary laboratory temperature, so that apparently the effect of the tension more than counteracted the effect of the cold. The venous pressure could also be raised by compressing the abdomen and vagus escape brought about in this way as pointed out by Hill and Barnard (1). In such procedure, however, the arterial pressure is also raised and if the vagi were intact it might be expected that the rise of aortic pressure would have the opposite effect and slow the heart by means of the depressor reflex. Apparently however a rule the rise of venous pressure more than counterbalances the effect of the rise of aortic pressure, but in one experiment the compression of the abdomen with the hand brought about a preliminary slowing of the heart which was followed by an acceleration although the blood-pressure had risen to a higher level, indicating that in this instance the rise of aortic pressure caused in the first instance a slowing of the heart which more than counterbalanced the rise of venous pressure (Fig. 2).
It was also noted that after raising the venous pressure by compression of the abdomen a strength of stimulus which brought about vagal inhibition might no longer do so. In such compression of the abdomen it was noted also that the effect became less if the compression was often repeated, while if the venous pressure was already high no further increase could be expected to cause further acceleration. It will of course be understood that what has been said above refers to escape from the minimal stimulus which will bring about inhibition.

**Prevention of the rise of venous pressure.** The rise of venous pressure which occurs in vagal stimulation can readily be prevented by introducing between the venous cannula and the manometer a compensator such as that described by Roberts(4) or a valve. It was found, as seen in Fig. 3, that if in this way the venous rise was prevented, vagus escape did not occur but as soon as the compensator was shut off and the venous pressure permitted to rise, vagus escape at once took place. In Fig. 3. × ⅔. Stimulation of vagus begun at first arrow and continued throughout. At the second arrow, which are corresponding points in the two tracings, the venous pressure was allowed to rise and there is at once an increase in heart rate.
carrying out this experiment great care has to be taken to insure that the venous cannula is quite free as the haemorrhage into the compensatory tends to lead to blocking.

*Lowered venous pressure.* As I pointed out in a previous paper, after severe haemorrhage the venous pressure becomes so low that an appreciable slowing of the heart does not alter the cardiac output per minute, since the filling is increased by the lengthened diastole. For this reason if the venous pressure is sufficiently low, there is little or no change in the arterial and venous pressures, and it is found that in such circumstances vagus escape does not occur. If the haemorrhage is less severe the escape is delayed appreciably, apparently because a large rise of venous pressure must occur before the cardio-accelerator mechanism is stimulated sufficiently. In Fig. 4 is given an example where the rise of venous pressure in the superior vena cava rose from 26 to

![Graph](image-url)

**Fig. 4.** In A in which the venous pressure rises from 26 to over 40 mm. there is considerable, but not complete, escape although the vagus was stimulated continuously commencing at the arrow.

B taken from the same animal after haemorrhage. Pr. = 110, the venous pressure has fallen proportionately very much more. The vagus was stimulated between arrows, there is no appreciable recovery of the normal rate. But it will be seen that the venous pressure never rose above a maximum of zero mm.
and a typical escape was brought about, while a few minutes later after severe haemorrhage which lowered the venous pressure appreciably and on stimulation it never rose above a maximum of zero, no escape occurred. It was also found that in the latter instance the strength of stimulus necessary to bring about even a great slowing of the heart was appreciably less.

The effect of haemorrhage was also seen if the loss of blood took place during the escape and it was found that in such circumstances the escape tends to disappear and the vagus action to become more effective as the haemorrhage proceeds (Fig. 5). This experiment is not, however, always successful since it depends on a narrow range both of strength of stimulus and degree of haemorrhage. In experiments controlled by taking the venous pressure at the same time, it was found that the normal rise of venous pressure on vagal stimulation was converted into an enormous fall by the haemorrhage.

The effect of the strength of stimulus on vagus escape.

Hough (6) and others have recorded that vagus stimulation had after a time no effect. Similarly in these experiments after vagal inhibition from which there had been complete escape, it was found that frequently the same strength of stimulation no longer would bring about inhibition. This has been noted even when there has been vagal stimulation without actual escape. It has been pointed out by MacWilliam (7) that during vagal inhibition there is diminished irritability even to subsequent vagal stimulation. In some animals a moderate stimulus allowed a partial escape only, that is although the heart rate recovered to a large extent recovery was not complete, which appeared to indicate that the strength of stimulus used was in excess of the counteracting stimulus brought about by the rise in venous pressure. Even when the escape was complete a strengthening of the stimulus usually brought about further inhibition. It is also observed most clearly that haemorrhage increased the sensitivity of the animal to vagal stimulation (see Figs. 4 A and 4 B). In two animals it was found quite impossible to stimulate the vagus by any strength of current, and this I understand has been with some other workers, e.g. Hough (6), a fairly common experience. In the animals referred to, it was found that the venous pressure was abnormally high, over 100 mm. H$_2$O, and on reducing this by bleeding the reaction of the animal to vagal stimulation became normal. This would appear to show that the venous pressure was so high that no amount of vagal stimulation could counteract it. The cause of this high venous
pressure is not yet clear. The experiments were carried out under conditions similar to scores of others, except that they were done during the heat wave when the animals had been kept and experimented in rooms over 80° F. It seems possible that the high venous pressure was brought about by the secretion of adrenaline which Cramer suggested occurs in such circumstances or to cardiac impairment produced at the early stage of the experiment by excess of volatile anaesthetic.
The relation of vagus escape to the nervous control of the heart.

Relation to so-called vagus tone. In these experiments animals with a marked vagus tone were chosen in order that any diminution in this tone would be more clearly evident. Normally in such animals section of the vagi brings about a very much increased rate of the heart and rise of blood-pressure. If, however, the vagi are cut during vagus escape it is found that there is no further increase in the heart rate. The absence of vagus tone may be shown in other ways. Nervous impulses passing down by the vagus were blocked by passing a constant current through each nerve. The blocking caused an increase in the heart rate similar to that caused by section of the vagi. When, however, conduction was blocked during vagus escape or immediately after it, there was no increase in heart rate (Fig. 6). The above experiments show conclusively that stimulation of the vagus brings about a disappearance of the normal vagus tone, even in the nerve which is not being stimulated. It has been clearly seen, however, that the loss of vagus tone is not wholly responsible for the escape as the latter may take place after section of both vagi. Bainbridge (2) could not find evidence of any other afferent path for the acceleration produced by venous injection than by the vagus, but it does not seem at all clear that his experiments were conclusive on this point. As it has been shown by Langley (8) and McDowall (9), using different methods, that afferent impulses pass from thoracic viscera by way of the stellate ganglion, it seems quite probable that impulses concerned in this reflex may also pass by way of afferent sympathetic fibres, and that this must be so is suggested by the marked effect of removal of the stellate ganglia.

Relation to the sympathetic. This can be most easily demonstrated by removal of the stellate ganglia. These are most readily exposed by detaching the second rib at its chondro-sternal junction, cutting down each side of the rib, taking care to avoid the intercostal arteries at the infra-costal margin, and forcibly dislocating the rib outwards, completing the exposure of the ganglia by blunt dissection. In some of these experiments the decrease of vagus tone was excluded by section of the vagi.

When the ganglia had been removed and the electrodes applied to the peripheral vagus in the neck, it was found that very slight slowing is maintained with little or no change (Fig. 7). A very slight escape is sometimes seen but this is not comparable with that seen normally and may be taken to be due to some direct effect of the rise of venous
pressure on the right side of the heart. The only limit, indeed, to vagi inhibition appears to be the life of the animal. The anoxæmia of venous congestion, as shown by Bolton(10), brings about an increased permeability of the capillaries and oedema and hence it is found that after stimulation of the vagus for a minute although the arterial pressure may recover, the rise in venous pressure is followed by a marked reduction, such as occurs in haemorrhage or in histamine shock. Vagus stimulation has been kept up for over an hour during which the blood pressure fell from 150 to 20 mm. of mercury. These results confirm those of Hough who concluded that vagus escape was certainly not due to vagus fatigue. The experiments indicate that stimulation of the sympathetic is as important a factor as loss of vagus tone.

**DISCUSSION.**

It may be reasonably concluded that there occurs during vagus escape a decrease in the action of the cardio-inhibitory centre or what Langley suggests should be called "vagus restraint" rather than "vagus tone," and the stimulation of the sympathetic, which taken together may be called a stimulation of what is best described as a cardio-accelerator mechanism, and from the evidence previously given in relation to venous pressure, it may also be concluded that the means by which the mechanism is stimulated during vagus escape is one which takes place normally in exercise, namely a rise in venous pressure.

Fig. 7. Arterial pressure, vagi cut, stellate ganglion removed, peripheral end of vagus stimulated between the arrows. No escape. From A to B the stimulating current was shut off temporarily.

Three pieces of evidence, namely the relation of venous pressure...
VAGUS ESCAPE.

Vagus restraint and of the sympathetic are all the more convincing as they are all quite separate yet are mutually supporting. It could indeed be most readily argued that the most likely thing to bring about such nervous changes under such circumstances as vagal stimulation would be a rise of venous pressure even if it had not been shown that this was brought about.

Although the above results appear to show fairly conclusively that the stimulation of the cardio-accelerator mechanism is the cause of the vagus escape, one other possibility requires careful consideration, namely that the fall of arterial pressure during vagal inhibition might, in accordance with Marey's Law, bring about a quickening of the heart. Were this the case it might reasonably be expected that the reduction of blood-pressure by haemorrhage would render the animal less sensitive to vagus stimulation, while the reverse is found to be clearly the case. Also it would be anticipated that were vagus escape due to fall of arterial pressure, it would occur whenever the arterial fall occurs, whatever the change of the venous pressure, and this we have seen above is clearly not the case. Further, when an animal was bled during the escape to an extent below that to which it was lowered by the cardiac inhibition, the result was increased slowing rather than quickening. It may then be concluded that the fall of arterial pressure is not an important factor in the production of vagus escape although possibly it may assist. In view of the above and the fact that we know that in exercise a cardiac acceleration may be brought about in spite of a rise of aortic pressure, it seems possible that the application of Marey's Law should be restricted to the operation of the depressor reflex by which there occurs a lessening of the depressor impulses normally passing up from the aorta when there is a fall of arterial pressure, unless it be made also to relate to simultaneous changes in the venous pressure.

The significance of vagus escape. The significance of the relation of the rise of venous pressure to vagus escape lies in the fact that it may be considered that such escape indicates the physiological mechanism by which an increased heart rate may be brought about in spite of increased vagus tone or increased reflex stimulation by the depressor nerves. That there must be some antagonism during the rise of aortic pressure in exercise between the depressor and accelerator mechanism is evident.

The significance of vagus restraint. From the above facts we are in a position to appreciate the significance of increased vagus restraint which we know is associated with habitual activity in man and in
animals. It will be evident that this increase will prevent each 
acceleration by a rise of venous pressure which would otherwise do 
but this restraint does not appear ever to have been associated with 
the fact that habitual activity also leads to greater efficiency on the p 
of the heart muscle. The more efficient the cardiac muscle the bet 
the heart can respond to increased filling, and the more capable it is 
increasing its output in accordance with the law of the heart. We 
there, however, no increased vagus restraint, the heart could not th 
full advantage of this increased efficiency since exercise would be 
about excessive acceleration with a shortened diastole and there wou 
be less time for filling. Vagus escape, then, by reducing the amount 
the acceleration for a given rise in venous pressure makes the he 
more capable of increasing its output with a minimum number of be 
presumably with a view to economising the energy of the animal 
is obviously more economical to have a fewer number of efficient con 
tractions than a larger number of less efficient contractions, althou 
both would have the same effect in increasing the cardiac output 
minute. It is also known that in repeated exercise there is bring 
about a considerable economy in muscular effort possibly from bet 
coordination which must result in less CO₂ being produced and a 
raising of venous pressure which would further supplement the econo 
of the heart.

SUMMARY.

Evidence is put forward that vagus escape is sufficiently account 
for by the rise of venous pressure which occurs during vagal stimulat 
There is found to be diminution in vagus restraint and stimula 
tion of the sympathetic and this may be spoken of as a local cardio-acceler 
mechanism. The significance of vagus escape and vagus restraint 
discussed on the basis of these results.

The expenses of this investigation were in part defrayed by a grant from the G 
ment Grants Committee of the Royal Society.

REFERENCES.
2. Bainbridge. Ibid. 50. p. 65. 1915.
6. Hough. This Journ. 18. p. 175. 1895.
11. McDowall. This Journ. 59. p. 42. 1924.
THE INFLUENCE OF ACID BASE EQUILIBRIUM ON THE ACTIVITIES OF BLOOD VESSELS.

By R. J. S. McDOWALL.

THE INFLUENCE OF ACID BASE EQUILIBRIUM ON THE ACTIVITIES OF BLOOD VESSELS.

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Since Gaskell's(1) original observation of the dilatation of blood vessels by the action of acid, the opposite effect, a constriction, has been described commonly to result from the action of alkalies, but in certain conditions also from the application of acids.

In some of the experiments which led to these observations (Fleisch(2), Atzler and Lehman(3)), those, namely, in which the method consisted in perfusion of the vessels with fluids at different reactions, the importance of maintaining capillary tone was not appreciated and, as Dale and Richards showed, this tone is rapidly lost in such experiments unless appropriate steps are taken to preserve it.

In others (Evans and Underhill(4), McSwiney and Newton(5)) the vessels were merely one of different forms of smooth muscular tissue, the behaviour of which was studied by immersion in fluids at different controlled reactions. McSwiney and Newton in this way found that starting with fluid at pH 7-5 the first changes in the alkaline direction caused contraction, the first changes in the opposite direction relaxation, as observed by Gaskell. Beyond pH 5-9, however, the effect of acid was to cause contraction increasing up to a maximum with increasing acidity. Finally, beyond that maximum, as was the case too beyond a maximum contraction to alkalinity, relaxation set in.

The work of Hemingway and McDowall(6) showed that for perfusion experiments it was possible to maintain the tone of the capillaries by the previous administration of chloralose and repeated intravenous injections of alkali before the death of the animal, if after that the perfusion fluid was Ringer’s solution at pH 7-6. It seemed desirable to study with the same technique the effect of changes in the reaction of the perfused fluid and to determine if possible whether the vessels behaved in a way that was comparable with the results obtained by McSwiney and Newton, and at the same time see whether any new
light could be thrown on the observations of Evans and Underhi
who also found conditions in which acid would cause contraction.

Method. The method adopted has already been described
McDowall and by Hemingway(7). It consists essentially of
fusing the vessels in situ from a reservoir of constant pressure and
recording the resistance of the vessels to the outflow by means of
a side tube communicating with a piston recorder. The perfusion
was a modified Ringer's solution with a composition of NaCl 0·9
KCl 0·042 p.c., CaCl₂ 0·024 p.c. heated to 37°, adjusted by the addi-
tion of NaHCO₃ or NaOH to the pH required. Arrangements were made
which different perfusion fluids could be utilised, but they were
used because it was found that more convenient graphical records
be obtained by the method adopted by Hemingway and McDow-
all in which the acid or alkali was injected through the tubing lead-
ing the arterial cannula. In each instance 0·5 c.c. was injected, and
the calculations made it was estimated that the fluid injected was dil-
uted approximately ten times by the time it reached the elements on
it acted. Since the effects described are only relatively quantita-
tive was not necessary to determine more accurately the actual dil-
ution. A small error is conceivably introduced by the fact that when
vessels are dilating and the perfusion fluid flowing more rapidly
injection becomes more diluted. Control experiments have, how-
However shown that this effect is negligible and, indeed, would tend to count
the results actually obtained.

As a rule the vessels employed were those of the hind limbs of
the animals. Perfusion was begun either half an hour after decerebration or the
four hours after chloralisation and alkalinisation. In the former
the animals are referred to as "unprepared" and are almost free
from anæsthetic, in the latter they are referred to as "prepared." As
found by Hemingway and McDowall, in such animals lactic
acid formation is delayed and the acid, as it is formed, is so neutralised
the reactions of blood vessels can be studied with a minimum of in-
fluence from the acid produced in the surviving tissue.

Effects of dilute acid. If the vessels of a "prepared" animal are
fused with Ringer's solution, having an alkalinity not less than pH
7·6, the classical vaso dilator effect of acid first described
by Gaskell is seen to occur with each of a series of injections. It is
effect brief duration, and at first rapidly recovered from, so that it can
be repeated several times. Tracings illustrating the recovery have
been published by Densham(8).
In “unprepared” animals, on the other hand, and when the alkalinity of the perfused fluid is less than pH 7.4, the vessels do not recover from the dilatation caused by a sufficient dose of acid, the tone falls and a stage is reached in which subsequent injections give the reverse effect, constriction, with a dose which previously gave dilatation. Even in “prepared” animals perfused with fluid at pH 7.6, a similar reversal may be obtained by giving still larger doses of acid.

The perfused vessels, then, not only of “unprepared” animals in which the accumulation of lactic acid has not been counteracted, but also, though only with larger doses of acid, or after several repeated doses, those of “prepared” animals, react to a sufficient amount of acid by constriction instead of dilatation.

A record of an experiment showing this is given in Fig. 1, where

![Image of graph showing dilatation and constriction responses to repeated injections of acid](image-url)

**Fig. 1.** The effect of acid (0.5 c.c. N/100 lactic acid, see text) on alkaline tone. The first few injections of acid cause a typical dilatation, but gradually it is seen that there becomes developed a constriction before the dilatation. Eventually constriction is the only effect obtained. The injections were made at each H. A piece of tracing showing dilatation between 3 and 4 has been omitted.

vessels originally in a condition which may be called that of “alkaline tone” were, during perfusion, treated by a series of injections of 0.5 c.c. N/100 lactic acid. The moments of injection are marked by the letter H and by an upstroke in the tracing, which is the constant mechanical effect of the injection of fluid whatever its nature into the system. The first six injections that are recorded caused simple dilatation (not allowed in this case to reach its maximum, in order to facilitate reproduction).
In the experiment recorded in Fig. 2 a similar series of injections of a stronger acid, \( N/10 \), were given. Each is seen to have caused the first instance a well-marked but transitory constriction. After each constriction the tracing returns to an equilibrium position, descends, that is to say, and becomes horizontal before the next injection, so as to show what the effect on the level of tone has been. Thus it will be observed that the first dose of acid recorded causes a constriction followed by considerable loss of tone; the constrictions caused by the second and later doses are followed by gradual recovery of this lost tone, so that after the fifth, the process continuing, the tone rises to a level higher than before the first dose. An “acid tone” is being substituted for the lost “alkaline tone” and the second arrow marks the turning point.

**Effects of dilute alkali.** Hemingway has recorded the effect of a series of injections of alkali, showing how the same dose comes to have a much greater constrictor effect after several repetitions and how this augmented constrictor effect can be diminished by acid and restored again gradually by a series of injections of alkali.

An experiment is recorded in Fig. 3, in which a series of injections of alkali (0·5 c.c. \( N/100 \) NaOH) were given during the perfusion fluid muscles originally in a state of “acid tone.” The injections are marked by arrows; the first caused merely dilatation: at the second arrow a small constriction is seen to precede the dilatation, but this fast tone becomes more and more pronounced with the later doses. This constriction has been made a point of special attention both by myself and by Hemingway who, in describing the similar sensitisation by alkali not only in perfused vessels but also in muscle from the uterus, show clearly that this increased sensitivity was not dependent on a reduction in tone, although commonly associated with a reduction of the latter.

The effect of alkali in increasing the action of drugs has long been known. This experiment, therefore, indicated conditions under which alkali may cause dilatation; at first that and nothing else, later, thought exp
H IONS ON BLOOD VESSELS.

continues to diminish with each dose, the immediate effect of each dose is constriction, and a constriction which, though it increases in amount

with each succeeding dose, nevertheless does not prevent the tone from continuing to diminish up to the tenth dose.

The conditions under which this dilatation occurs depend upon such accumulation of acid that the passage of alkaline fluid through the vessels, though it produces the immediate constriction regularly seen when there is normal, "alkaline," tone, nevertheless takes some time to wash the acid out of them and restore any degree of alkaline tone.

In some preparations the recovery from the alkaline constriction becomes less and less complete and a sustained alkaline tone eventually is produced. At the same time the immediate reaction to alkali becomes less (Fig. 4). Such a result is possibly explained by the acid of the tissues being eventually neutralised by the
injection and the alkalinity of the perfusion fluid being then sufficient to maintain the alkaline tone.

It is clear, however, that the effect of dilute acids is also of dilute alkalies on the diameter of the vessels may either to constrict or dilate them, according to the conditions that prevail at the time. When there is no accumulation of alkalies constrict, acids dilate; when acid has accumulated, a point is reached at which acid constricts and may lead to a tonus that corresponds to nothing in the normal animal, and then alkalies are found to cause dilatation. On the approach of rigor mortis such a condition of "acid tone" appears to supervene naturally and in the ordinary course of things; for then the injection of alkali causes dilatation (see Fig. 5).

![Fig. 5. The effect of alkali in rigor mortis. At 1, 2, 3 and 4, respectively, 0.25 c.c., 0.5 c.c. and 0.5 c.c. N/100 NaOH was injected. The first three doses were without effect, but the fourth dose gave marked relaxation.](image)

does perfusion with fluid at pH 7.4, though not at pH 7.1. When "acid tone" is established the fluid issuing from the venous end has been found to be not more acid than pH 6.9. If the injected fluid leaves all the capillaries at the same time, the reaction of the fluid left in all the capillaries is the same and not more acid with some than others, "acid tone" is induced by a very low degree of acidity. The seat of such "acid tone" appears to be the arterioles, since it is relaxed by acetyl choline and by nitrites, but not by histamine. If the capillaries were the seat of constriction in "acid tone" a small dose of histamine insufficient to affect the arterioles, would be expected to dilate and allow an easier escape of fluid, which is not found to be the case. It appears, therefore, that if capillaries are at any stage constrictor effect in them very rapidly gives place to a later phase of the action of the hydrogen ion, reached more slowly by the buffered muscle, that of final, fatal, irreversible relaxation. Dr Low tells me that he knows of no evidence for believing that capillaries
pass into a state of tone under the action of acid. The tendency to edema in "acid tone" also points to the capillaries being dilated in this condition.

A general correspondence seems to be recognisable between these observations and those of McSwiney and Newton on smooth muscle immersed in fluid at different values of pH, which they have summarised in a curve. At pH 7.5 alkali caused constriction, acid relaxation: on the acid side of pH 5.9 additions of acid caused contraction, alkali relaxation. The correspondence is qualitative only, the conditions of the experiments recorded here not allowing a quantitative correspondence to be detected: indeed, a quantitative correspondence should not probably be expected, because here smooth muscle is not the only tissue involved: there is no reason why capillaries should behave as smooth muscle and, as we have seen, there is reason for thinking they do not. The correspondence also extends to the extreme end on the acid side of the curve given by McSwiney and Newton; injections of acid, continued long enough, cause finally irreversible dilatation. The observation of the extreme effect of alkalis by the methods here used is rendered impracticable by complete closure of vessels before it can be reached.

From the above it is evident that in carrying out perfusion experiments it is necessary to pay special attention to the reaction of the perfusion fluid and of any substance which may be added to it. It may readily be demonstrated that the apparent passing off of the action of a drug on blood vessels is due not to a loss of sensitivity to the drug but to the production of acid by the dying tissues.

**SUMMARY.**

The effect of dilute acids and also of dilute alkalies on the diameter of the vessels may be either to constrict or dilate them, according to the conditions that prevail at the time. The conditions under which these results occur are described.

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REFERENCES.

2. Pleisch. Pflüger’s Arch. 171. p. 86. 1918.
THE EFFECT OF CARBON DIOXIDE ON THE CIRCULATION. Part I.

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THE EFFECT OF CARBON DIOXIDE ON THE CIRCULATION. Part I.

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In 1918 Yandell Henderson [1918] found that in anaesthetized animals over-ventilation caused a fall of blood-pressure. This was shown by Dale and Evans [1922] to be due to the effect upon the medulla of the flushing out of carbon dioxide. In a more recent paper, Vincent and Thompson [1928] have emphasized that a certain degree of hyperpnea will cause a reduction of the blood-pressure in man. These investigations were, however, dealing with short periods of forced breathing but not with a profound change in the tension of carbon dioxide: indeed, they state definitely that the rapid and deep breathing performed for 30 seconds did not cause apnea. Collier, Densham, and Wells [1927], on the other hand, in an investigation in 1927, confined their attention to the effect of over-ventilation maintained sufficiently long to produce a fall of alveolar carbon dioxide and prolonged apnea, and found that in 60 p.c. of the subjects examined the apnea was not accompanied by a fall of blood-pressure. This work supports that of Henderson [1920], Hill and Flack [1910] and of Boothby [1913] in Oxford, all of whom pointed out that forced respiration did not always bring about a fall of blood-pressure in unanaesthetized man. This has since been confirmed by Schneider [1930]. The present investigation arose from the finding that in certain circumstances an over-ventilation sufficient to cause a prolonged apnea in many animals does not cause a fall of blood-pressure. Indeed, the evidence goes to show that the fall of blood-pressure when it occurs during over-ventilation may depend on the anaesthetic. This is shown by the following experiments:

The effect of over-ventilation in animals under chloralose.

This effect depends on the animal under investigation, and the results may conveniently be described in two categories:

1. Those in which a fall is caused; and
2. Those in which no fall, or even a rise, is caused.
(1) This has already been dealt with adequately by Dale and Evans [1922].

(2) If a suitable adult animal is anaesthetized with chloralose and allowed to remain undisturbed for two or three hours, the fall in blood-pressure caused by over-ventilation is often negligible and may be considered to be wholly due to mechanical interference, since at the moment the over-ventilation by means of a bellows ceases the blood-pressure returns at once to normal. Commonly there follows a temporary rise of the blood-pressure above normal (Fig. 1A). The efficiency of the over-ventilation in washing out the carbon dioxide is undoubted since respiration may remain at a standstill for over a minute, and marked tetanic spasms known to be produced by over-ventilation are evident. Further, as we shall see, the same over-ventilation produces a fall in the same animal under ether.

The absence of the depression that occurs in other circumstances is not related to the height of the blood-pressure, and in each instance has been taken to ensure that the animal was not in any way affected. This precaution was obviously desirable, since in an animal otherwise

Fig. 1. An example of over-ventilation (AR-O): (A) under chloralose anaesthesia, (B) in the same animal after the subsequent administration of ether. In (A) the over-ventilation was sufficiently severe to produce tetanic twitchings of the muscles. In (B) a large fall of blood-pressure occurred, although the over-ventilation was appreciably less.
anæsthetized there is a limit to the extent to which the blood-pressure may be lowered by washing out carbon dioxide.

In two animals apparently otherwise normal the over-ventilation actually caused a rise of blood-pressure, but they are important as they apparently serve as a key to the problem (Fig. 2), in that they indicate that under some circumstances a definite pressure effect may be brought about by the proceeding.

Fig. 2. The animal was over-ventilated between the arrows.

The effect of over-ventilation in animals under ether.

In all animals under ether anaesthesia the typical result is seen which was obtained by Dale and Evans (Fig. 1B). Any degree of over-ventilation sufficient to cause apnoea is always accompanied by a fall of blood-pressure.

If the ether is administered to an animal already anaesthetized with chloralose all degrees of fall in blood-pressure may be recorded with an equal degree of over-ventilation, as judged by the length of the apnoea (Fig. 3).

It is observed, however, that not only does the total fall of pressure vary, but under the ether anaesthesia the fall of pressure is rapid and the recovery slow, while under chloralose alone such fall as occurs is slow and the recovery is relatively rapid; moreover, after over-ventilation
Fig. 3. A continuous series of over-ventilation in an animal under chloralose. At $E$ ether was administered. At $EO$ it was removed. The series shows the effect of ether in increasing the fall due to over-ventilation, though in each instance the apnoea resulted from the same. The rise fell immediately after $E$, is partially due to the ether itself. The depth and rate of the artificial
the blood-pressure may rise to a higher level than before and remain at that level for several minutes. This may occur, although the arterial pressure has not fallen during the over-ventilation.

The effects of over-ventilation on the decerebrate animal.

Dale and Evans [1922] recorded that over-ventilation caused a fall of blood-pressure in the decerebrate animal, but at that time it was not known that the effect of ether is so prolonged as Macdonald [1926] has shown it to be. He has shown, for example, that the depressor action of minute doses of adrenaline is not seen in the decerebrate animal if sufficient time is given for the ether to wear off.

In the present experiments I have found that, if time is given to exclude the effect of the ether, over-ventilation does not always cause a fall of blood-pressure (Fig. 4).

Fig. 4. The effect of over-ventilation in a decerebrate animal. Record of blood-pressure and respiration. The animal was over-ventilated between the arrows.

The influence of over-ventilation on reaction to posture.

Although the blood-pressure does not fall, it is evident that the vasomotor centre has been profoundly affected by the over-ventilation as the experiments of Dale and Evans suggest. This is seen in those animals whose blood-pressure recovers well after they are placed in the vertical feet down position. In some animals such recovery is complete, unless they have been over-ventilated, in which case they fail to recover, although the blood-pressure has not been appreciably changed by the over-ventilation (Fig. 5). This failure is not dependent in any way on
Fig. 5. Record of blood-pressure of cat under chloralose. In each instance at A the animal was placed in the vertical feet down position and at B it was returned to the horizontal position. At first it was breathing normally, at OV it was over-ventilated, at N it breathed normally but a mixture of 5 p.c. CO₂ and 95 p.c. oxygen was given; at OV again the animal was over-ventilated. The failure of the circulation to respond to posture is seen during the periods of over-ventilation.
the mechanical effect of the over-ventilation or on any change in the "respiratory pump" which was shown by L. Hill [1895] to be important in recovery; for similar results are obtained if the animal is caused to over-ventilate itself by stimulation of a sensory nerve, and in animals in which after over-ventilation, as sometimes occurs, the respiratory centre has ceased to act and which are kept alive by artificial respiration. In such circumstances the changes in the vasomotor centre are brought about by changes in the extent of the artificial respiration; recovery of the tone of the vasomotor centre takes place if carbon dioxide and oxygen are administered (Fig. 6). Spontaneous recovery of the centre, however, is often prolonged, as tested by the response to posture, although the respiration of the animal becomes normal.

Fig. 6. Record of blood-pressure of a decerebrate cat breathing naturally throughout. At A the animal was placed in the vertical feet down position and at B it was returned to the horizontal position—in each instance. At D a mixture of 5 p.c. carbon dioxide and 95 p.c. oxygen was administered. In this instance the over-ventilation occurred as a result of the sensory stimulation of the decerebration.

The effect of over-ventilation on limb volume.

The method used was to place the limb inside a plethysmograph fitted with a very thin rubber cuff made from a toy balloon. An im-
The important modification of the usual method was the use of Batenik cement instead of paraffin for attaching the rubber to the skin. The preparation (designed for the purpose of attaching rubber soles to leather) has been found to be an ideal preparation for attaching rubber to skin. The preparation is readily available in tubes, it makes a firm and tight junction with the skin in a few minutes, and by its use what has been generally recognized as an uncertain operation—because of the difficulty of obtaining a joint that is air-tight and at the same time not compress the limb—has become extremely simple.

In the experiments of Dale and Evans it was found that over-ventilation caused an increase in the volume of the limb while, if the limb was denervated, no appreciable change occurred. In unanaesthetized man a decrease of limb volume was noted by Nahun [1918] and Schneider [1930].

![Fig. 7. Record of blood-pressure (B.P.) and of the volume of a denervated hind limb in an animal under chloralose. The animal was over-ventilated between O and N.](image)
Under chloralose anaesthesia there is a fall in the volume of the limb in the intact limb, and still more definitely in the hind limb in which the anterior crural and sciatic nerves have been cut (Fig. 7).

When the arterial pressure falls, the fall in limb volume may in some degree be considered to be increased by the fall, but this effect is much less than might be imagined since a greater fall of blood-pressure caused by other means—e.g. by stimulation of the peripheral and of the vagus—causes less reduction in limb volume.

This diminution of volume on over-ventilation can be shown definitely to be an active process. It occurs whether or not the over-ventilation causes a fall of blood-pressure (Fig. 8). In one very significant experiment, after the animal had been under the anaesthetic for seven hours and the reactions had become somewhat slow, the over-ventilation caused a fall of blood-pressure; but this was slowly recovered from while the limb volume fell throughout (Fig. 9).

The most striking proof that the reduction of the limb volume is due to an active process is the fact that ether abolishes the fall in limb volume caused by over-ventilation in an intact or denervated limb, and the
negative result, obtained by Dale and Evans, is obtained. Skinning the limbs made no difference to the result (Fig. 10).

**Fig. 9.** Record of blood-pressure (b.p.) and volume of denervated hind limb (LV) of a cat seven hours under chloralose. Between O and N the animal was over-ventilated at H 0.05 mg. ergamine phosphate was injected as a control. Corresponding O are shown on both records. The arc described by the writing point of the recorder is shown.

**Fig. 10.** Record of blood-pressure (b.p.) and hind limb volume (LV) of a cat under chloralose, nerves intact but limb skinned.

In Fig. 11 is seen the effect of administering ether to an animal under chloralose. Under chloralose alone, in Part I of the tracing, the ventilation causes a fall of limb volume. On the administration of ether (2) this diminution passes off, although the blood-pressure has fallen to a greater extent than before, while, as the effect of the
Fig. 11. Record of blood-pressure (B.P.) and of the volume of a denervated hind limb \((LV)\) of a cat under chloralose. The animal was over-ventilated between \(O\) and \(N\) on five occasions. At \(E\) ether was inhaled and at \(EO\) the ether was taken off. In (1) the over-ventilation causes a fall, while under the ether at (2) the over-ventilation did not affect limb volume appreciably. In (3) and (4) the fall of limb volume returned but disappeared again after the re-administration of ether in experiment 5.
passes off the volume diminishes again, (3) and (4). The effect of blood was again repeated at E in (5), in which the over-ventilation was such that the volume diminishes again, (3) and (4). The effect of the ether in dilating the vessels, as shown by Dunlop [1929], is confirmed in these figures.

Here we see the explanation of the admittedly discordant results obtained by Dale and Evans who found in animals in which the experimental nervous system had been destroyed that over-ventilation caused an increase of blood-pressure, while in other animals a denervated limb did not show any diminution in volume. The difference appears to have been that in some limbs volume was recorded in anaesthetized animals, while the increase in blood-pressure was obtained from carcases which no longer required an anaesthetic. It is interesting to remark that the ether cuts out the dilator effect of over-ventilation, just as Dunlop showed it could cut out the constrictor effect of small doses of adrenaline.

**DISCUSSION.**

The fact that over-ventilation does not always cause a fall of blood pressure in man, and may not in animals anaesthetized with chloralose, opens up some very interesting points.

It is evident that the loss of tone caused by washing out the carbon dioxide does not affect all blood vessels alike.

The explanation suggested is that the over-ventilation has two effects, a dilatation of vessels in certain regions of the circulation resulting in a loss of tone in the vasomotor centre, and constriction in other regions produced by a different mechanism; when there is no fall it is because these two effects compensate each other, and when the pressure of the vessel is because the second effect outlasts or exceeds the first. Ether and the machinery responsible for this second or compensating effect of over-ventilation, just as Dunlop showed it could cut out the constrictor effect of small doses of adrenaline.

A large number of experiments have been carried out to determine the nature of the compensation, their main objects being to detect the compensation into operation, so that it would not be available to compensate for the over-ventilation. These were especially histamine, pituitary extract, skinning and evisceration of the animal. No procedure or substance other than ether and chloroform was covered which would cause the over-ventilation to bring about a fall in blood-pressure in an animal under chloralose in which this did not take place.

That the compensation is humoral rather than nervous is shown by the experiments on the volume of the denervated limb. The absence of cardiac acceleration, dilatation of the pupil and the absence of a
blood-pressure negative the production of any vaso-constrictor substance such as adrenaline or pituitary extract.

The possibility of the skin vessels being specially concerned was suggested by the fact that, in ordinary fainting when there is a general dilatation of internal vessels, there is intense skin pallor. It cannot be said that the skin vessels have constricted as a result of the fall in blood-pressure, since the pallor persists after the pressure has returned to normal. This I have confirmed in a student who fainted during a class demonstration.

It has been suggested, according to Luciani [1911], by Leidenheim that the vessels of the skin are differently controlled from those of the muscles. Over-ventilation in many persons is accompanied, e.g., in the writer, by intense pallor; and it has been found by Collier, Densham and Wells [1927] that in an individual whose blood-pressure has not lowered by over-ventilation, a fall occurred if the skin vessels were paralysed by a hot bath. An actual diminution of the skin circulation during over-ventilation in man has been shown by G. N. Stewart [1911] using his calorimeter method. This has been confirmed by Schneider [1930].

Further, the action of ether inhalation on the vessels of the skin is very marked; the vaso-dilatation in man is generally recognized. In animals there is, as shown by Dunlop [1929], a large increase in the limb volume, and this indicates why the action must be looked upon as the nature of a paresis. The experiments in which the limb was skinned, however, indicate that the compensation is not confined to the skin.

The simplest explanation of the compensation appears to be that just as the capillaries are dilated by carbon dioxide and the centre is stimulated by carbon dioxide, so the opposite may occur if the carbon dioxide is washed out. That alkalinization of the capillaries causes them to constrict has been described by Stricker, Goluben, Tarchanoff [1921] and by Hemingway and McDowall [1926], while Dale and Evans have shown that in an animal whose central nervous system has been destroyed, and which presumably was no longer under the influence of anaesthetics, over-ventilation causes a rise in blood-pressure.

This view is supported by the experiments of Collier, Densham and Wells [1927], who compared the effects of over-ventilation with and without compression of the veins to a limb upon the electrical resistance of the skin. They showed that the effect was very much greater if the carbon dioxide was allowed to be washed out of the limb than if it was not.

We may consider that the diminution of the activity of the vasomotor
centre results in a dilatation principally of relatively large vessels that as a result of the over-ventilation the peripheral resistance is to smaller and more peripheral vessels. This is supported by the fact that the reaction to histamine may be enhanced by over-ventilation although the blood-pressure has not fallen (Fig. 12).

![Image of Fig. 12](image)

**Fig. 12.** The effect of over-ventilation on the response to histamine (ergamine phosphate) injected intravenously.

It is of interest to note that such a transference of the peripheral resistance to more peripheral vessels may be of importance in regard to this resistance more liable to be reduced by the metabolites of the blood which come into more immediate contact with the smaller vessels. It is the increased ventilation which may occur before anticipated and assessed may be of value.

The explanation indicates also why after over-ventilation the blood-pressure may rise above normal under chloralose. The peripheral constrictor effect on the vessels may be considered to outlast the dilator effect since if the more peripheral vessels become closed the opening must depend on the accumulation of metabolites locally, the vasomotor centre immediately recovers its activity because there is circulating through it.

This explanation of the results has a new and very important corollary that the normal carbon dioxide content of the blood maintains a peripheral dilatation of minute vessels and it maintains a central stimulation of the vasomotor centre.
SUMMARY.

Over-ventilation under chloralose has been shown to cause two effects: dilatation of vessels due to central effect, and the other a constriction of smaller more peripheral vessels due to the effect of washing out carbon dioxide locally.

Either effect may predominate, and the result be a fall, no change, or a rise in blood-pressure.

Ether abolishes the more peripheral effect.

The reaction of the circulation to changes in posture are shown to be profoundly affected by over-ventilation.

The evidence suggests that the normal carbon dioxide of the arterial blood exercises a dilator effect on the more peripheral vessels.

Reasons are given which indicate that these results are applicable to normal man.

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REFERENCES.

Jollier, Densham and Wells (1927). Quart. J. Exp. Physiol. 18, 291.
Dunlop (1929). J. Physiol. 67, 144.
Nahun (1918). Referred to by Henderson, Prince and Haggard, J. Pharm. 11, 203.
Schneider (1930). Amer. J. Physiol. 91, 130.
Stewart (1911). Amer. J. Physiol. 23, 190.
Stricker, Goluben and Tarchanoff (1921). Quoted by Hooker, Physiol. Rev. 1, 112.
ON VARIATIONS IN THE ACTIVITY OF THE CARDIO-INHIBITORY CENTRE.

By R. J. S. McDOWALL.

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ON VARIATIONS IN THE ACTIVITY OF THE CARDIO-INHIBITORY CENTRE.

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The object of the experiments to be described was to define the conditions which determine the activity of the cardio-inhibitory centre. This centre is in a more or less continuous state of activity, referred to commonly as "vagus tone." I prefer the term "vagus restraint," which was suggested to me by the late Prof. Langley, as it avoids the rather loose word "tone." The amount of vagus restraint present at any moment can be determined by cutting the vagi or, better, since it can be done repeatedly on the same animal, by merely blocking the passage of impulses down them by Bernstein's method, using a constant current of 2 to 4 volts (Fig. 1). But since the cardio-inhibitory centre can be put into action reflexly by stimulation of the central end of one vagus with the other intact and the response to a given stimulus may vary according to the state of activity of the centre, it may be possible to gauge this activity by gauging its reflex excitability. In the experiments to be described both methods have been used, and the results obtained have corresponded so as to show that the reflex excitability may be taken as a measure of that activity of the centre which results in vagus restraint. Consequently, in most of the experiments here recorded it is the variations in the reflex which have been used as an indication of the condition of the centre.
In any case it is necessary to standardize the degree of anaesthesia, such experiments, and it has been found most satisfactory to work animals under a degree of chloralose anaesthesia in which the pupils constricted, but the conjunctival reflex was present.

The cardio-inhibitory reflex.

In order to interpret the results obtained, it is necessary to define features of the reflex response which are characteristic, for it is remarkable that, in spite of the familiarity of the reflex, little work appears to have been done on these lines.

Latent period. When the peripheral end of the vagus is stimulated the onset of the cardiac slowing is instantaneous, but when the central stimulated reflexly (Fig. 2) the time of onset may vary considerably. The animal has been rested, not only may the onset of slowing be delayed but the maximum effect as the stimulation proceeds is only partially developed. If the stimulus is repeated at frequent intervals the cardiac slowing becomes more rapid and the maximum effect is produced sooner. It is indeed, evident that an effect of the stimulation is to make the cardiac centre more excitable in the sense that it is more quick to respond to a stimulus.

After-discharge. In striking contrast also to the effect of stimulation of the peripheral end of the vagus (Fig. 3) is the time taken for the effect of the stimulation to pass off when the central end is stimulated. Instead of passing off immediately it may continue for several minutes.
and in certain circumstances, which are discussed later, for several hours (Fig. 4).

Fig. 3. Shows the effect of two successive stimulations of the peripheral end of the vagus (P.E.). It is seen that the second stimulation is less effective. This would not be the case if the inhibition were produced reflexly by stimulating the central end.

Fig. 4. The central end of the left vagus was stimulated between the arrows. After-discharge is well seen. The lower record is one of venous pressure.

Fig. 5. The central end of the vagus was stimulated for a long time. After being slowed the heart quickens (fatigue of centre), but the arterial pressure continues to fall (depressor reflex).

Effect of repeated stimulation. If, immediately after recovery from stimulation of the peripheral end of the vagus, the stimulus is repeated,
it is found that the same degree of slowing is not obtained (Fig. 3). It is already described by Hough [1895]. To obtain the same degree of slowing a stronger stimulus is necessary or the animal must be bled; reasons already described [McDowall, 1926]. When, however, the centre is stimulated reflexly, there is no reduction in the response unless this procedure is repeated many times.

If it is repeated many times or continued for a long period, evidence of central fatigue occurs. But in that case it is of interest that the fall in blood-pressure still occurs or is continued (Fig. 5). That this is due to fatigue of the arc and not to fatigue of the peripheral mechanism is shown by the fact that the heart may be kept slowed by stimulation of the peripheral end of the vagus for over an hour if steps are taken to prevent vagus escape by bleeding the animal [McDowall, 1926]. The absence of fatigue in the depressor reflex has already been described by Bayl [1893]. The respiratory waves show that the failure of the cardiac inhibitory reflex is not due to asphyxia, the result of a cessation of respiration: the same result is obtained also under artificial respiration.

Reflexes antagonistic to the cardio-inhibitory reflex.

If the central end of a mixed spinal nerve is stimulated with a faradic current and the central end of the vagus stimulated, the inhibitory reflex may be counteracted (Fig. 6). The extent to which this may be varied in different animals. In some it has not been possible to halt exactly the vagus activity by stimulation of the spinal afferent; in others it completely disappears. The duration of the effect of the antagonistic reflex also varies in different animals. Why the duration of the acceleration effect of the stimulation of the sciatic should vary in different animals is a point of some interest. This will be made the subject of a separate investigation.

After the effect of the antagonistic reflex has worn off, there follows a period during which the cardio-inhibitory reflex is much more active (Fig. 6). In that case it may be possible to stop the heart completely. Even in those animals in which stimulating the sciatic causes no reduction of vagus activity, there is, immediately after the blood-pressure has returned to the normal, a short period during which the centre is hyper-excitable (Fig. 7).

In an animal with both vagi intact this increased excitability (which may show itself by a temporary and spontaneous slowing of the hear rate) repressed vagus restraint) immediately after the stimulation of the sciatic nerve.
Fig. 6. A series of stimulations of the central end of the vagus (L.C.E.). At A the sciatic nerve was dissected. The stimulation so produced caused at first a reduction of the cardio-inhibitory reflex, but when this passes off the reflex is increased.

Fig. 7. The central end of the left vagus was stimulated, from A to B in each instance. At X the central end of the sciatic was dissected. Note the increased effect of vagal stimulation immediately after the effect of sensory stimulation has passed off and the blood-pressure has returned to its original level as compared with the effect after a longer interval. Stimulation at A-B before X had no effect.
has ceased. Fig. 8 shows a series of stimulations of the central end of the sciatic, and it is seen that after each stimulation the slowing that follows becomes more and more marked as if the vagus centre had been 

Fig. 8. With both vagi intact successive stimulations (A-B) of the central end of the sciatic are followed by increasing degrees of vagus restraint. The recording was slowed at X-X to facilitate reproduction. At V.C. the vagi were cut.

more and more excitable as the stimulation progressed. In this instance the dependence of the slowing on the vagi was shown by section of the nerves.

The possibility of the increased activity of the inhibitory reflex due to sympathetic exhaustion was excluded by the fact that similar results occur after removal of the stellate ganglia and suprarenal g. And that stimulation of the sciatic has then just as great an effect as before—indeed, the slow heart makes the effect more marked than usual.

After the stimulation of the sciatic has been repeated several times...
so of blood-pressure becomes less and less sustained. In some animals is then found that prolonged stimulation produces, after a preliminary thickening, a slowing of the heart. This fact suggested that the pressor reflex has a direct effect on the vagus centre (Fig. 9), and further evidence of this is the fact that, after ergotamine has been given to paralyse the sympathetic, stimulation of the sciatic causes only a slowing of the heart (Fig. 10). I have repeated this observation on four different animals, but it is not easy to repeat as it appears to depend on the exact action of the ergotamine on different animals.

It does not appear that the rise of pressure commonly produced by the pressor reflex is itself responsible for the slowing, for a temporarily increased arterial pressure produced by occluding the aorta does not result in slowing except while the blood-pressure is actually being raised. Moreover, a gentle stimulation (e.g. that produced by dissection of the vagus) and insufficient appreciably to raise the blood-pressure produces delayed slowing (Fig. 11).

It must be understood that all animals do not give this delayed slowing and that the experiments which are here recorded were carried out on those animals which, over a period of four years, preliminary experiments showed to be the most suitable. When unsuitable, the animals were used for other purposes. The suitable animals were those which might be described as vago-tonic and which have, initially, a slow heart. Such cats are undoubtedly more commonly found in winter and autumn than in spring, but accurate data on this point are being collected. In five successive years this work had to be abandoned in early spring owing to lack of suitable animals.

The effect of asphyxia.

This was produced by causing the animals to re-breathe their own expired air from a small rubber balloon or by tying to the tracheal tube a long piece of tubing or by producing cerebral anaemia by clipping off
the carotid arteries and clamping the vertebral arteries by a vertebral clamp [McDowall, 1930].

It is well known that cerebral asphyxia or cerebral anaemia stimulates the cardio-inhibitory centre and produces cardiac slowing. It has however, been pointed out [McDowall, 1929] that if the animals have rested under chloralose until all the sensory stimulation set up during anaesthetizing and preparing the animal has worn off, the period of cardiac

slowing may be preceded by a period of cardiac acceleration. (An example of such acceleration due to asphyxia is shown in Fig. 14.) During this period the cardio-inhibitory reflex is in abeyance, although the depressor is very active (Fig. 12) and vagus restraint has completely disappeared.

In suitable animals (see p. 423) after the asphyxia has been allowed to pass off, a period of slowing occurs (Fig. 13), and both the cardio-inhibitory reflex and, in the intact animal, vagus restraint are increased.

This additional restraint produced by the asphyxia is in no way different from normal vagus restraint and, what is still more unexpected
is reduced initially by subsequent asphyxia which causes, as at first, marked acceleration before the slowing (Fig. 14).

To avoid confusion it may be noted that the post-asphyxial slowing described is not due to heart block, a condition which is known to be

![Fig. 12. Stimulation of the central end of the vagus during asphyxia. Prior to the asphyxia similar stimulation gave marked slowing.](image)

produced by very severe asphyxia [Roaf and Sherrington, 1910, Lewis and Mathison, 1910]. This condition when so produced is not improved by subsequent asphyxia. I have been fortunate in securing an instance in which a slow heart due to heart block was produced by the severe asphyxia, and later after the heart had recovered a delayed slowing

![Fig. 13. The original rate of the heart is shown at the beginning of the tracing. At X the animal was asphyxiated for two minutes. Note the delayed slowing after the asphyxia has had time to pass off.](image)
due to increased vagus activity occurred (Fig. 15). In this experiment the heart was exposed and the occurrence of the heart block verified by inspection. Asphyxia was produced by cessation of the artificial respiration.

The effect of asphyxia is then the same as that of stimulation of the central end of the sciatic, except that the former if continued longer will of itself more readily stimulate the cardio-inhibitory centre. Slowing after asphyxia occurs in those animals in which the asphyxia by not cause rise of arterial pressure and in other animals after the injection of a dose of ergotamine, when the blood-pressure actually falls during asphyxia (Fig. 16).
ACTIVITY OF CARDIO-INHIBITORY CENTRE. 427

The production of sinus arrhythmia.

In several animals asphyxia or the subsequently increased activity of a cardio-inhibitory centre was accompanied by marked sinus arrhythmia. At each inspiration there was a marked cardiac acceleration. Repetition of the procedure which brings it about tended to cause the arrhythmia to become more marked. That the arrhythmia depends on the vagus can readily be demonstrated by blocking or section of the vagi, the administration of atropine.

![Diagram](image)

**Discussion.**

It has been seen above that the state of the cardio-inhibitory centre may be studied by investigating changes which occur in the heart rate, the effect of section of the vagus, and by stimulation of the central end of the vagus. Of special interest is the after-discharge of the centre when stimulated and the fact that mild asphyxia and sensory stimulation which produce cardiac acceleration may be followed in many animals, after the acceleration has passed off, by a period of cardiac slowing due to increased vagal activity as indicated by the effect of vagal section and an increase of the cardio-inhibitory reflex. How this late effect is brought about is of some debate. There is no evidence that the sympathetic has become exhausted, since the slowing may at once be caused to disappear by asphyxia or sensory stimulation; indeed, the increased vagus restraint appears in every way to be like normal vagus restraint.

It may be suggested that since asphyxia and sensory stimulation commonly cause a rise of blood-pressure this might be the cause of the later slowing. That this, however, is not the explanation is shown by the
fact that this slowing occurs even in those animals in which a rise in blood-pressure has not been caused (Fig. 11). Also a rise of blood-pressure produced by pressure on the abdominal aorta does not have such an effect. The slowing produced by severe asphyxia and in some animals by Taylor longed sensory stimulation in circumstances when the sympathetic have been exhausted and after ergotamine, suggests that the vagus is stimulated directly by mild degrees of asphyxia and by sensory stimulation, although the effect is masked by simultaneous stimulation of the sympathetic; but since the after-discharge of the vagus is longer than that of the sympathetic, a delayed slowing results. A similar but peripheral effect may occasionally be seen in the frog. If the sino-auricular junction is stimulated by a too strong current which stimulates the muscle directly. In these circumstances the heart hastened during the stimulation, and the vagus effect appears when the stimulation ceases.

The delayed slowing is like the phenomenon described by Sherrington as "rebound" when a muscle inhibited reflexly takes its result when the inhibitory stimulus ceases, a greater tone than before. When the cardiac slowing persists we must consider that not only is there been after-discharge but that a sustained facilitation or centralization has taken place in the reflex arc, which is responsible for the prolongation of vagus restraint.

Since, in vigorous exercise, conditions may arise which involve sensory stimulation and very mild asphyxia, it would seem justifiable to suggest that the slow heart which is found in those who habitually do large amounts of exercise and the temporary slowing which takes place after the accelerating effects of exercise have passed off, may be due to an increased activity of the vagus brought about as described above.

The importance of such a mechanism must be considerable in exerting to the output of the heart.

It has been emphasized by Starling that with greater filling of the heart during diastole, there is, within certain physiological limits, correspondingly greater output per beat. This increase of systolic output is, however, limited by the right auricular reflex of Bainbridge and causes cardiac acceleration and shortening of diastole.

It is evident, then, that when, during the process of training, the heart becomes more efficient as a muscular pump and capable of pumping out more blood per beat, it is necessary also to train or increase the strength of the nervous mechanism by which the undue shortening of diastole is prevented.
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It has long been recognized that vagus restraint is best marked in
nals which habitually take large amounts of exercise [Clark, 1927].
In man, similar observations have been made. It was recorded by
lor (1891) that hill shepherds and others engaged in laborious oc-
ons have a pulse rate much below the average. Later, Pembrey and
and (1908) found that physical training causes a slowing of the pulse.
not appear to have been determined whether such slowing is due
creased vagus activity or merely to the greater capacity and muscu-
ty of the heart which exercise is known to produce, but Crawford
has shown that the acceleration produced is greatest at the time of
when physical activity is greatest.

These facts suggest that we may consider vagus restraint as a corollary
the Law of the Heart, and we see the advantage of the existence of
anism by which the vagus restraint of the heart is increased as the
art becomes more capable of pumping out more blood per beat. As a
ult of the activity of the vagus a given rise of venous pressure will
use less cardiac acceleration than it otherwise would, and a longer time
owed for filling. At the same time a greater variability in the cardiac
be possible. Thus a greater adaptability to exercise is brought
out.

The facts given above suggest that a new outlook on the purpose of
re-inhibitory reflex is necessary. It is usually considered that it
primarily a protection against high arterial blood-pressure, but we
ow that in exercise the blood-pressure may be double that at rest and
panied by cardiac acceleration while no apparent harm results. It
uggested, therefore, that the primary function of the cardiac vagus
es is in relation to the adaptation of the heart to the requirements of
ercise as indicated above.

SUMMARY.

The activity of the cardio-inhibitory centre has been investigated by
ying in different conditions the rate of the heart, the effects of
ulating the centre by various means, and the effects of section of the
agi.

It has been shown that sensory stimulation and asphyxia, although
accelerate the heart and abolish the cardio-inhibitory reflex, result
en in a condition in which the vagus centre is more excitable and in
which the normal vagus restraint of the heart is increased.
Evidence is given which indicates that this change is due to an increase in discharge and facilitation of the cardio-inhibitory centre.

It is suggested that the slow pulse produced by prolonged exercise and by training is similarly produced, and it is indicated that the influence of the vagus is related to the adaptation of the heart to the requirements of exercise.

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REFERENCES.

Spontaneous movements of blood-vessels. By R. J. S. McDowall.  
(Preliminary Communication.)

The existence of rhythmical variations in the circulation has been known for many years, but up to the present it has been generally assumed that these changes are of central origin. Such rhythmical movements have been observed by many early investigators. More recently it has been noted (Kravkov) that similar changes occur in the arteries of mammals and they occur quite independently of heart or central nervous system, while graphical records of similar movement in excised rings or spirals of arteries, especially after the action of adrenalin, have been obtained by other observers.

During perfusion of the pulmonary circulation with Ringer-Locke fluid (without bicarbonate) waves of contraction and relaxation have been found to occur frequently in young and robust rabbits and cats, and by connecting the inlet tube to a water manometer and piston recorder graphic records of such waves are obtained if the pressure be suitably adjusted. The waves are not always regular; and in different animals they may vary from one or two to ten per minute, continuing it may be for several hours. Pituitary extract, adrenalin and temporary distension of the lung alveoli have a stimulating effect.

A tracing showed that each contraction caused complete occlusion of the pulmonary circulation, as evidenced by cessation of flow from the exit tube. The waves are regular, at the rate of one and a half per minute and continued for three and a half hours.

The experiments are being extended to the systemic circulation, in which the author has already found similar waves. It seems certain that the existence of such spontaneous contractions and relaxations will have to be considered in questions regarding variations of pressure hitherto attributed to the vasomotor centre.
The influence of the depressor fibres of the vagus on the capillaries. By R. J. S. McDowal.

If in the cat, the blood-pressure is reduced by stimulation of the central end of the vagus (cardiac effects being excluded), the usual fall in pressure caused by the injection of histamine is greatly reduced or may be almost abolished. Striking results have been obtained, showing that the extent of the fall in blood-pressure due to a given dose (0.01 mg.) of histamine which is rapidly recovered from, is inversely proportional to that from stimulation of the depressor fibres of the vagus. If the stimulation is carried out during a marked histamine fall, the action of the depressor is similarly much reduced, and may be seen only in the maintenance of the pressure at a low level without any further fall. Simultaneous stimulation and injection when the blood-pressure is at a normal level causes a larger fall than either singly.

Provided the anaesthetic and dosage are adequate the injection of histamine and such stimulation in a curarised cat both cause a fall in venous pressure.

The above results suggest that the depressor fibres of the vagus have a similar action to histamine which dilates the capillaries only (Dale and Richards) and consequently when one has lowered blood-pressure the other can no longer do so to its full extent. They also suggest, for the first time in mammals, the existence of a general capillary vaso-dilator mechanism under nervous control.

The signal was specially designed to permit of several being placed one above the other with a minimum of space intervening. It is on the principle of some of the large commercial magnets. The cores are prolonged beyond the coils and bent as required. It is made by Hawksley and Sons. The drawing shows actual size.
An easy method of recording venous pressure.

By R. J. S. McDowall.

The method consists essentially of connecting the vein to a bicarbonate manometer recording directly on the drum by means of a hollow vulcanite float carrying a writer. The cannula used is of the ordinary arterial type, but of larger bore and of sufficient length to pass into the thorax or abdomen according to whether the femoral or the external jugular is used. For prolonged experiments the length is essential as with shorter cannula the vein is liable to be kinked, while a minimum of dissection is carried out that the vein may be maintained in its natural alignment by its own attachments. Special attention is paid to the bevelling of the cannula in order that the opening be not directed against the wall of the vein.

The manometer may be a straight tube such as a narrow burette, if it is convenient to have the animal on approximately the same level as the drum of the kymograph. A three-quarters saturated sodium bicarbonate is used to prevent clotting and does no serious harm if a little gets into the animal.

The float is bell-shaped, and may be made from a small fountain-pen cap made thin and air-tight. This will easily carry a light aluminium writer.

Pressures from $-10$ to $100$ may be recorded easily and no serious difficulty is experienced in experiments lasting several hours.

The method obviates the necessity of piston or bellows recorders which are liable to leak.
A small combined air and animal warmer for use on ordinary tables. By R. J. S. McDowall.

The warmer has been designed to facilitate the carrying out of mammalian work by students. It is on the principle of the ordinary electric heating pad with an arrangement for heating air incorporated in it. Special attention has been paid to the waterproofing. Its thickness is less than half an inch so that the decapitate or decerebrate preparation may be readily fastened over it to a board. The warmer is made inexpensively by C. E. Jackson, 12, Westfield Road, Leeds.

The method consists essentially of using the chest cavity as a plethysmograph and recording changes of lung volume during constant artificial respiration.

The muscles are retracted from the side of the sternum about the fifth interspace. An opening is made into the chest, the little finger inserted to tear the pleura, a flanged cannula inserted and attached to a volume recorder. The muscles are allowed to slip back and the wound made airtight by a purse-string suture. The descent of the diaphragm is reduced by bandaging the abdomen but it is not usually necessary to take any steps to immobilise the chest wall.

In this way changes in bronchiole calibre may be shown which are difficult to demonstrate by the tracheal-pressure method, and the use of delicate oncometers is avoided.
On the survival of striped mammalian muscles. By A. Hemingway and R. J. S. McDowall, King’s College, London. (Preliminary Communication.)

In 1913, one of us (R. J. S. McD.) described certain striped muscles of the hedgehog which were capable of survival for long periods and which contracted even at 0°C. It has now been found that under certain circumstances the ordinary skeletal muscle of mammals can be made to survive for long periods at ordinary temperature. Ordinarily such muscle, even if kept at body temperature and well supplied with oxygen, dies within an hour or so.

The method of preparation consists of anaesthetising the animal, e.g. with chloralose, and injecting intravenously saturated sodium bicarbonate solution. In the case of an average cat, 20–30 c.c. may be injected 2–4 c.c. at a time at intervals of 10 minutes. The animal is subjected to temporary asphyxia from time to time by closing the trachea and after 2–3 hours is bled to death.

Preparations of striped muscle taken from an animal so treated will survive if kept stretched in a moist chamber for 24 hours at ordinary room temperature and for at least 48 hours if kept in ice. The preparations may be used instead of frog's muscle for ordinary class work and are extremely sensitive to changes of temperature.

It has also been found that even if alkali be not injected the tissues of an animal so prepared survive for many hours.
The effect of alkali on blood sugar. By M. A. Battie
and R. J. S. McDowall, King's College, London.

The injection of 2 c.c. saturated sodium bicarbonate solution intravenously into a cat under amytal anaesthesia causes a definite but temporary fall of blood sugar which may subsequently be succeeded by a rise. A similar fall has been obtained in man when 20 grams have been taken by the mouth. Confirmatory evidence exists in the literature.

In view of the work of Clark and of Macleod and his co-workers the results support the suggestion that the action of alkali is related to parasympathetic activity, both possibly acting upon the same structures.
The relation of alkali to the parasympathetic. By R. J. S. McDowall, King’s College, London. *(Preliminary communication.)*

The injection of alkali intravenously into cats under chloralose and undisturbed results in a marked slowing of the heart, constriction of the pupil and increased gastric tone. This relation of alkali to the size of the pupil and to gastric tone has already been observed by many independent workers.

In the case of the heart the slowing is not to be considered a grossly toxic action, for the state of the animal is such that it responds with great readiness to all forms of sensory and sympathetic stimulation by an increased heart-rate while at the same time the pupil dilates. In the early stages the vagus restraint of the heart is very marked, but later section of the vagi or the administration of atropine do not increase the heart-rate. The effect of stimulation of the peripheral end of the vagus is much increased. These results taken together with the fact that CO₂ has the opposite effect suggest that the so-called sympathetic-parasympathetic balance is closely related to acid-base equilibrium.
Class experiments in leucocytosis. By R. J. S. McDowall.

It is found that if individuals breathe to and from a bag (a small air cushion with a mouthpiece fitted is convenient) there is a marked increase in the leucocytes in the peripheral blood, which may number over 15,000 per cu. mm. The number returns to normal, and even below, on over-ventilation. The experiment is convenient for class purposes, as it indicates the ready variability of the leucocyte count. The differential count shows that the increase is chiefly in the polymorph-nuclears.

A convenient method of demonstrating local leucocytosis is to cause hypoæmia in one hand by hot water and to compare the two sides.

The principle is an old one, being that of the spirometer and other similar apparatus with a fluid seal, but by improvement of the design friction is reduced to a minimum, while the curvature of the bell permits a large excursion of the lever. The centre of the curvature of the bell and of the weight is at the fulcrum, and if the centre of gravity of the lever system is also exactly at the fulcrum the lever and bell are balanced at all positions, and for all practical purposes the entrance of equal amounts of air into the bell is recorded by equal excursions. The apparatus cannot leak. It is made by C. F. Palmer.
A central chemical control of the heart rate.

By R. J. S. McDowall. (King's College, London.)

Provided adequate measures are taken to avoid the effects of sensory stimulation and of extensive operative procedures, asphyxia of the cerebral centres in a chloralosed cat, whether produced by general asphyxia, occlusion of the cerebral arteries, cerebral compression, or by supplying asphyxial blood from another animal, causes a marked acceleration of the heart. This occurs after the vagi have been divided and the suprarenal glands have been removed. The acceleration takes place prior to the better known slowing of the heart which occurs in asphyxia or cerebral anæmia from central stimulation of the vagus.

The acceleration is not related to any changes in pressure in the various blood vessels and must be looked upon as being due to the chemical effect of the asphyxia on the sympathetic. This is supported by the fact that the cardiac acceleration may be much delayed by over-ventilation of the animal prior to the production of cerebral anæmia. The central control of the heart rate may thus be somewhat similar to the control of respiration.
The effect of carbon dioxide on certain reflex activities.
By R. J. S. McDowall, King's College, London. (Preliminary communication.)

If a decerebrate animal is overventilated, the characteristic rigidity disappears and the muscles become quite placid, but the rigidity returns if carbon dioxide is caused to accumulate, due precaution being taken to prevent oxygen want. There appears, however, to be an optimum concentration of carbon dioxide.

On the circulation the effect of sensory stimulation and the capacity of an animal to recover its blood-pressure if placed in the vertical feet-down position are much reduced by overventilation, whether or not the overventilation has caused any alteration of blood-pressure.

These results suggest that if the respiratory centres are considered as the upper ends of reflex arcs, then the well-known stimulating effects of carbon dioxide on these centres are not specific, but are common to many reflex arcs (but not all).
A vertebral clamp. By R. J. S. McDowall.

A clamp has been devised by means of which the vertebral arteries at their entrance to the atlas can be occluded without removal of the skin. It is made of \( \frac{3}{4} \)" brass, tapered to \( \frac{1}{8} \)" at the jaws, which are wedge-shaped as the shading indicates.

The clamp, together with carotid occlusion, provides a convenient method of testing the activity of the vasomotor and other centres which are stimulated by sudden anæmia, and also an easy way of demonstrating how the reactions of the intact or decerebrate animal differ from those of the spinal animal. The reactions of the spinal animal are obtained in a few minutes on application of the clamp and clipping of the carotids.
**A method of recording the movements of isolated bronchi.**

By R. J. S. McDowall and J. W. Thornton (King’s College, London).

The method consists essentially of perfusing the bronchi through the trachea, the fluid making its exit through scarifications on the lung surface. The resistance to the outflow is recorded by means of a side tube leading from near the canula, to a manometer. A suitable perfusion fluid is that of Van Dyke and Hastings (Amer. Jour. Physiol. 1928, 83, 563). It contains: NaCl 0·659 p.c., KCl 0·046 p.c., CaCl₂ 0·005 p.c., MgCl₂ 0·009 p.c., Na₂HPO₄ 0·01 p.c., Na₃HPO₄ 0·008 p.c., NaHCO₃ 0·252 p.c.

Substances to be examined are injected through the pulmonary circulation which is separately perfused. They may be injected directly into the bronchial perfusion, but practical difficulties prove this to be less satisfactory. By use of the method all the usual reactions of the bronchi to drugs can be easily demonstrated. The sensitivity of the apparatus is shown by the fact that the constriction and dilatation effected in the guinea-pig’s lung by the action of histamine and adrenaline respectively, may extend completely across an ordinary kymograph paper. This will represent an alteration in pressure of at least 30 to 40 cm. of water, following, for example, a dose of 0·01 mg. of histamine.
The term 'psychogalvanic reflex' has been given to the fall in the electrical resistance of the skin which occurs during mental effort or emotion. It is probable that the fall in resistance is not the sole change which occurs, but from the work of Thouless it is evident that it is by far the greatest change concerned. Various explanations have been sought for by individuals whose interests lay in special directions and who were not fully acquainted with the literature of the subject or with the physiology of the factors concerned.

It will be shown below that the fall in resistance can readily be explained as being the result of constriction of the blood vessels of the skin. In the past, this conception has been ignored because of the act first noted by Veraguth, that the reflex was not abolished by the cutting off of the blood to the part concerned. Since, however, it has become realised, largely as the result of the investigations of Krogh, that the peripheral vessels are independent of the blood pressure, such negative evidence carries no weight.

The Influence of the Circulation on the Resistance of the Skin.

In the past too little attention has been paid to this aspect of the problem. In 1924, however, Ave-ling, McDowall and Wells carried out a series of experiments on chloralosed or decerebrate animals in which it was found that all procedures calculated to bring about vaso-constriction in the skin, e.g., hemorrhage, adrenaline and cold, caused a fall in the electrical resistance; while conditions producing vaso-dilatation, e.g., obstruction of the venous return, caused a rise. They found that the fall could be brought about by sensory stimulation in a decerebrate animal, thus showing the elementary nature...
of the reflex, and suggested that the term 'v.
constrictor' reflex should be substituted. It should be stated that conclusive evidence was obtained that the change in electrical resistance was not brought about by activity of the sweat glands. This was the hypothesis of previous pharmacological action of pilocarpine and atropine. It was actually shown that pilocarpine, in the sweat stage when the blood-vessels are dilated, caused an increase in resistance, although it may be preceded by a fall in the palor stage. In this point the results of Waller were confirmed. In final condemnation of the sweat theory, it may be stated that Golla recorded an example of neurotic hyperhidrosis in which sweat literally dripped from the patient who gave a normal reflex. It is inconceivable that such activity would not interfere with the reflex were it due to increased glandular activity.

The work has now been further extended by Waller, who has shown in a very simple series of experiments the details of which will be given in a forthcoming paper, that any alteration of the circulation through the skin of the hand causes a considerable change in electrical resistance, greatly in excess of the change occurring in the reflex. For example, if the cerebrospinal fluid which normally keeps up the tone of the vasomotor centre be reduced by over-ventilation, the procedure producing an obvious pallor of the skin, the fall in resistance may amount to 20-30 per cent. of the original resistance. On the other hand, if the peripheral vessels be dilated by preventing the venous return by compression of the arm with a sphygmomanometer cuff at a pressure of 50 to 60 mm of mercury, there is a marked rise in resistance.

It is, however, important to note that all these experiments can only be carried out if conditions are as indicated below, are such that vasomotor symptoms can show itself; while it is not until the subject is thoroughly accustomed to the procedure of the experiment that the effect of psychical states can be got rid of.

THE INFLUENCE OF THE CIRCULATION ON THE REFLEX.

It has long been known that in cold weather it is very difficult to obtain the skin constrictor reflex, and indeed, it is a routine procedure amongst psychologists to wash the hands in warm water in such circumstances. It is evident that if the cold causes the blood to be thrown out of the skin vessels to be constricted, no further constriction may be expected. Mere compression of the skin vessels by the electrodes may prevent the reflex from occurring, for pressure will interfere with the circulation.
There is little doubt that this counts for the fact that it is most readily obtained from the palms of the hands and the soles of the feet, where the superficial blood-vessels in these regions are protected by a greatly thickened stratum corneum. This may readily be observed by pressing the finger to the palm and back of the hand and comparing the pressure necessary to cause an evanescent pallor. There seems little doubt that the failure to obtain a rise in resistance in blushing is due to the fact that the vessels in the face are exposed, since Wells has shown that hyperemia of the hand, produced by ungling the hand alternately into hot and cold water, gives a marked result. In the usual method of obtaining the reflex there is added to the pressure of the electrodes the cold due to evaporation of the saline by which they are kept moist, while the skin becomes sodden. All these factors may interfere with the appearance of the reflex. Similarly, the reflex is abolished by drugs which cause marked dilatation and paralysis of the skin vessels, such as large doses of alcohol and atropine.

It is important also to remark that many observers who have been unable to explain the fact have noted that there is great difficulty in obtaining the reflex in patients suffering from arterial disease such as arteriosclerosis.

**Evidence of Vaso-Constriction during the Reflex.**

It is stated by Krogh that if the ear of an unanaesthetised rabbit is observed, the occurrence of the slightest unusual sound causes the blood-vessels in that region to become constricted; while Carrier, working in the same laboratory, has recorded closure of the skin capillaries of man during a thunderstorm which caused much apprehension in the subject. Hemingway in this laboratory, using Lombard's method, has found that there is commonly a closure of the capillaries of the skin during conditions which produce the reflex. The constriction is, however, limited to certain capillaries, while others remain permanently open. To be certain of these changes it is necessary to observe a given area of skin for several days in order to be thoroughly familiar with the normal state of the region; and due precautions must be taken to prevent the capillaries being affected from other causes during the observations.

It would be expected from the foregoing that if the reflex is caused by vaso-constriction, there ought to be a diminution in the volume of the limb as shown...
by the plethysmograph. This has been thoroughly investigated by Golla, and in a Croonian lecture he states that he not only found that there was a constriction of the limb, but also that the time relation and the degree of constriction corresponded to the change in electrical resistance. We have fully confirmed these results, which may readily be demonstrated by the 'rubber glove' method.

On searching the literature the extremely interesting fact has come to light that this was the first experiment of its kind ever done by Mosso, the inventor of the plethysmograph. Mosso records that so important did he consider the experiment that he visited Ludwig in Leipzig to demonstrate it. So impressed was the 'father of physiology' by the reduction in the volume of the limb of the subject, Prof. Paglianni, that he wrote in German on tracing "Enter the lion."

Mosso goes on to relate how the volume of the limb changed in a subject passing from 'seen' to 'unseen'. He gives the explanation of the common saying "Cold hands and a warm heart."

Since the blood flow through the skin influences an individual's temperature sensations, a number of common sayings such as "the blood running cold," "the pallor of fright," "eat till you grow cold," may be considered to have been placed on a definite physiological basis.

Taken together with the experiments on animals, it appears clear that the reflex is a very elementary one which may be brought about without co-operation of the higher centres, as the result of sensory stimulation. It should therefore be known as the constrictor reflex and may be considered as part of the mechanism by which the animal normally prepares itself to the anticipation of muscular exercise or defence. In man it occurs not only on sensory stimulation, e.g. pin-prick, but also in anticipation of the stimulus. Here we may look upon threatening movement as a conditioned stimulus which has developed as an effect of experience. The fact that many of the emotional stimuli affect civilized man may bring about a reflex so associated with sensory stimulation physiological and apparently teleologically, suggests that in response to such stimuli the individual is in a sense, defending or preparing to defend himself. The problem appears to offer an excellent line of psychological investigation.
EFFECT OF ANAESTHETICS ON THE LUNGS.
(Preliminary Communication.)

BY R. J. S. McDOWALL, M.B., D.Sc., M.R.C.P.EDIN.
(In the Department of Physiology, University of Leeds.)

The issue of this Journal for November 11th, 1922, was published the report of the discussion at the Annual Meeting of the British Medical Association on broncho-pulmonary complications following operations under anaesthesia, and it was strange coincidence that the succeeding article should be on the effect of anaesthetic vapours on tissues, in which Flemming collected a very interesting series of experiments which showed their detrimental effects on tissues and living organisms in general. In the first article stress was placed on the irritant effect of the vapours on the lungs; in the second no special emphasis was laid on the effect on the lung tissue.

It does not seem to be appreciated that the lung tissue may, apart from mere irritation, suffer serious damage as a result of actual contact with the vapour, apart from concentration in the blood.

Until quite recently knowledge of the function of the lung tissue was comparatively small, apart from the fact that the lungs were adapted for the supply of oxygen to the blood. The function of the bronchial muscles has been largely ignored, and the physiology of the pulmonary circulation has been avoided, largely because of the experimental difficulty involved in its study and the negative results obtained by several well-known investigators. From book to book it had become quoted that the vasomotor mechanism in the lungs was negligible. Why there should be such an amount of muscular tissue in the lungs remained unexplained.

Much controversy centres round the action of adrenaline on the pulmonary circulation, as it is accepted that generally this drug acts only on tissues supplied by the sympathetic nervous system. While many observers have obtained negative or indefinite results, others, including Plummer, Stirling, and Sharpey Schaefer, have brought forward good evidence that adrenaline constricts the pulmonary vessels as it does the systemic. This suggests that the vessels have a sympathetic control, although in the light of more recent knowledge referred to below, this has not been reinvestigated.
On a Cortical Flexor Tone in the Fore-Limb of the Cat, with Observations on the Hemiplegic Attitude in Man.

BY

D. M. BLAIR and R. J. S. McDOWALL.

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1933.
A CORTICAL FLEXOR TONE IN THE FORE-LIMB OF
THE CAT, WITH OBSERVATIONS ON THE HEMI-
PLEGIC ATTITUDE IN MAN.

BY D. M. BLAIR AND R. J. S. McDOWALL.

(From the Departments of Anatomy and Physiology, King's College, London.)

Various clinical conditions in man associated with tonic spasm have been studied from time to time in relation to the classical picture of experimental decerebrate rigidity in animals. In particular, attempts have been made to relate the postural effects seen in clinical cases of hemiplegia and paraplegia to the position assumed in animal decerebrate rigidity; and in comparing and contrasting the human and animal pictures attention has been drawn to one striking difference, that while in the animal the fore-limb shares with the hind-limb a position of rigid extension, in man the arm is usually in a position of rigid flexion and adduction. Recent papers by Manson and Ferguson (1930) and by Brain (1927), for example, emphasize this difference and contain brief reviews of earlier discussions of the clinical counterpart of animal decerebrate rigidity.

The following observations seem to have a direct bearing on this problem of difference. They are put forward with all due reserve in that they are observations made on animals under general anaesthesia. But it may be claimed with some justice that phenomena seen under successive stages of general anaesthesia are not unconnected with the effects produced by experimental or pathological lesions of the brain. For, in general, the successive stages of anaesthesia reflect effects on successive brain levels. And, as will be seen, our observations are supported by experimental results and throw a suggestive light on pathological conditions. Careful observation of the behaviour of both animals and man under anaesthesia is indeed likely to provide a fruitful field for investigation of cerebral function.

In cats under avertin anaesthesia we have repeatedly noted a stage at which the hind-limbs are rigidly extended while the fore-limbs are rigidly flexed and adducted. As anaesthesia deepens beyond this stage, a position is assumed of extensor rigidity in all limbs, which is succeeded in turn by a stage of complete relaxation of all limbs comparable to
what is termed "surgical anaesthesia" in human operative practice. These stages have been observed to occur in reverse order when an animal is recovering from deeper anaesthesia. The stage of flexed adducted fore-limbs with extended hind-limbs has been noted most regularly when avertin has been given intravenously during preliminary ether anaesthesia. In one consecutive series of eight cats anæsthetized in this way the stage was seen distinctly in six, indefinitely in one, and not at all in another. In the last case a considerable amount of ether was given before giving avertin. This particular stage has been observed much more irregularly when ether alone, or avertin alone, was employed.

At the stage referred to, the animal is completely unconscious; while recovering from it no signs of struggling are seen until a much lighter stage of anaesthesia is reached. The position of the limbs is entirely unchanged by altering the position of the animal as a whole, or of its head and neck in relation to its trunk.

As this position preceded, in deepening anaesthesia, the stage of quadrupedal extension resembling the attitude of decerebrate rigidity, it seemed likely that it was related to supra-mesencephalic function. We therefore investigated the effect on this posture of removal of cerebral cortex. It was found that a suitable removal of cortex on one side caused the flexion in the opposite fore-limb to be replaced by extension. It was more difficult to observe on the trephined animal the typical stage of rigidly flexed fore-limbs and rigidly extended hind-limbs, because the deep anaesthesia induced before trephining was not always promptly recovered from. The amount of avertin by then given in some cases was apt to induce a delayed effect going on to the production of complete muscular relaxation, lasting, it might be, for many hours. The blood-pressure in such cases remained normal, so that this condition was not one of surgical shock, but rather an intense "sleep" condition, such as has been known to occur at times in the clinical use of avertin. But, nevertheless, in some animals we were able to observe, after trephining, the position with rigidly flexed fore-limbs and rigidly extended hind-limbs; unilateral removal of cortex was then followed by extensor rigidity in the opposite fore-limb. In some other cases where, after trephining, both fore-limbs persisted in a condition of only slight rigidity and partial flexion, and on removal of cortex on one side little or no change in the attitude of the limbs took place, the fore-limb on the side of cortical removal was found to resist passive extension slightly or even to respond with a definite flexor pull, while the fore-limb, the cortical connections
of which had been interfered with, now showed no such signs of flexor tone.

Thus we found that this tonic flexor position of the fore-limb which is "released" at a certain stage of anaesthesia, is abolished by contralateral removal of cerebral cortex, just as we had previously noted that it disappeared with deepening anaesthesia. It therefore seems to be maintained by cortical influence.

An attempt was made to determine more precisely whether the maintenance of this flexor tone was associated with any particular area or extent of cortex upon ablation of which the flexor tone disappeared. Removal of cortex was done on one side only, also first on one side and then on the other side. Always purely contralateral effects were noted. The motor area was identified by electrical stimulation. Suitable precautions were taken to prevent drying of exposed cortex.

When removal of cortex was strictly confined to the motor area, no alteration in the incidence of this fore-limb flexor tone was observed to follow. Nor was any change seen when cortex was removed behind the motor area, on the lateral aspect of the hemisphere, and the motor area was left intact. But removal of the motor area plus an extent of cortex posterior to it rather greater in size than the motor area itself brought about a loss of flexor tone previously present in the opposite fore-limb, or caused a more definite condition of rigid flexion and adduction previously present to be replaced by rigid extension.

Removal of cortex anterior to the motor area produced no appreciable result until part at least of the motor area also was removed; then the most striking result was increased extensor rigidity of both fore-limb and hind-limb on the opposite side, as has already been described by Warner and Olmstead (1923) to take place on extirpation of the frontal cortex. These authors do not mention any difference of effect in the fore- and hind-limb; we observed that while stimulation of the cut surface of the frontal region diminished distinctly the rigidity of the contralateral hind-limb, a slight flexor tone appeared in the contralateral fore-limb.

According to our observations, therefore, the maintenance of the flexor tone in the fore-limbs does not seem to be localized in any particular part of the cortex by itself. The parietal area seems to be specially concerned, but a fairly extensive ablation of cortex in this region does not bring about loss of the flexor-tone unless the motor area also is destroyed. Removal of the motor area alone does not affect the flexor tone, but we have never seen this tone disappear upon removal of any
other area of cortex while the motor area remained intact. Loss of the flexor tone seems to follow upon cutting off the motor area plus a considerable extent of adjoining cortex.

How far this flexor rigidity which we have studied in the fore-limb of the cat corresponds to the clinical flexor rigidity of the arm in man can be at present a matter for conjecture only. Rigid flexion of the arms and extension of the legs is often seen in early stages of general anaesthesia in man. Sherrington has stated, in a personal communication referred to by Brain (1927), that in monkeys prior to deep anaesthesia, there is frequently a long-maintained flexor position of the fore-limbs. It may quite well be the case that in man, owing to the high degree of integration throughout the cerebral cortex, cutting off a localized part of the cortex by a pathological lesion (as the motor area in hemiplegia) may so interfere with cortical function as a whole as to "release" a flexor tone in the arm, just as is done in incomplete anaesthesia. We have demonstrated that in the cat a cortical fore-limb flexor tone can persist after ablation of the motor area. May it be that the extensor rigidity of the arms, more rarely seen in patients with cerebral lesions, indicates a more extensive removal of cortical control than that of the motor area only, as is the case in the cat?

But the main significance of our present observations, in relation to the problem of flexor rigidity of the arm in man, is the demonstration that in the cat extensor rigidity of the hind-limbs may co-exist with either extensor or flexor rigidity of the fore-limbs, under different conditions. It is therefore unnecessary to force a strict comparison between the complete "decerebrate rigidity" posture in animals, and the human clinical posture of flexed arms with extended legs. If flexor rigidity and extensor rigidity are both found in the fore-limbs in animals, it is beside the point to compare the human flexor position with the animal extensor position only, and to seek an explanation of the difference in posture in the altered normal use of the fore-limbs in man.

Brain (1927) has suggested that the hemiplegic position with flexed arm and extended leg represents a "release" of the primitive anthropoid erect attitude. But it is surely unsound to argue that pathological interference with normal function of the human brain may "release" an atavistic attitude which in a lower animal is the outcome of the activity of a normally acting brain—to argue in other words, that a localized pathological lesion has the effect of putting back the hands of the evolutionary clock. The work of Richter and Bartemeier (1926) is a striking demonstration against this argument: they showed that the
decerebrate attitude in sloths reproduces in detail the upside-down hanging posture peculiarly characteristic of these animals themselves. Brain's demonstration that, when the body of a hemiplegic patient is brought into the quadrupedal-standing position, the flexed arm then becomes extended, is merely a demonstration of the activity of proprioceptive and labyrinthine reflexes, which he admits must be brought into play in order to produce this phenomenon (extension of the arm does not follow mere passive flexion of the leg upon the trunk).

Our investigation lends some support to the suggestion of Kinnier Wilson (1920) that the flexed arm position in man is an incomplete form of the decerebrate posture in animals. On the basis of our observations in the cat, we would put it that the flexor position of the arm is the result of incomplete decerebration and depends on some remaining cortical influence.

**Summary.**

1. A fore-limb flexor position seen in cats under avertin anæsthesia is described.
2. Evidence is given of the cortical nature of this flexor tone.
3. The bearing of these observations on the human hemiplegic posture is discussed.

**REFERENCES.**


ON THE USE OF COMMON COMPOUNDS OF CARBON IN DISEASE, WITH SPECIAL REFERENCE TO CHOLERA.*

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Introductory.—To the credit of Joseph Black, a graduate of the University of Edinburgh, stands the recognition of the fact that carbon dioxide, the product of breathing, is identical with the "gas silvester" discovered by van Helmont to be the product of burning charcoal and of fermentation. What more eloquent appreciation of what we owe to Black can there be than the letter¹ written to him by his great French follower, Lavoisier: Il est bien juste, Monsieur, que vous soyez un de premiers informés des progrès qui se font dans une carrière que vous avez ouverte et dans laquelle nous nous regardons tous comme vos disciples. It is, however, remarkable how these early discovered facts have overshadowed the subsequent development of the use of carbon dioxide as a possible therapeutic agent. At first sight the view seems logical; carbon dioxide is a product of combustion, it will not support life, it is got rid of by the body; how, then, can it be of value to the body?

Carbon Dioxide and Respiration.—To another great Edinburgh man, J. S. Haldane²—happily still with us—we owe the full appreciation of carbon dioxide as the great stimulant of respiration. Others had made the suggestion but none had shown it so convincingly. This discovery marks the beginning of what we might call the "respiratory epoch" of carbon dioxide in which attention was directed to the finding that the body did not get rid of all its carbon dioxide and that the arterial blood after passing through the normal lungs contains more than twice as much carbon dioxide as oxygen. It was shown when the carbon dioxide in the arterial blood is reduced by excessive ventilation of the lung the normal desire to breathe disappears until the carbon dioxide has again accumulated. If, however, an anaesthetised animal is over-ventilated the subsequent cessation of respiration may be so prolonged that the animal may die from oxygen-want

* The Parkin Prize essay of the Royal College of Physicians of Edinburgh, 1930.
before sufficient carbon dioxide has accumulated to stimulate the respiratory centres already depressed by the anaesthesia.

The importance of these findings is at once apparent in relation to surgical anaesthesia during which respiration may be stimulated by operative procedures and for reasons just described respiration may cease. It has therefore become common practice to administer carbon dioxide with anaesthetics in order to maintain the stimulus to the centres. For this reason carbon dioxide has replaced largely the administration of oxygen generally, for it is now realised (Barcroft \(^3\)) that provided the respiration is sufficiently deep and frequent and the air-passages are not obstructed the atmospheric air contains sufficient oxygen practically to saturate the blood with oxygen and it is obvious the administration of even pure oxygen can be of little or no value. Where, however, the air-passages are partially blocked with fluid or respiration is inefficient and the blood passes through the lungs without becoming saturated, the administration of oxygen is of the greatest value. This may occur in bronchitis and pneumonia.

In pneumonia there occurs the well-known rapid, shallow breathing which the experiments of Dunn \(^4\) in relation to poison gases indicate is due to an undue irritability of the endings of the vagus in the lungs and an exaggeration of the Hering-Breuer reflex. This reflex normally limits the depth of respiration, since, whenever the lungs become distended or compressed, impulses pass up to the medulla and the inspiration, or expiration as the case may be, is cut short. In experimental animals, section of the vagi at once causes a slowing and deepening of the respiration.

The rapid shallow respiration does not aerate the alveoli properly, since the alveolar air is not replaced at each breath, and oxygen-want, with all its attendant dangers, especially its effect on the heart, is produced. It has now been fully demonstrated (Meakins and Davies \(^5\)) that in such circumstances also the efficient administration of oxygen is of great value.

More recently it has been shown by McDowall \(^6\) that the action of the vagi in limiting respiration is abolished by the accumulation of carbon dioxide and by adrenaline. This, indeed, must occur normally, otherwise we should be unable to breathe deeply when we take physical exercise. At first sight it may be objected that the shallow breathing itself brings about
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an accumulation of carbon dioxide. Unfortunately, however, such an accumulation as we have seen is accompanied by the very harmful oxygen want, weakening, not only the heart, but the general body resistance. The administration of a mixture of 5 per cent. carbon dioxide and 95 per cent. oxygen is therefore to be recommended. It is of interest to note that some physicians, from purely clinical observations, have found it beneficial to administer adrenaline as a routine in pneumonia. Quite apart from its action on the bronchi and the Hering-Breuer reflex, this compound is the best cardiac stimulant known, and has a markedly stimulant action on respiration (McDowall). This is not to be confused with the so-called "adrenaline apnoea" which occurs in anaesthetised experimental animals if large doses of adrenaline are injected intravenously but which is not observed in unanaesthetised animals, or man, injected subcutaneously.

More recently, the use of carbon dioxide has been advocated for an entirely different reason. It is alleged that the localisation of a lobar pneumonia to one lobe is due to the lodgment of a plug of mucus in a bronchus. Carbon dioxide is therefore administered to dilate the bronchi by its direct action and by the secretion of adrenaline which it produces. This may be enhanced by the injection of adrenaline. According to Coryllos, Birnbaum, Henderson, Haggard and Radloff, the removal of the plug is followed by a crisis before the usual period.

It is evident, then, that the administration of carbon dioxide and oxygen has more to recommend it than is generally recognised.

Carbon Dioxide after Tracheotomy.—Although not strictly relevant to the subject of the essay, this subject appears somewhat cognate, and there are few more interesting instances of the application of pure science to practical affairs than in the use of carbon dioxide after tracheotomy to relieve laryngeal obstruction. It has long been recognised that the relief by tracheotomy of long standing and severe laryngeal obstruction was not infrequently followed by the death of the patient an hour or so later. An investigation of such a case showed that the carbon dioxide content of the alveolar air was very high and it was evident that carbon dioxide was being got rid off by the kidney. The body was found, as indicated by the urea: ammonia ratio and the urinary acid to be compensating for a carbonic acidæmia by getting rid of acid other than by the
lungs. Physiological principles, therefore, indicated that relief of the obstruction would be followed by so rapid and so increased loss of carbon dioxide from the lungs that respiration would cease and death result. On the suggestion of the author, a piece of rubber tubing was tied to the tracheotomy tube to increase the "dead space" and so prevent the undue loss of carbon dioxide. Instructions given for an inch of the tubing to be cut off each hour. At the same time, carbon dioxide was made available for administration if necessary. This treatment brings about adequate retention of carbon dioxide and has been found to be completely successful (Negus\(^9\)).

**Carbon Dioxide and the Defences of the Body.**—But carbon dioxide is important not only in relation to the maintenance of external respiration but also in relation to internal or tissue respiration, for the blood gives up its oxygen most relunctantly in the absence of carbon dioxide. The full significance of this point is not by any means clear, but its implications are far-reaching in a large number of conditions especially in febrile states in which there is raised body temperature and possibly pain, for such a temperature may stimulate respiration, and cause a washing out of carbon dioxide (Bazett and Haldane\(^10\)). The extent to which this interferes with tissue respiration has never been investigated, but it is evident that the reduction of the defences of the body by reducing oxidative processes may be considerable. If this effect can be shown to be true, a strong case will be made out not only for the reduction of body temperature but also for the administration of carbon dioxide.

The defences of the body may be shown (McDowall\(^11\)) to be still further affected by the influence of the carbon dioxide on the mobilisation of leucocytes. When carbon dioxide is administered there is a marked polymorphonuclear leucocytosis which must add appreciably to the bactericidal power of the actively circulating blood. This fact may be demonstrated by causing the subject to re-breathe his own expired air from a bag, and the experiment is so easily carried out that the procedure makes an excellent class exercise. This procedure causes oxygen-want as well as the accumulation of carbon dioxide but the former merely serves to enhance the action of the carbon dioxide. The importance of a good leucocytosis is apparent in pneumonia in which the blood picture may give some indication of the prognosis, but how far an artificially
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provoked leucocytosis might be of value in fevers has not been investigated.

It may be noted that this procedure, or the injection of adrenaline—another carbon compound—which has a similar effect, do not appear to have been used in the diagnosis of malaria in which the parasite may appear only occasionally. It is suggested that by this means the parasites which have congregated in organs such as the spleen might, like the leucocytes, be thrown into the active circulation and be more readily recognised.

Carbon Dioxide and the Circulation.—The importance of carbon dioxide in relation to the circulation lies in the fact that in cholera death often occurs from circulatory collapse consequent on a marked reduction of the blood volume, and we now know that the normal mechanisms which tend to such collapse are in part regulated by carbon dioxide. Its importance in fevers generally lies in the nature of hyperpyrexia itself. This, there is good reason to believe, is essentially due to a reduction of heat-loss consequent on the redistribution of blood, involving a withdrawal of blood from the skin. Our modern conception of this subject we owe largely to Barbour,12 whose conclusions, although not final, have led to a very much fuller appreciation of the subject. It is true that in fever there is an increased heat production, but there is much evidence that such an increase, as that occurring in exercise or hyperthyroidism, does not of itself produce fever. In the early stage of fever the withdrawal of blood from the skin is generally appreciated. The most striking example is in malaria when the patient is pale, even blue, and shivering although his body temperature may be well above normal, but most of us are unfortunately only too familiar with the shivery feeling and the "looking a little pale" which apparently precedes an attack of influenza. These are signs and symptoms of the withdrawal of blood from the skin. Not infrequently, the greater the sensation of cold the greater the rise of temperature, as in malaria or the rigor of septicæmia. The withdrawal of blood from the skin in fever has been conclusively shown by Stewart,13 who has actually demonstrated a diminished heat-loss in the early stage. Eventually, however, when the temperature is very high, the skin becomes hot to the touch since the heat-regulating centre gains the upper hand and there is an excessive heat-loss although this is not so large as it ought to be for the
height of the temperature. The effect produced appears to indicate that the centre is set a higher level than normal, but it is evident that this is really due to the competition between the skin and the internal organs for the available blood.

It has been pointed out that in fever the heat-regulating mechanism is not wholly out of order. If placed in a hot bath the individual will sweat, or if cooled unduly he will shiver.

Why the withdrawal of blood from the skin occurs is a matter of debate. It may be, as suggested by Barbour,\textsuperscript{12} because fluid passes with the tissues and a condition like hæmorrhage is produced. It is considered that the toxins cause a breakdown of the tissues, and so increase the osmotic pressure of their protoplasm. Water is therefore attracted from the blood. Or it may be because the blood vessels have become dilated internally which take up the blood. In this connection it may be remarked that Lauder Brunton recorded that loss of blood might cause an increase in body temperature.

These facts indicate to what extent the state of fever is dependent on the state of the circulation and, as we shall see they have an important bearing on the use of carbon dioxide and of the antipyretics.

**Local Action of Carbon Dioxide.**—Certain isolated actions of carbon dioxide on the circulation have long been known. Severini,\textsuperscript{14} showed that carbon dioxide dilated capillaries, and although this was subsequently denied by Roy and Graham Brown,\textsuperscript{15} it was later shown by Krogh\textsuperscript{16} to be correct. This we may easily demonstrate in ourselves. If a piece of the skin of the back of the hand is rendered anaemic by pressing on it with the finger for a few minutes, respiration in that area ceases, carbon dioxide and lactic acid accumulate, and when the finger is withdrawn the area which has been blanched is now flushed as a result of local dilatation of vessels. The experiments may be carried out on a larger scale by a tourniquet on the arm. The cessation of the circulation is followed by a marked hyperemia. It has been suggested (Lewis\textsuperscript{17}) that the dilatation is due to an "H" or histamine-like substance because of the more complete evidence that a histamine-like substance is produced when the skin is damaged. The release of the tourniquet does not, however, give rise to any other sign of histamine absorption and there appears to be no adequate reason for believing that the substances responsible are other than carbon dioxide and lactic acid, the more so, as it has been shown by Bayliss,\textsuperscript{18} that during asphyxiation there is dilatation of a limb placed in a plethysmograph.
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This subject is of indirect interest in relation to carbon dioxide therapy as it forms the basis of Bier's treatment for infection of the limbs. Temporary congestion is induced by obstructing the venous return and the subsequent flushing of the affected parts brought about by a similar local accumulation of metabolites, of which carbon dioxide is probably the most important. The experiments also suggest that if it is beneficial to place an infected or oedematous limb in a bath of oxygen, it will be still better to place it in an atmosphere of oxygen plus carbon dioxide.

The Central Effects of Carbon Dioxide.—It is in the central effects of carbon dioxide that its greatest possibilities as a therapeutic agent in regard to the circulation become apparent.

It has long been known that asphyxia of an animal causes an enormous rise of the arterial and venous blood pressures. The animal is caused to breathe its own expired air from a balloon containing just as much air as is needed at a single breath. Such an experiment causes both the accumulation of carbon dioxide and oxygen-want, but that the effect produced is in part at least due to carbon dioxide is seen by causing the animal to breathe a mixture of over 95 per cent. oxygen and 5 per cent. carbon dioxide.

During the War this problem was taken up by several American workers (Henderson and Harvey\textsuperscript{10}), who pointed out that over-ventilation caused a fall of blood pressure and, if brought about by sensory stimulation in an anaesthetised dog, produced a condition of low blood pressure comparable with surgical shock. They further demonstrated that the blood pressure could be made to return to normal by administering carbon dioxide. They also postulated a somewhat cumbrous and unnecessary theory of a veno-pressor mechanism which they claimed was involved and which prevented the return of blood to the heart.

Although it was later shown that all surgical shock was certainly not due to such a cause, the experiments drew attention to the possible importance of carbon dioxide in the normal maintenance of vascular tone and began what we may call the "circulatory epoch" in the therapeutic use of carbon dioxide. They also explained the results of Crile\textsuperscript{20} and of Mummery\textsuperscript{21}, who had shown that the blocking of sensory nerves mitigated against the production of shock. These investigators had presumed that the blockage of the sensory nerves protected
the vasomotor centre from exhaustion. Later observation (Malcolm, Porter, Seelig and Joseph) showed that the centre was not exhausted and might actually in some instances respond to sensory stimulation, and the results remained unexplained until the relation of the respiration to the vasomotor centre was recognised. We may now conclude that the sensory stimulation stimulates the respiratory centre and that the over-ventilation caused the fall of blood pressure.

The subject was further investigated by Dale and Evans, who elaborated and confirmed many of the essential points. They found that if an etherised animal was over-ventilated with ordinary air the blood pressure fell, but that if it was then ventilated to the same extent with expired air, the blood pressure recovered. They showed that these results were due to loss of the specific effects of the carbon dioxide and not due to the alkalisation of the blood produced by the loss of the carbon dioxide, since alkalisation produced by the intravenous injection of alkali did not produce the same effect. The specific effect of carbon dioxide in relation to the vasomotor centre appears to be closely akin to that in relation to the respiratory centre and to be explained by the fact put forward by Jacobs that, while other acids may have the same effect, carbon dioxide, although possibly acting in virtue of its hydrogen ion concentration is much more effective because of its power to penetrate animal membranes.

The researches of Dale and Evans lead to the conclusion that carbon dioxide was largely responsible for maintaining the tone of the vasomotor centre and that if it was washed out the centre became depressed.

These important results appear at first sight to be negatived by the undoubted fact that over-ventilation in unanaesthetised man does not necessarily cause a fall in blood pressure provided the ventilation has not been so violent as to interfere mechanically with the circulation through the lungs and although it has been sufficiently efficient to cause a prolonged apnoea. This failure of the blood pressure to fall in unanaesthetised man appears to be due to two causes (Collier, Densham and Wells): the effort of carrying out the over-ventilation and the increased tone produced by the washing out of carbon dioxide from the peripheral vessels. The conclusion that the washing out of carbon dioxide reduces the activity of the vasomotor centre is not therefore impugned.
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The effect of carbon dioxide in maintaining the activity of the vasomotor centre is also seen in response of the circulation to changes in posture (McDowall\textsuperscript{25}). In a considerable proportion of cats placed erect in the feet down position, there is, as in man, no fall of blood pressure. If, however, such animals are over-ventilated there is invariably such a fall. Carbon dioxide appears then to be essential for the proper functioning of the vasomotor centre.

In fever, therefore, when, as a result of the increased body temperature, there is increased ventilation, the vasomotor centre is liable to lose its tone and the distribution of blood towards the affected parts in the body is liable to be interfered with. This interference will be appreciably reduced by the administration of carbon dioxide and, as we shall see later, by cooling the surface of the body.

In cholera, the importance of the fully functioning vasomotor centre is all the more apparent, since in this condition the excessive diarrhoea so reduces the amount of fluid in the body that the blood becomes greatly concentrated and so reduced in amount that the blood pressure may fall to a dangerous extent. Every effort, then, must be made to maintain the maximum activity of the vasomotor centre in order to maintain the blood pressure.

Similarly, in secondary wound shock, although there is evidence that it is due to the absorption of toxic products which dilate capillaries (Dale and Richards\textsuperscript{29}), the importance of carbon dioxide in maintaining the tone of the vasomotor centre is nevertheless considerable.

Evidence has been put forward by McDowall\textsuperscript{30} that not only is recovery of the blood pressure after an injection of histamine due to activity of the vasomotor centre, but that the response is profoundly affected by carbon dioxide. This latter point has not yet been published. The hyperpyrexia of fever, by tending to over-ventilation, causes a loss of carbon dioxide and this must seriously interfere with the power of the body to compensate for the toxic effects of bacterial products on capillaries.

**Carbon Dioxide and the Heart Rate.**—If carbon dioxide is administered in a mixture rich in oxygen to a man, or to an animal which has been suitably prepared, there is a marked increase of the heart rate but no evidence of reduced output (Dale and Evans\textsuperscript{25}). At first sight this seems definitely to
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contradict the results of experiments with the perfused heart and with the heart-lung preparation, but it is now realised that in the case of the perfused heart the perfusion fluid used is not buffered like the blood; the addition of the carbon dioxide therefore causes the fluid to become markedly acid. In the heart-lung preparation, the heart is no doubt affected, the defibrinated blood is used while the making of the preparation causes such cardiac acceleration that it is difficult to demonstrate even the increased rate which is produced by carbon dioxide. It appears, then, that the results with the intact animal with an intact nervous system and not subjected to extensive surgical procedure are the more reliable.

It has now been shown that the accumulation of carbon dioxide in the blood produces cardiac acceleration by bringing about a central stimulation of the sympathetic and a reduction in the normal restraining influence of the vagus (McDowall). The final proof of this is provided by cross circulation experiments in which the head of one animal is supplied with blood from another animal, and changes in the cerebral circulation can be produced without affecting the rest of the animal. An increase in carbon dioxide in the blood supplying the head causes acceleration.

It does not appear likely that this chemical control of the heart rate is used in moderate exercise, but it is evidently available in times of stress. The various points in connection with the action of carbon dioxide on the heart are, however, important, as they emphasise that the administration of the gas does not immediately impair the heart as experiments on the isolated organ might lead one to suppose and the therapeutic use of the gas is therefore not contra-indicated on account of the heart, when its administration for its effect on respiration and the vasomotor centre is desirable.

The Relationship of Carbon Dioxide to Adrenaline.—In fevers generally there is good evidence, as emphasised by Cramer, that there is a generally increased sympathetic activity, and we know that adrenaline has a similar action.

In the treatment of fevers, therefore, the relationship of these two compounds of carbon have a special significance, for not only is there evidence that carbon dioxide causes a secretion of adrenaline, but the injection of small doses of adrenaline produce the same effect as an increased central action of carbon dioxide. They both, for example, accelerate
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the heart and respiration (McDowall 7). The former fact is not to be confused with the deleterious action of carbon dioxide upon the isolated heart, nor the latter with the better known observation, first shown by Oliver and Schafer, 33 that large doses in anesthetised animals cause a temporary cessation of respiration. Both carbon dioxide and adrenaline in the intact animal stimulate the processes which are concerned with the protection of the body and which are used in exercise and may be considered to enhance the action of each other.

In the past there has been considerable debate as to whether or not carbon dioxide causes a secretion of adrenaline, but the evidence is now all in favour of its doing so. The best proof of its occurrence appears to be that given by Anrep and Daly, 34 and by Kellaway. 35 The former supplied the lower half of a dog including the suprarenals from a heart-lung preparation and found that if the dog was asphyxiated there was a marked cardiac acceleration in the heart-lung preparation which was only connected to the asphyxiated dog by means of blood. Similarly, Kellaway 35 showed that when a cat in which the cervical sympathetic had been cut was asphyxiated there was marked dilatation of the pupil, a fact which cannot be explained unless it is presumed that some substance like adrenaline is carried by the blood to the pupil. From what we know of the other effects of asphyxia, we must presume that the effects are in part due to the accumulation of carbon dioxide as well as to oxygen-want.

These experiments support the experiment of Cannon, 36 who showed that asphyxia causes acceleration of the denervated heart.

The use of carbon dioxide and adrenaline have the further advantage in that they stimulate the sympathetic and thereby inhibit the activity of the bowel. For a similar reason in cholera Rogers advocates the administration of atropine, another carbon compound, night and morning.

Carbon Dioxide and the Nervous System.—It now seems clear that the effects of carbon dioxide are not confined to the circulation and the respiration, but are quite definitely exerted on the nervous system as a whole.

If an animal is decerebrated below the level of the red nucleus, it develops characteristic decerebrate rigidity, but if such an animal is over-ventilated the rigidity disappears. With the administration of carbon dioxide, the rigidity returns (McDowall 38).
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It may be shown also that the effect of sensory stimulation upon respiration is markedly decreased by over-ventilation and increased by carbon dioxide.

Already there are important indications of the possible use of carbon dioxide as a general stimulant of the nervous system. Indeed, it is interesting to note that its action on the respiratory and vasomotor centres is, after all, essentially on nervous tissue. Thus we enter what we may call the "nervous epoch" of carbon dioxide, which, since it includes the others, may be considered the most fundamental of all. If a man over-ventilates voluntarily, curious "heady" sensations, which may amount to unconsciousness, are brought about. These have never been satisfactorily explained, since we now know that they occur whether or not the over-ventilation has caused a fall of blood pressure. It appears not unlikely that the nervous system as a whole requires a certain amount of carbon dioxide in order to act normally, but the problem of why exactly carbon dioxide is necessary must be left for future investigation.

It seems almost justifiable to assume that the generally tonic effects of exercise are due in part to the action of carbon dioxide.

We may conclude, therefore, that although there is no record of carbon dioxide having been used for the purpose, there are adequate reasons for suggesting its use in many conditions in which the nervous system requires to be toned up before the patient is able to take ordinary exercise.

**Sodium Bicarbonate** (NaHCO₃) and **Gum Arabic**.—This salt is needed whenever intravenous medication becomes necessary. In the severe diarrhoea of cholera, for example, the excessive loss of fluid from the bowel rapidly leads to great depletion of the body fluids and the life of the patient is endangered from this cause alone. Normal saline is of some value in making up the blood volume, but it has a relatively low osmotic pressure, and, like the fluid of the blood itself, is not held in the blood against the forces which attract it into the intestine. The intravenous injection of saline, first introduced by Latta of Leith and subsequently developed by Rogers in India, has now become one of the routine procedures in the treatment of cholera. Rogers used a hypertonic saline made by merely increasing the concentration of the sodium chloride in ordinary Ringer's fluid, but this has the great disadvantage of being rapidly excreted by
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the kidney. A similar difficulty was experienced during the War in the treatment of surgical shock, and to avoid it gum arabic was introduced (Bayliss). This is really a carbon compound not unlike glucose itself. It is not rapidly metabolised and is retained longer in the blood stream than simpler compounds. It was originally recommended that a 6 per cent. solution should be used, but more recent work indicates that concentrations up to 25 per cent. injected slowly are best (Erlanger and Gasser). Slow injection is essential, as it may readily be shown that the injection of viscous fluids have great difficulty in getting through the pulmonary circulation and considerable strain is thrown on the right side of the heart. The benefit of the more concentrated gum arabic is that it tends to draw fluid from the tissues. In cholera the fluid has been actually lost from the body and cannot be recovered into the blood vessels, but the raising of the osmotic pressure of the blood much above normal tends to prevent the excessive loss of fluid by the bowel.

Even in surgical shock, the injection of gum saline has not met with all the success which might be expected. One reason for this undoubtedly is that the solution tends to be on the acid side of neutrality and steps must be taken to prevent this by the addition of another carbon compound, sodium bicarbonate or sodium carbonate.

It cannot, however, be over-emphasised, and it is too often forgotten — especially in surgery — that the best and most natural method of getting fluid into the blood stream is by the alimentary canal.

The use of alkalies in fever is also of value when the patient's store of glucose has come to an end, and difficulty arises in the combustion of the fat similar to that which occurs in diabetes. Here, again, the bicarbonate is of value in neutralising the β-hydroxybutyric acid which may be formed. The occurrence of an acidosis produced in this way has been produced in starved rabbits by keeping them in an atmosphere of moist hot air.

The Use of Carbohydrates.—Although, strictly speaking, it cannot be considered that carbohydrates have a direct curative value, they are so intimately concerned with the normal defences of the body that they have been considered worthy of inclusion in this essay.

* The use of the carbohydrate gum arabic has already been discussed.
It has been emphasised, especially by Cramer, that in fever there is a generally increased action of the sympathetic part of the autonomic nervous system. This is nowhere more marked than in the digestive system. The dryness of the mouth of a febrile patient is typical of the state of the alimentary canal as a whole, for it has been adequately shown that increased sympathetic activity causes diminished secretion of digestive juices (Moll, Langdon Brown). The movements of the canal are also affected. Although actual data by means of X-ray have not for obvious reasons been obtained, we must assume from the work of Elliott that there is a contraction of the pyloric and ileocolic sphincters together with a general immobiliation of the alimentary tract. Hence, in those fevers in which there is no intestinal irritation, constipation is the rule and the appetite is poor. The general inactivity of the alimentary canal is very liable to lead to a diminished intake of nourishment.

Fortunately, the body has in glycogen a store of easily-available fuel which is converted by increased sympathetic activity into glucose (Claude Bernard, Macleod), but if the fever continues for longer than a few days, this store becomes exhausted and, unless the patient absorbs more carbohydrate, it must utilise protein and fat as fuel. For this reason febrile patients rapidly lose weight.

It is commonly assumed that a patient when in bed does not require a diet of full calorific value, but this is fallacious, for the general metabolism is definitely increased in fever, for the increased body temperature hastens all the chemical processes concerned in metabolism and there are probably other factors concerned. The calorific value of the diet should therefore be well above the resting requirements, otherwise the patient will lose weight.

In fever, therefore, everything is done to give foods to the patient which are readily digested; amongst these, carbohydrates take first place, as they throw a minimum strain on the organs of excretion and act as protein sparsers. Further, they do not stimulate heat production like protein. Several invalid foods are available in which the carbohydrates may be digested prior to their being given. Considering, however, that the primary idea of such pre-digestion is to convert starch into monosaccharides and eventually glucose, it is remarkable that glucose itself is not more extensively used in fevers. It can
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be purchased relatively cheaply, it is not so sweet as sugar and can easily be flavoured to suit the palate. This is by far the most direct method of administering energy to the body and its more extensive use would certainly lead to its becoming still cheaper.

In cholera, it is desirable to rest the bowel as much as possible, and the administration of glucose intravenously is strongly advocated, the more so as intravenous injection of fluids forms part of the almost routine treatment for the maintenance of the blood volume. Solutions of glucose up to 25 per cent. have been authoritatively recommended (14), but it must be remembered that there is no real advantage in injecting large quantities in this way since glucose in the blood above the renal threshold is excreted by the kidney; at least if the fluidity of the blood is such that the kidneys can excrete. There is, however, no reason why dilute glucose should not be injected into any part of the body like saline. It will then become more slowly absorbed. Concentrated solutions are liable to cause pain.

Failure to supply sufficient carbohydrates leads to the body using its protein and store of fats which, being incompletely burnt, produce an acidosis, and which must be to the detriment of the patient. In hyperpyrexial starved rabbits carbohydrates relieve such an acidosis. These facts suggest the importance of avoiding carbohydrate starvation in fever.

From the point of view of the circulation, because of its excretion, glucose like sodium chloride is, however, not so suitable as gum arabic for increasing the osmotic pressure of the blood with a view to preventing excessive loss of fluid.

The Therapeutic Use of Carbon Monoxide.—The therapeutic use of such a poisonous compound as carbon monoxide appears at first sight ludicrous. If inhaled in large quantities it forms carbon monoxide haemoglobin which prevents the normal amount of oxygen from being taken into the blood and so produces oxygen-want. It is in this way death by ordinary coal-gas poisoning occurs.

The effect of small doses of this substance, however, has received very little attention, but the possible value of small degrees of oxygen-want cannot be ignored, for we are familiar with the beneficent effect of oxygen-want produced by life at a high altitude. Oxygen-want in the body as a whole causes general sympathetic stimulation (as seen by the dilated pupil,
the accelerated heart and the contraction of the spleen) and the activation of the bone-marrow. It is possible, then, that small amounts of carbon monoxide might be of value in promoting such states. In asthma the benefit of carbon monoxide has been definitely established. It has, for example, been recorded that a sufferer during an attack essayed to commit suicide by placing his head in a gas oven, only to find that his asthmatic attack at once passed off. So relieved was the patient that he and his doctor gave subsequently used coal gas in the treatment of asthma. He found that its effects were as beneficial as adrenaline, the great sympathetic stimulant. How far, then, carbon monoxide in small quantities might be of value where it is desired to stimulate the sympathetic as is done by adrenaline or to paralyse the opposing parasymathetic, as is done by atropine, offers an untouched field for research.

Alcohol.—In these days the use of alcohol as a therapeutic agent appears to be passing into disuse, yet there are few compounds of carbon which in the past have been generally used therapeutically in febrile states by doctor and layman alike. There have been several reasons for this. The drug is liable to be abused. The older pharmacologists showed that its action was essentially that of a paralysant, while pathologists and bacteriologists emphasised that it brought about a lowering of the general body resistance (Clark, 45 Cushing 46). It was also considered that its use as a stimulant depended solely on its reflex stimulating action from the mouth and stomach.

There seems, however, a very reasonable possibility that many of the views of twenty years ago may require revision, and that the old-fashioned general practitioner was more justified than he knew in prescribing the drug. Several circumstances contributed to this change of view: one was the War, during which individuals exposed to the most trying climatic conditions certainly had not their resistance reduced by its use, unless habitual over-drinkers; indeed, much benefit was claimed. This is all the more remarkable since it undoubtedly causes a lowering of body temperature through dilatation of the superficial vessels. If the exposure has ceased at the time the alcohol is taken, then this is not a serious matter. The others have been the results of more recent physiological experiments.

One of the great uses of alcohol has been in the treatment of pneumonia in which fever is high; another has been
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to relieve cardiac cases; yet until recently no experimental
evidence supported its use for it had not been shown that
alcohol directly benefited the heart.

It has, however, now been shown by experiments on
animals (McDowall 47) that alcohol causes a profound lowering
of venous pressure and, as subsequently agreed by the late
Professor Cushny, there is good evidence that such a lowering
of venous pressure occurs in man. This lowering of venous
pressure must be of enormous value in relief of the heart in
giving it less work to do during the critical period of pneumonia.
It also stimulates the respiratory centre (Clark 45). In cardiac
disease, also, it has been abundantly shown (Eyster 48) that one
of the earliest signs of cardiac failure is the rise of venous
pressure which, like that which occurs in exercise, must tend
to throw undue strain on the heart by causing it to fill unduly.
The reduction of such a high venous pressure must bring
considerable benefit. In the high temperatures of fevers,
alcohol has the advantage of reducing body temperature by
increasing the heat-loss from the skin through the dilatation
of the vessels.

The use of alcohol in the prevention of infection of the
respiratory tract is founded on a less secure experimental
basis, but is nevertheless suggestive. It is agreed that persons
leading an outdoor life even at low temperatures are less liable
to respiratory infection than others. This is generally explained
as being due to the beneficial flushing of the mucous membranes
which occurs as a reaction to the cool air. Alcohol is excreted
by the respiratory tract to some small extent and it is very
possible that the flushing of the tract which takes place during
the excretion has a similar effect.

For completeness, the effect of dilute alcohol in stimulating
gastric juice may be mentioned. The introduction of the
fractional test meal has made it possible to demonstrate most
clearly that it causes a marked secretion of gastric juice, so
much so, that in recent important investigations dilute alcohol
was used as a routine stimulant in order to study the mechanism
of the control of gastric acidity (Maclean 49). This, together
with the sense of well-being which is promoted as a result of
the paralysis of the higher centres, would appear to justify the
use of alcohol as a therapeutic agent in faulty digestion. It
may be added that there seems little doubt that a good
digestion plays a large part in the normal protection of the
body against intestinal infection such as cholera. This is indicated by the ordinary standards of water purity. Thus a water which contains *B. coli* in 10 c.c. but not in 1 c.c. is deemed safe for consumption, although most municipalities demand a higher standard. The fact, however, that there may be *B. coli* in 10 c.c. merely indicates that the colon bacteria are sufficiently few to be digested, and to be rendered innocuous. This is supported by the evidence that while the introduction of bacteria in the stomach may be harmless, the placing of similar bacteria directly into the intestine may result in severe intestinal infection.

Another aspect of the therapeutic use of alcohol is its use as a food. That it is extremely easily absorbed and burnt in the body there is no doubt, and it may therefore theoretically be considered a food. It is not, however, justifiable to consider this as a main argument in favour of its use, as the amount of carbon which can be given in this form is, because of the paralysant action on the nervous system, extremely small.

Short of this, its use in reasonable quantities offers a method of supplying energy when the absorptive powers of the individual may be very low. It is doubtful, however, if it has much advantage over glucose in this respect.

**The Use of Antipyretics in Fevers.**—The use of antipyretics in fevers has often been discussed and those commonly used such as phenacetin and antipyrine, are carbon compounds. In discussing the question, we are at once involved in the larger problem of the nature of fever, which has already been briefly discussed on a previous page. Suffice it to say that fever has been abundantly shown to be primarily due to a reduction of the heat-loss and the antipyretics reduce temperature by increasing the loss of heat by the skin. In view of the fact that increased body temperature increases the power of the body to resist bacteria (Colebrach, Eidinow and Hill, Eidinow and Hill), it is an interesting problem to consider how far it is beneficial to reduce body temperature hyperpyrexia, but it will be generally agreed that if the high temperature produces signs of seriously affecting the nervous system, action must be taken. Even then it is probably better to cool the body by sponging or a tepid bath than to give antipyretics, although they may be more convenient. The cool bath has the advantage that, unlike the antipyretics, it reduces the body temperature without interfering with the vascular reactions to the condition from
Use of Common Compounds of Carbon

which the patient is suffering and gives him more blood to deal with the affected part. In the treatment of typhoid fever this treatment has been commonly adopted. We may indeed conclude on general grounds there is little justification for the use of the antipyretics except in dealing with special infections or where special symptoms, such as intense headache, are present. Treatment by direct cooling has also the additional advantage that the excessive respiration produced by the high temperature is reduced and the body retains the carbon dioxide which is such an important factor in its defences against the invasion of bacteria.

REFERENCES.

Those marked with an asterisk give further references to original papers containing experimental data of the work quoted.

1. Lavoisier, Quoted from Grant’s History of the University of Edinburgh.
2. Haldane, J. S.,* Respiration, Yale Univ. Press, 1921.
5. Meakins and Davies,* Respiratory Function in Health and Disease, Oliver and Boyd, 1927.
R. J. S. McDowall

29 Dale and Richards, Journ. Physiol., 1918, lxxi., 110.
33 Oliver and Schafer, Journ. Physiol., 1895, xviii., 230.
35 Kellaway, Journ. Physiol., 1919, liii., 211.
37 Bayliss, Medical Research Committee Report, 25.
42 Claude Bernard, Comp. rend. Acad. de Sc., 1848, xxvii, 249.
43 Macleod,* Monograph of Physiology, Longmans, 1928.
44 “Memorandum on Medical Diseases in Tropical and Sub-Tropical War Areas,” H.M. Stationery Office, 1919.
51 Eidinow and Hill, B. M. J., 1930, i.

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The Variation of Arterial Elasticity with Blood Pressure in Man. Part I.

By J. C. Bramwell, R. J. S. McDowall, and B. A. McSwiney.
The Variation of Arterial Elasticity with Blood Pressure in Man
(Part I).


(Communicated by Prof. A. V. Hill, F.R.S. Received December 7, 1922.)

(From the Physiological Laboratory, Manchester.)

In a recent paper (1) Bramwell and A. V. Hill showed that the velocity of the pulse wave is a measure of the elasticity of the arteries, according to the formula:

\[
\text{Velocity} \quad \text{(in metres per sec.)} = 3.57 \div \sqrt{\text{Percentage increase in volume per mm. Hg. increase of pressure.}}
\]

They showed also, both from the data of Roy (2), and by direct measurement on an isolated artery, that the pressure of fluid inside an artery plays an important part in modifying the velocity of the pulse wave, the velocity increas-

* Working for the Medical Research Council.
In the same series the extensibility of the artery under the bandage was calculated from the formula of Bramwell and Hill, the extensibility being given in terms of the percentage increase in volume per mm. of mercury increase of pressure.

<table>
<thead>
<tr>
<th>Mean effective pressure</th>
<th>0</th>
<th>10</th>
<th>20</th>
<th>30</th>
<th>40</th>
<th>50</th>
<th>60</th>
<th>70</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean extensibility</td>
<td>5.3</td>
<td>4.3</td>
<td>3.3</td>
<td>2.0</td>
<td>1.3</td>
<td>1.0</td>
<td>0.6</td>
<td>0.4</td>
</tr>
</tbody>
</table>

Horizontally, mean effective pressure, i.e., difference between diastolic pressure and pressure applied externally; vertically, mean extensibility, i.e., the percentage increase in volume of artery per millimetre of mercury increase of pressure.

Here it is seen that the relative extensibility decreases as the internal effective pressure becomes greater. This investigation is being continued along the lines indicated above, in order that the relative elasticity of the arteries may be investigated at the higher effective pressures obtainable by means of a suction armlet.
Variation of Arterial Elasticity with Blood Pressure in Man. 454

Summary.

A method is described by which the extensibility of an artery in living man may be measured at all internal pressures up to the diastolic pressure. As in the case of an isolated artery, the extensibility decreases as the internal pressure is increased.

We are indebted to Prof. A. V. Hill for suggesting this research, and for much valuable assistance and advice throughout.

REFERENCES.
(3) A. V. Hill, ibid., vol. 54; 'Proc.,' p. cxvii (1921).
A CROSS-STRIATED MAMMALIAN MUSCLE PREPARATION. By R. J. S. McDowall. (From the Department of Physiology, Edinburgh University.) (With nine figures in the text.)
A CROSS-STRIATED MAMMALIAN MUSCLE PREPARATION. By R. J. S. McDowall. (From the Department of Physiology, Edinburgh University.) (With nine figures in the text.)

ORDINARY mammalian muscle is disadvantageous for experimental work, since it dies soon after removal from the body unless kept at about body temperature and perfused with oxygenated blood or other suitable fluid.

Although the retractor penis of the hedgehog, which consists of plain muscle, is known to live for a long time after removal from the body and without perfusion, it does not seem to be generally known that certain cross-striated muscles of the same animal retain their functions equally well under these circumstances, and are otherwise not unsuitable for experimentation under ordinary laboratory conditions.

The muscles in question are those concerned with the rolling of the animal into a ball and the subsequent unrolling. These muscles and their actions are described by Huxley in his Anatomy of the Vertebrata. They are composed, as already stated, of cross-striated fibres, although it must be stated that in some of them appearances are seen which suggest incomplete histogenesis.

They fall into two groups, according to their form and attachments. One, the orbicularis dorsalis, a very thick circular band of fibres, plays the chief part in the curling up of the animal. It is, however, so closely incorporated with the skin that it cannot readily be dissected off without lacerating its fibres. The other group, which is concerned in starting both the rolling and the unrolling process, is formed of straight, parallel-fibred muscles which arise from the trunk and are inserted into the skin. There is no difficulty in dissecting them out in their whole length (5-7 cm.) without damage. Removed from the body and kept at ordinary laboratory temperature, without perfusion or special oxygenation, they continue excitable for at least twenty-four hours. They contract on stimulation at all temperatures, from 0° to 40° C.

In the experiments shown in the illustrations accompanying this paper the Keith-Lucas method of stimulation was employed. By this method the whole diameter of a muscle is made to complete a circuit between two electrolytic solutions: thus all the fibres of the muscle are stimulated and

1 The observations embodied in this paper were made four years ago. It was intended to pursue the investigation further in the following year, but the war prevented this intention being carried out; and as the author is still on military service, it has been thought well not to delay publication any longer.—[Ed.]
the polarising action of metal electrodes is avoided. The apparatus was arranged so that it could be immersed in a vessel of water and raised or lowered in temperature at will, the temperature being recorded at about 1 cm. distance from the muscle (fig. 1). The following points have been made out in the course of these experiments:

**FIG. 1.**—Diagram of apparatus employed.

A, B, muscle chamber in two parts, which fit together exactly; C, hole in the bottom of part A, through which one end of the muscle strip, E, is passed; A and B are filled with Ringer's solution; D, D', platinum electrodes in the Ringer; F, thermometer indicating the temperature of the fluid; G, muscle lever; K, K, outer vessels forming a water jacket to the muscle chamber; H, H, inlet tube for passing either warmed or cooled water into the water jacket; I, I, siphon for drawing water off; L, lamp; M, gutta-percha covered wire passing through water jacket.

By the above arrangement any current passing from D to D' must traverse the whole thickness of the muscle.
Fia. 2. — Typical muscle-curve obtained on a moderately fast drum. Time-tracing 100 v. per sec.

Fia. 3. — Curves of incomplete tetanus, at rates of stimulation of from 54 to 74 per minute.
1. If the muscles are kept stretched they retain their excitability for a much longer time than when unweighted.

![Graph showing muscle contraction in response to single induction shocks of varying intensity.](image1)

**Fig. 4.**—Ordinates showing the extent of contraction in response to single induction shocks of varying intensity.

- a. 600 Kronecker units.
- b. 1000 Kronecker units.
- c. 2000 Kronecker units.
- d. 3000 Kronecker units.
- e. 4000 Kronecker units.
- f. 5000 Kronecker units.
- g. 6000 Kronecker units.

![Graph showing muscle contraction in response to rapidly repeated stimuli of varying intensity.](image2)

**Fig. 5.**—Curves showing the extent of contraction in response to rapidly repeated stimuli of varying intensity. The numbers below each curve indicate the numbers of units on a Kronecker coil.

2. Muscles which have been removed from the body remain excitable longer than those which are left in situ.

3. On stimulating the weighted muscle, it passes fairly quickly (after
Fig. 6.—Curves illustrating the effect of varying temperatures on the hedgehog muscle.

Fig. 7.—Fatigue curve of hedgehog muscle, taken at room temperature.
a latent period of about 0.04 second) into the contracted condition; but relaxation occurs only very gradually and occupies a long time (fig. 2).

4. In consequence of the length of the relaxation period, the summation of stimuli can be produced and tetanus obtained by excitations which recur at unusually long intervals (fig. 3).

5. Within limits the amount of contraction is proportional to the

![Figure 8](image-url) Fatigue curve from a muscle which had been already completely fatigued and then subjected to a prolonged period of rest. The curve on the right is taken after the muscle had been more heavily weighted. (At the beginning of the experiment the stimuli were more frequent than afterwards.)

![Figure 9](image-url) Comparison curves from a muscle which had not been previously fatigued. On the left unweighted, on the right weighted.

strength of the stimulation (fig. 4 for single excitations and fig. 5 for multiple excitations). On tetanisation with strong currents the muscle contracts to as much as one-fourth of its original length.

6. As with other muscles, the periods both of contraction and of relaxation are shortened by heat and lengthened by cold (fig. 6).

7. The preparation lends itself well to the investigation of the effects of fatigue (fig. 7), and especially to demonstration of the fact that muscular fatigue may be recovered from, even in the mammalian preparation, without the necessity for any call upon the circulating fluid. Thus a muscle
which had been completely fatigued gave, after a prolonged rest, a series of contractions (fig. 8) very little if at all inferior to those yielded by the similar muscle of the opposite side, which had not been stimulated (fig. 9).

Incidentally it may be noted that the tracings on the right of figs. 8 and 9 show that the contracture which is usually described as characteristic of fatigue is not seen if the muscle be sufficiently weighted.

I have to thank Dr John Tait for suggesting the search for a surviving muscle-preparation in the hedgehog.
BIBLIOGRAPHICAL REFERENCES.

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1. Number.
2. Name of author.
3. Title of book (or article if wanted).
4. Title of journal.
5. Year of publication.
6. Number of volume.
7. Number of page (if wanted).

Capital letters should not be used in the titles of papers except at the commencement and for German substantives.


Examples:—

(33) CARNOT and CHASSEVANT, Compt. rend. soc. biol., 1905, lix. 106.
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THE EFFECT OF ADRENALINE ON LEFT AURICULAR PRESSURE.
By R. J. S. McDowall. (From the Department of Physiology, University of Leeds). With eight figures in the text.

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THE EFFECT OF ADRENALINE ON LEFT AURICULAR PRESSURE.
By R. J. S. McDowall. (From the Department of Physiology, University of Leeds). With eight figures in the text.

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In relation to the action of adrenaline on the pressure in the left auricle not only has considerable variety of result been obtained by different observers but there has been discordance of opinion as to how these results should be interpreted.

For example, Wiggers (1) is unable to accept the view that a fall in left auricular pressure is due to pulmonary constriction as he found an increased flow of blood from a pulmonary vein when he injected adrenaline. He concludes that the fall of pressure is (omit) produced by a more complete draining into the left ventricle consequent on greater relaxation being induced by adrenaline. To explain why the output is not necessarily increased in such circumstances he finds it necessary to put forward the highly hypothetical suggestion that the extra blood is retained in the left ventricle. It will be seen that if in certain circumstances his conclusions may be partly true they are by no means justifiable as a general statement and that the hypothesis put forward is not only unnecessary but disproved.

The special object of this research has been to demonstrate the various factors which may affect the results when adrenaline is injected and to show how pulmonary constriction may affect, not only the left auricular pressure, but also the pressure in the aorta.

The majority of observers, Plumier (2), Petitjean (3), Wiggers (1), Fühner and Starling (4) and the present writer have found that there is most frequently a fall in the left auricular pressure when adrenaline is injected, but when all the factors are considered, it will be seen that a fall, no change, or even a rise is not inconsistent with pulmonary constriction.

Theoretical considerations.

A fall in left auricular pressure may result from (1) increased efficiency of the left ventricle as a pump, (2) from diminished flow from the pulmonary veins as a result of constriction of the lung vessels.

A rise in left auricular pressure may be caused by (1) lessened efficiency of the left ventricle, (2) by increased flow from the pulmonary veins more than sufficient to overcome the effect of the pulmonary constriction, and (3) by backward pressure through the mitral valve.

With regard to (3) a great deal of attention has been paid in the past. It
has however been amply shown by Bradford and Dean (5), also by Sharpey Schaefer and Lim (6), that the normal left ventricle can withstand a considerable rise in aortic pressure, produced mechanically, without there being evidence of backward pressure. The more so is this true when the heart-beat is augmented by the action of the drug on the organ itself.

It appears almost certain that the finding of evidence of backward pressure has been the result of carrying out the experiments in animals whose hearts were already impaired, or of compressing the aorta to raise the pressure too suddenly and to an extent which is much in excess of what is likely to occur on the injection of adrenaline. In this connection, it has been the experience of the present writer that old cats whose hearts were flabby and whose left auricular pressure was unusually high are more prone to show evidence of backward pressure than young active animals in which the left auricular pressure was low.

Experiments are given in this paper which show clearly that the possibility of backward pressure being the cause of the rise of pressure which occurs in the pulmonary artery may be put out of account except where there is cardiac failure (e.g., Fig. 1).

Fig. 1. — Cat, 4000 gm., light ether, vagi cut, adrenaline 0.07 mg.
To show the simultaneous effect of an injection of adrenaline on the pulmonary, left auricular, and carotid pressures. It is seen that there is a fall in the pressure in the left auricle at the same time as a rise in pressure in the pulmonary artery. Such a rise in pulmonary pressure obviously cannot be due to backward pressure as many have contended.
The effect of adrenaline on left auricular pressure

**Method.**

In all the experiments cats were used, but young animals were selected when possible. In the first instance they were anaesthetised with ether and subsequently with chloralose. Where deep anaesthesia was required, the ether was continued throughout. Left auricular pressure was registered by tying a cannula into the left auricular appendix and connecting it to a recording manometer after the manner described by the writer (7) for recording venous pressure.

**Experimental results.** — As has been indicated, the effect of adrenaline depends entirely on the conditions under which the experiment is done. For convenience therefore the results are grouped under the main factors which influence them.

**The influence of the vagus.** — With the vagi intact and under conditions in which vagal inhibition is evident, there is found to be a marked rise in left auricular pressure (Fig. 2). In this animal the vagi were not cut and cardiac slowing is well seen. The pressure in the left auricle began to fall, but on the onset of the inhibition there is a sharp rise in auricular pressure which again falls when
the inhibition passes off. It has been observed that when the vagus is stimulated, with each characteristic drop of the aortic pressure there is a corresponding rise of auricular pressure. This rise may be looked upon as somewhat of the nature of an experimental error since the cardiac slowing does not depend on the rise in aortic pressure but on the effect of the autacoid on the vagus centre. This has been shown by Heinekamp (8), and Brown (9), and has been confirmed by the present writer using the modification of the mercury valve recently described by Roberts (10).

If the vagus be cut, there is the well known rise in the systemic and pulmonary circulations, but in the normal cat no change, or a fall in left auricular pressure (Fig. 1). These observations are in accordance with the findings of Plumier. It is well known however that vagal inhibition does not always occur although the vagus is intact; it may be from shock or anaesthetic: and in such circumstances the same result is obtained as if the vagi were cut.

The influence of the right ventricle and pulmonary constriction. — These two factors may be taken together conveniently as they are both responsible for the rise which occurs in the pressure in the pulmonary artery and have a directly opposed effect on the left auricular pressure. Were there no other factor concerned, the effect of pulmonary constriction on auricular pressure must be to cause a fall, from a reduction of the amount of blood reaching the pulmonary veins. But it has to be remembered that it has been shown by Starling and his collaborators that the output of the heart is not reduced by increased resistance except momentarily. What is true of the whole heart is presumably true of the right side. The right ventricle rapidly accommodates itself to the increased pressure in the pulmonary artery and the amount of blood passing through the pulmonary circulation remains unchanged. Further as a result of the action of the autacoid on the heart, there is increased efficiency of the right ventricle, and provided the venous pressure is adequate there may be increased output of the right side of the heart and an increased amount of blood entering the left auricle in spite of the pulmonary constriction.

An experiment has been devised to demonstrate the importance of this response of the right ventricle in the maintenance of the output of the heart on the injection of adrenaline. The pulmonary arterial pressure is kept constant by means of a compensator or mercury valve (10). In these experiments a compensator similar to that referred to above has been used. The cannula connected with the compensator is introduced into the pulmonary artery by the method of Sharpey Schafer (11).

Figure 3 shows the result of such an experiment. If the pulmonary pressure be prevented from rising during the whole period of the action, a distinct diminution of the aortic rise is seen compared with the result of a similar dose injected as a control. It is however more instructive to cut out the compensator
The effect of adrenaline on left auricular pressure

Due allowance must be made for the fact that the simultaneous points are not exactly above each other. From C to OC the pressure in the pulmonary artery was prevented from rising and during this period there is a fall in left auricular pressure and the fall in aortic pressure is abrupt. As soon however as the pulmonary pressure is permitted to rise, the auricular and aortic pressures cease falling. Tracings taken before and after this one as controls were normal.

when the systemic pressure has begun to fall, as has been done in figures 3 and 4. At the beginning of the experiment when the pressure in the pulmonary artery is maintained constant it is seen that the rise in aortic pressure is comparatively short-lived and that there is a fall in left auricular pressure. As soon as the compensator is shut off however there is an immediate rise in pulmonary pressure and a recovery of the auricular. The aortic pressure which had begun to fall is now seen to cease falling, and as often as not there is a definite rise in aortic pressure at this point.

It must be obvious that if for any reason the right ventricle is impaired, it may be from asphyxia or the anaesthetic during the preliminary anaesthetization or from other damage, the response of the right ventricle may be delayed or absent. Further, attention has been drawn by Sharpey Schafer and Lim (6) to the fact that on intravenous injection the drug reaches the pulmonary vessels
before the systemic and the heart, and it has been found that the response is
first seen in the pulmonary vessels. Under light ether anaesthesia this has been
found by the writer to be particularly noticeable. This factor will tend to exag-
gerate any impairment of the right ventricle which there may be and the effect

![Diagram](image_url)

**Fig. 4.** — Cat, 2750 gm., ether, chloralose, vagi intact, adrenaline 0.03 mg.

From C to CO any extensive rise in pulmonary pressure was prevented by use of a compen-
sator. It is seen that the aortic rise and fall are very abrupt. At CO the pulmonary cannula
was clamped off and the pulmonary pressure allowed to rise (although this cannot be seen),
with the result that there is a recovery of the aortic pressure. Due allowance must be made
for the difference between the simultaneous points.

will be seen on the aortic pressure as a dip in the aortic rise. This point is
dealt with in some detail below but it is the experience of most who have given
many injections of adrenaline that not infrequently irregular tracings, similar
to figures 3 and 5, of the rise of aortic pressure occur.

Sometimes the fall in aortic pressure is very abrupt and it has been found
that a similar sharp fall may be obtained if the rise in pressure in the pulmonary
artery be prevented. In figure 4 for example the aortic tracing has almost a
spiked appearance. Such a rapid rise and fall cannot be due solely to the con-
traction and relaxation of the smooth muscle of the arterioles and it cannot be
considered that the cardiac stimulation has worn off so soon. That the rapid
fall is due to diminished output of the heart, the result of the pulmonary con-
striction lessening the flow of blood from the pulmonary veins, there appears
to be little doubt. It has been customary to consider such a rapid fall as due to
temporary giving way of the heart under the increased strain put upon it. Such a weakening of the heart would certainly cause a rise in left auricular
The effect of adrenaline on left auricular pressure

pressure, while it is seen below that there is a corresponding fall in left auricular pressure.

The characteristic effect of pulmonary constriction is therefore a fall in left auricular pressure, but this effect tends to be masked to a greater or less degree by the augmentation of the right ventricle. When for any reason the pulmonary vessels respond appreciably earlier than the right ventricle then the cutting off of the blood from the left side of the heart may be very evident.

The influence of the left ventricle. — It has been stated already that if there is no vagal inhibition the injection of adrenaline usually results in a fall of left auricular pressure and it has been shown that under certain conditions this may result from pulmonary constriction. It remains therefore to examine the view so strongly held by Wiggers (1) that the fall is entirely due to increased efficiency of the left ventricle.

The matter has been dealt with by Fühner and Starling, who found that the fall in left auricular pressure was not necessarily associated with an increased output of the left ventricle. Objection has been made to this conclusion on the grounds that in the heart-lung preparation the factors are only "supposedly under control" and because it was not shown that the extra blood drained from the auricle was not retained in the left ventricle.

No attempt is made to show that the ventricle may not play an important part in the lowering of the auricular pressure especially if the heart has been depressed previously, as there is undoubted evidence that this does occur. Under such circumstances and so long as there is no mitral incompetence from cardiac dilatation the injection causes a large fall in the auricular pressure and it has been found that the more the auricular pressure has been raised in this way, the greater the fall after adrenaline. This point is important when the influence of anaesthetics is dealt with.

In the ordinary blood pressure experiment it is not always easy to be certain that there has been no change in the cardiac output, as any diminution which occurs may not be sufficiently rapid or large to prevent an aortic rise.

In the present experiments, however, it may be presumed that the peripheral resistance has been increased and the heart stimulated, both of which effects last for a period of at least one minute. If then, there has been a fall in aortic pressure during this period it must be assumed that it is due to diminished cardiac output. A fall in auricular pressure in such a case cannot then be due to increased efficiency of the left ventricle. It must be due to diminished flow from the pulmonary veins (Fig. 5).

A study of the relation of the auricular fall to the changes which occur in aortic pressure throws further light on the subject. It is seen that the auricular fall commonly bears no relation to the amount of rise in the aortic pressure and may vary independently. Further it has been found that the auricular fall is
Note that as soon as the left auricular begins to fall the aortic rise is converted into a fall. (Measure from simultaneous points.) A fall in aortic pressure when the peripheral resistance is being increased and the heart stimulated by the adrenaline can only be interpreted as being the result of pulmonary constriction when it is accompanied by a fall in left auricular pressure. The subsequent rise in auricular pressure is considered to be due to cardiac failure as the animal was in poor condition.

often very short-lived compared with the aortic rise. It has however been observed that the auricular fall is often closely related to the "step" which frequently appears on the aortic rise (Figs. 5, 6 and 7) both in time and in extent. The larger the auricular fall, the more pronounced the step, which may become almost a dip. This may be seen even when there has been backward pressure in a bad heart as indicated by an unduly flabby musculature and an unusually high left auricular pressure. In figure 6 the first effect of the adrenaline has been to cause an abrupt rise of auricular pressure upon which is superimposed the fall which corresponds to the step in the aortic pressure. This animal was recovering from deep anaesthesia and it is seen that both the step in the aortic and the fall in the auricular pressure become more marked. A similar result may be obtained when there has been no evidence of backward pressure (Fig. 7). It has been found possible by varying the anaesthetic to vary both the step and the fall as desired (see below).

This relation between the left auricular fall and the step in the aortic rise suggests the probability that they are both due to the same cause, and the only
Fig. 6. — Cat ♀, 2650 gm., ether, chloralose, vagi cut, adrenaline 0.02 mg.

The animal was very flabby with much cardiac fat, and the abrupt rise in left auricular pressure is characteristic of cardiac failure. It is also seen in vagal inhibition. Superimposed upon the rise of auricular pressure is seen a fall due to the cutting off of blood from the left side of the heart by the pulmonary constriction. Further evidence of this conclusion is seen in the occurrence of a corresponding dip in the aortic pressure. The animal was recovering from deep anaesthesia and a tracing four minutes before showed the auricular fall and aortic dip less marked. This tracing was obtained at a demonstration before the Physiological Society.

cause which can explain them is a diminution in the amount of blood reaching the left side of the heart.

The influence of volatile anaesthetics. — It has been shown by the present writer that the effect of amyl nitrite (12) and histamine (13) may be reduced or abolished by deep and prolonged anaesthesia. It is readily shown that the fall in left auricular pressure which occurs with adrenaline also disappears or is greatly
reduced. It may at first sight be considered that this is purely a cardiac effect, but were this so the aortic pressure would be affected also, as may be demonstrated if the anaesthetic be pushed still further. It is found that the auricular fall may be reduced without there being any marked change in the aortic rise. When in the same animal consecutive doses of similar strength give a response of similar extent, then it may be presumed that the output of the heart has been the same in both cases and that any alteration which has occurred in the extent of the left auricular fall must be due to causes other than change of output.

**FIG. 7.**—Cat, ether, chloralose, vagi cut, adrenaline 0.15 mg.

*Fully described in text.* Other injections showed that the higher the auricular pressure was the greater was the fall caused by the adrenaline; indeed in this animal a fall of 50 mm. H₂O was on one occasion obtained. But for the fact therefore that the auricular pressure began a little higher the difference would be more marked. In a tracing taken between these two an intermediate stage in the disappearance of the dip was seen. Compare figure 6.

Figure 7 gives an example of this point. A is the result of an injection of adrenaline under light anaesthesia and B the effect of the same dose under deep anaesthesia only four minutes later. It is seen that there is a diminution of the auricular fall while there is practically no change in the extent of the aortic rise except that the step on the rise has disappeared. But for the fact that the auricular pressure was slightly higher in the case of B when the injection was made, the diminution in the auricular fall would have been still more marked. In other experiments it has been found possible to cause the auricular fall to disappear altogether or even be replaced by a rise but at this stage there were obtained signs of cardiac impairment in a diminished aortic rise. (See also figure 6 during recovery from anaesthesia.)

The disappearance or diminution of the auricular fall must be due to either cardiac weakening or the direct effect of the anaesthetic upon the lungs. In view of the fact that it is not necessarily associated with any diminution in cardiac efficiency it must be considered that the action of the anaesthetic on
The effect of adrenaline on left auricular pressure

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the lungs is the cause. This conclusion is supported by the fact that as the auricular fall becomes less there is also a disappearance of the step in the aortic rise which there is every reason to believe is the result of the pulmonary constriction. It is however admitted that the effect of the anaesthetic on the lungs may be and is frequently supplemented by the effect on the heart.

The effect of artificial respiration.—This point does not appear to have received attention by previous observers and may readily be the cause of confusing results. The recording of left auricular pressure necessitates the opening of the chest, and the maintenance of the cannula in its proper place makes it difficult to close the chest again. All experimenters have therefore worked under artificial respiration. Now when the chest is open, it is possible to keep the animal alive by an amount of respiration which by no means distends the lungs fully. It is well known that if the artificial respiration be excessive the pulmonary resistance may be so increased that the right ventricle may not be able to overcome it and the aortic pressure falls. If however the respiration has been inadequate previously and the lungs have become like full sponges, then the opposite occurs when the ventilation is increased. The pressure rises both in the pulmonary artery and in the left auricle due to the driving out of the extra blood from the lungs. When the lungs are in the relaxed state, adrenaline causes a rise in left auricular pressure, due it would seem to the driving out of the extra blood by the constriction of the pulmonary vessels. If on the other hand the extra blood be first driven out of the lungs by increasing the respiration, the usual fall in pressure is obtained (Fig. 8). The importance of this observation lies in the liability to neglect this factor. It is convenient when the cannula is being introduced to reduce the ventilation to a minimum and still more so is this true if the outflow from the pulmonary veins is to be measured by the method of Wiggers. Full ventilation is also very liable to disturb the position of cannulae in this region. Results therefore which have been obtained without due regard to this factor cannot be considered reliable.

The hypothesis of Wiggers (1) that the fall in left auricular pressure may be due to the retention of additional blood in the left ventricle requires but little notice. He attempts to account for an increased flow of blood from the pulmonary veins associated with a fall in left auricular pressure. It does not appear to be by any means certain that the conditions of the experiment were those in which a fall in left auricular pressure could be expected, especially with regard to the respiration. Wiggers apparently obtained a fall in left auricular pressure under all circumstances since no statement is made to the contrary except in relation to the influence of the vagus nerve, already referred to. This has not been the experience of the present writer for reasons shown. Further, Wiggers argues that an increased outflow from the pulmonary veins makes it impossible that left auricular fall is due to pulmonary constriction. He
neglects the just as obvious argument that the augmentation of the two ventricles, which normally work in harmony, may be considered to balance each other so far as the left auricular pressure is concerned and that the extent of the pulmonary constriction is the deciding factor regarding any change which may take place. The effect of the pulmonary constriction will depend on the conditions under which the experiment is made.

Unless there is certainty that all the factors affecting the result have been excluded it is quite unnecessary to consider such a hypothesis as that of Wiggers. This hypothesis, since it presumes retention of blood in the left ventricle necessitates, as he states, increased dilatation of the organ. That adrenaline does increase the dilatation is undoubted and it may readily be seen on the isolated heart, but it is still more obvious that the contraction is also increased and the possibility of incomplete emptying of the ventricle is more remote than under normal conditions.

All the results got can readily be explained in the way suggested in this paper.
And from the experiments given above it is evident that a fall in left auricular pressure may be caused by constriction of the pulmonary vessels, and that in some cases this may be also in part due to increased efficiency of the left ventricle.

**SUMMARY.**

Experiments have been carried out which demonstrate the different factors which affect the pressure changes in the left auricle when adrenaline is injected.

These are seen to be the action of the vagus, of the right ventricle, of the pulmonary vessels, of the left ventricle, of the anaesthetic and of the artificial respiration.

After the vagi have been cut it is usual to get a fall in left auricular pressure with adrenaline. This fall is shown to be due largely to constriction of the pulmonary vessels by the adrenaline; often, but not always, supplemented by increased action of the left ventricle.

This research was assisted by a grant from the British Medical Association. I wish to thank Messrs. Parke, Davis and Co., for their kindness in providing me with adrenaline for the investigation.

**REFERENCES.**

(1) Wiggers, Physiological Reviews, 1921, i, 239.
(2) Plumier, Journ. physiol. et path. gen., 1904, vi, 655; 1905, vii, 484.
(3) Petitjean, Ibid., 1908, x, 401.
(4) Führer and Starling, Journ. Physiol., 1913, xlvi, 286.
(5) Bradford and Dean, Ibid. 1884, xvi, 294.
(6) Sharpey Schafer and Lim, Quart Journ. Exp. Physiol. 1919, xii, 157.
(9) Brown, Ibid., 1916, viii.
BIBLIOGRAPHICAL REFERENCES.

Contributors are requested to place their bibliographical references at the end of their articles, drawing attention to each by a bracketed number in the text, and avoiding footnotes as much as possible. Each reference should appear as follows:

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THE ACTION OF AMYL NITRITE ON THE PULMONARY CIRCULATION. by R. J. S. McDOWALL. (From the Physiological Laboratories of the Universities of Edinburgh and Leeds.) With seven figures in the text.

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THE ACTION OF AMYL NITRITE ON THE PULMONARY CIRCULATION. BY R. J. S. MCDOWALL. (From the Physiological Laboratories of the Universities of Edinburgh and Leeds.) With seven figures in the text.

(Received for publication 8th May, 1922)

Since the work of Lauder Brunton (1), the vasodilator action of nitrites has been looked upon as one of the classic facts in physiology. Yet it has become accepted (Osler) that such drugs are of no value in the treatment of haemoptysis because they do not reduce pulmonary pressure. This statement can no longer be considered correct. The want of a convenient method of recording pulmonary blood-pressure has caused very few investigations to be made of the lesser circuit, but now that a convenient method is available, it has been possible to appreciate factors in connection with the pulmonary circulation which have been unrecognised and have accounted for many of the negative results.

Many observers (Dixon) (2), have shown that if the lungs be perfused, the addition of nitrites to the perfusion fluid causes an increased flow through the organ; this has been interpreted as due to vasodilator action. But it has never been shown that nitrites cause a fall in pulmonary pressure in the living animal; indeed Bradford and Dean (3) state that amyl nitrite actually causes a rise of pressure in the pulmonary artery.

In view of the evidence brought forward by Sharpey Schafer (4) that stimulation of the central end of the depressor nerve causes a fall in pulmonary pressure in the rabbit, a reinvestigation of the action of nitrites on the pulmonary circulation of living animals appeared desirable.

The experiments were carried out on cats. At first decerebrate preparations were used to obviate any action of narcotics or anaesthetics; but later, light ether anaesthesia was employed. The pressure in the pulmonary artery was recorded by the method introduced by Sharpey Schafer. It consists essentially of the introduction of a cannula through the wall of the right ventricle near the orifice into the pulmonary artery, and securing it in position by a purse-string suture in the epicardium. The details followed were those already published in this Journal (4), but my experience has shown that the method of bevelling the cannula so that its opening is always towards the lumen of the artery is of considerable importance. For unless special attention is paid to this point the opening may be directed against the wall of the artery, and there is liability to blocking. In my earlier experiments, the chest was sewn up with the lungs distended to insure negative intra-thoracic pressure, and the
animal was allowed to breath naturally; but later it was found that artificial respiration did not interfere with the changes in the pulmonary circulation, provided it was not excessive. The actual amount of artificial respiration used was the minimum which would maintain the circulation easily, an amount which could be gauged by regulating it so that the respiratory waves on the

carotid pulse were not greater than with natural respiration before the chest was opened.

On inhalation of amyl nitrite, there is, as shown in the figures, a marked fall in pulmonary as well as in systemic pressure.

Such a fall might be due to three causes. There may be direct action on the pulmonary blood-vessels causing diminished resistance; there may be a capa-

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**Fig. 1.** — Cat. Wt. 2500 grm. Light ether anaesthesia.

P, pulmonary pressure in mm. Hg; C, pressure in the carotid artery in mm. Hg; R, respiration; S, signal line showing period of inhalation; T, time in minutes; SP, simultaneous points.

This tracing shows the typical effect of the inhalation of amyl nitrite on the pulmonary and aortic pressures. In this instance the chest was sewn up after insertion of the pulmonary cannula, and the animal allowed to breathe naturally. It is seen that the two curves are not parallel and that there is a fall in both pressures.
city effect from dilatation of blood-vessels throughout the systemic circulation resulting in less blood reaching the lungs; or the heart may be weakened by the action of the drug. It will be seen that the weight of evidence is in favour of a primary effect on the pulmonary vessels being the important factor.

![Graph](image_url)

**Fig. 2.** Cat. Wt. 3000 grm. Light ether anaesthesia. Lettering as in Fig. 1. Natural respiration.

A marked interruption of the pulmonary fall is seen, and may be interpreted as being due to more blood reaching the right side of the heart as a result of diminished systemic resistance and before the pulmonary has dilated sufficiently to accommodate the extra volume. The commencement of the pulmonary fall before the aortic is well seen. This result was obtained three times in the same animal and the interruption was seen on many other tracings. It occurs concurrently with a rise in the right auricular pressure.

It is evident that the pulmonary fall in a large number of instances, if measured from simultaneous points, begins appreciably before the systemic fall (fig. 2). In some cases where the blood pressure is high, there is a marked fall in the pulmonary pressure with no change in the systemic (fig. 3).
The existence of a pulmonary dilator mechanism is further shown by the action of anaesthetics. These diminish and in some cases obliterate the pulmonary fall; which indeed, as will be seen later, may be replaced by a rise. This effect is most easily obtained by chloroform, although it can be got by very deep ether-anaesthesia.

In one case ether-anaesthesia was pushed to failure of the respiration and heart; the inhalation of amyl nitrite caused a temporary rise in pulmonary blood pressure. A parallel fall in both had already begun as the result of heart failure, and the anaesthetic had to be shut off and artificial respiration given to save the life of the animal. With a fresh inhalation on recovery, only the typical fall in the pulmonary occurred. Other instances have been obtained in which the anaesthesia was not pushed to the extent of causing cardiac effects.

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1 This is not a new observation, for in 1880 Mc Kendrick, Coats, and Newman (5) found that anaesthetics, especially chloroform, interfere with the circulation through the lungs.
but sufficiently to reduce or even abolish the pulmonary effects, while the systemic fall was well marked (fig. 5).

The author (8) has observed that under other conditions also an aortic fall need not be accompanied by a pulmonary fall. This may be seen on the injection of histamine or the second dose of a pituitary extract. Both of these cause typically a fall in the aortic and a rise in the pulmonary pressure.

A fall in the aortic without a change in the pulmonary system may be also produced mechanically by the releasing of a previously compressed abdominal aorta or common iliac.

It has to be noted, as in the case of raising of aortic pressure by compression (3) that any secondary pulmonary change is dependent on the efficiency of the heart.

If the latter is enfeebled, a rise or a fall of the pulmonary pressure may be caused by mechanical pressure or its release, as above; but if the experiment

![Diagram](image.png)

**Fig. 4.** — Cat. ♀. Wt. 2500 gr. Natural respiration.

Light anaesthesia. An uninterrupted pulmonary fall has occurred which may be taken to indicate that the lung circuit has dilated sufficiently to accommodate the extra blood received from the venous side.

is carried out on a fresh animal and not at the end of an experiment, the pulmonary pressure is almost or quite unaffected.
The occurrence of a marked aortic fall without any pulmonary change is the strongest possible argument against the suggestion that an aortic fall must cause a fall in the pulmonary.

Although the pressure in the pulmonary artery cannula bears exactly the same relation that carotid pressure does to aortic, there are some who, while accepting changes in the carotid pressure, are unwilling to accept the results deduced from pressure in the pulmonary artery, without consideration of the pressure in the right and left auricles.

An investigation of these pressures has therefore been made; but it only serves to support the reliability of results based upon pressure changes in carotid and pulmonary arteries. Pressure in the left auricle was recorded by a cannula tied into the auricular appendix; in the right auricle by a long cannula passed down the jugular vein. In both, the pressures were taken with a water manometer, recording by means of a hollow vulcanite float carrying a writer. The float was made from a light fountain-pen cap fitting in a narrow burette.

It has been noted that on inhalation of amyl nitrite there is usually a fall in venous pressure, but the fall is not immediate. The present investigation
shows that not infrequently there is a rise in venous pressure but most frequently a rise followed by a fall, the cause of which is evident on further experiment. It is clearly shown in fig. 6 that if an animal be given a dose of amyl nitrite there is a delayed fall in the right auricular pressure. If another inhalation be given after a short interval, there is a rise followed by a fall, and if given during the fall, there is a marked rise, followed by a comparatively small fall, if any.

The effect depends on the state of the capillaries which were shown by Bernheim (6) and by Krogh to be dilated by amyl nitrite. On the systemic circu-

![Fig. 6. — Showing the effect of amyl nitrite on right auricular pressure.](image)

Cat. ♀. Wt. 2210 gr. Natural respiration. Light ether anaesthesia. C, carotid pressure; R. A., pressure in right auricle in mm. Hg. A portion of the tracing occupying two minutes, in which an intermediate result was obtained from a further inhalation, has been cut out.

It is seen that on the first inhalation of amyl nitrite there is a very slight rise of auricular pressure followed by a marked fall. On giving another inhalation, when the arterial pressure has almost recovered but the auricular pressure is still low, the rise in the auricular pressure is the more pronounced change, while the subsequent fall is insignificant. The period of the second inhalation may be looked upon as that at which the arterioles have recovered, but the capillaries are still dilated and insensitive to the action of the nitrite. See text.

lation, the first action of the drug is to allow more blood to reach the venous side by dilatation of the arteries with the result that right auricular pressure
rises. Then begins the dilatation of the capillaries, which soak up the extra blood like a sponge, causing the pressure to fall again.

If the capillaries be already dilated from a previous dose or from histamine-like shock, then only the rise in pressure is seen, due to more blood getting through to the venous side.

An appreciation of these facts throws light on the interruption of the pulmonary fall which occurred in a considerable number of cases (fig. 2). During the early part of amyl nitrite action in animals in which the capillaries are partially dilated or immobile, more blood reaches the right side of the heart and there is an increased output of the right ventricle with increased pressure in the pulmonary artery, depending on whether or not the pulmonary vessels are dilating sufficiently rapidly to accommodate the extra blood.

The interruption of the pulmonary fall is coincident with the rise in right auricular pressure. Should the dilatation of the pulmonary vessels be sluggish or abolished by the action of anaesthetics, the rise may be the only change seen.

This appears to be the explanation of the rise in pulmonary pressure obtained by Bradford and Dean (3) when amyl nitrite was inhaled. These observers used morphia and chloroform, which, they state, gave, "a very perfect anaesthesia".

The effect of more blood reaching the right side of the heart is particularly well seen in rabbits, in which the pulmonary rise is readily observed. Such a condition would be expected where there are comparatively immobile capillaries, and the main effect of amyl nitrite is to allow blood to pass more easily from the arterial to the venous side.

This is in accordance with the fact that histamine shock due to dilatation of capillaries is not obtained in an anaesthetised rabbit, suggesting immobility of the capillaries in this animal.

It has been noted by Sharpey Schafer and Lim (7) in relation to adrenalin and by the present writer (8) in relation to pituitrin that rabbits are more liable than cats to such forward effects of the systemic circulation upon the pulmonary.

The occurrence of such a change as a fall in the pressure in the pulmonary artery when the right auricular pressure is maintained (or it may be rising) shows clearly, apart from other evidence, that a capacity effect of the systemic upon the pulmonary circulation plays no rôle in the early part of the pulmonary fall.

Left auricular pressure was next considered, and it was found that changes similar to those in the right auricle occur. But it has to be remembered that with inhalation the pulmonary capillaries are affected before the arterioles, and the dilatation of the capillaries tends to obscure the lessening of pulmonary resistance, as the blood is soaked up by the rapidly dilating capillaries, result-
ing in a fall of left auricular pressure. If however, when the lung capillaries are fully dilated, a further inhalation is given, there is a rise in left auricular pressure owing to the dilating arterioles allowing more blood through to the left side of the heart. This extra input into the heart is further seen in an increased output, and consequent rise of aortic pressure (fig. 7).

The only other recorded observation on this point is that of Winkler who noted that when there was a fall in left auricular pressure, it was not in proportion to the carotid fall.

There seems to be little doubt that it is a lessened pulmonary resistance, acting in this way, which accounts for the short rise in aortic pressure, which as noted by Dixon and Ransome (9) occasionally occurs before the charac-

![Image](image.png)

**Fig. 7.** — Cat. ♀, Wt. 2750 gr. Art. resp. C, carotid pressure; LA, pressure taken in left auricle. Three inhalations.

The first inhalation of amyl nitrite causes a delayed fall in the left auricular pressure, as the pulmonary capillaries are first affected by the drug. Once the capillary bed is dilated more blood passes through to the left side. That the rise in left auricular pressure thus caused is really due to increased blood flowing to the heart, is seen by the rise in aortic pressure as a result of increased output.

teristic fall on inhalation of amyl nitrite. A tracing in which carotid, pulmonary, and left auricular pressures were taken simultaneously, indicated that this opinion is correct.

A word is necessary regarding the possibility of cardiac effects. Apart from the fact that amyl nitrite may, by decreasing aortic pressure, cause slight quickening of the heart, no definite action of the drug on the heart has been demonstrated; but the present investigation contains sufficient evidence that the pulmonary fall is not due to cardiac weakening. In cardiac effects the parallelism of the pulmonary and aortic curves is very noticeable; in the usual amyl nitrite tracings there is a striking lack of parallelism, and the amount of fall in the pulmonary pressure bears no relation to a fall in the
aortic. A cardiac effect could not explain those instances where there is a fall in the pulmonary with no distinct change in the aortic and *vice versa*. It may therefore be concluded, that the inhalation of amyl nitrite causes dilatation of the pulmonary bloodvessels and a consequent lowering of pulmonary blood-pressure, and that the bloodvessels of the lungs are not different from the vessels of the general circulation in their response to nitrites.

**Summary**

It is shown that amyl nitrite causes a lowering of pulmonary blood-pressure. Evidence is brought forward to show that there is direct action on the pulmonary bloodvessels, and this is supported by the findings in the auricles. The existence of a vasodilator mechanism in the lungs is rendered probable.

A revision of the present position of nitrites in the treatment of certain lung diseases is suggested by the results of these experiments.

**REFERENCES**

(3) **Bradford and Dean**, Proc. Roy. Soc. 1880, xlv ; Journ. Physiol. 1894, xvi ;
(4) **Sharpey Schafer**, This Journ. 1919, xii.
(6) **Bernheim**, quoted by Lauder Brunton in Text-book of Materia Medica and Therapeutics, 1880.
(7) **Sharpey Schafer and Lim**, This Journ. 1919, xii.
(9) **Dixon and Ransome**, Journ. Physiol., 1921, lv.
BIBLIOGRAPHICAL REFERENCES.

Contributors are requested to place their bibliographical references at the end of their articles, drawing attention to each by a bracketed number in the text, and avoiding footnotes as much as possible. Each reference should appear as follows:—

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(Received for publication 2nd February 1925.)

Since it has now been definitely shown, especially as a result of the work of Dale, Hooker, Krogh, and their co-workers, that the capillaries may alter their calibre independently of the arterioles, a great deal of new information regarding the vasomotor mechanisms of the body will require revision in the light of our new knowledge.

It is, for example, evident that considerable alteration may take place in the capillary area without any alteration in arterial blood-pressure. Blood-pressure may be influenced by any of the factors on which it depends: the heart, the blood volume, and the peripheral resistance, together with the elasticity of the arteries. It is, however, well known that certain compensatory mechanisms exist by which an animal can accommodate itself to loss of blood, as after a moderate haemorrhage the blood-pressure does not fall. Any fall of pressure, of arterial or venous pressure, brings about an increased activity on the part of the vasomotor centre and increased peripheral resistance. An analogous condition was shown by Dale and Laidlaw (1) to be brought about if the capillary area is dilated and the animal, as it were, bleeds into its capillaries. As, however, was recently pointed out by the writer (2), should the capillary dilatation not be severe, the blood-pressure may be prevented from falling by reflex mechanisms.

It becomes, then, increasingly desirable to detect any compensatory alterations in arterial tone which may have occurred, although there may be no change in arterial blood-pressure.

Velocity of the Pulse-Wave Method.—As pointed out by Moëns, and more recently emphasised by A. V. Hill, the velocity of the pulse-wave depends on the internal pressure and the elasticity of the arteries. The velocity of the pulse-wave may be calculated (Bramwell and Hill (3)) to be equivalent to 3.75 times the square root of the elasticity, the latter being expressed as the percentage increase in volume per millimetre of mercury increase in internal pressure, i.e.:

\[ V = 3.75 \text{ percentage increase in volume per mm. Hg. increase of pressure. } \]
For a given arterial pressure, then, the velocity of the pulse-wave is an indication of the elasticity of the blood-vessel. But variations in the elasticity in the living animal within a comparatively short period can only be due to changes in the tone of the arterial wall.

In the method described below advantage is taken of the above facts, as it will be obvious that variations in the velocity of the pulse-wave in an artery for a given internal pressure must indicate changes in the tone of the artery. The velocity of the pulse-wave in the aorta may be measured and utilised for this purpose.

The carotid and femoral arteries are dissected out and tied off by a double ligature. The arteries are then divided between the ligatures. The free central ends of the arteries are tied to tambours so that they pull on the tambours slightly. At each beat of the heart the thrust of the pulse-wave is communicated to the free end of the artery and is transmitted to the tambour.

The puff of air produced by the tambour is made to cool down a hot wire after the method of the Tucker microphone or the Hill hot-wire sphygmograph, and the change in the resistance of the hot wire is at once shown on a string galvanometer. The connexion to the string galvanometer may be made by the use of a Wheatstone bridge as used by Hill, a battery bridge as used in the usual sound-ranging apparatus, or a transformer as used by EINTHOVEN in a similar method for recording heat sounds. The second method was used in the present investigations.

The difference in the times of arrival of the pulse-wave at the carotid and at the femoral artery is the time taken for the wave to travel the difference of the distances of these two points from the heart. This distance can be determined, after the experiment, by dissection and actual measurement, and for practical purposes this can be considered the aorta.

By the use of the method several interesting results have been obtained. It is well known that the arterial blood-pressure quickly recovers from the result of a small hemorrhage, and that the recovery is due to increased vasomotor tone. That the large vessels take part in the vasomotor response is made clear by this method, for it is found that there is an appreciable increase in the velocity of the pulse-wave in the aorta. In the same way, too, it may be shown that small doses of histamine, from which an animal apparently recovers completely, bring about a similar increase in the tone of the aorta, thus indicating that the effect of the histamine is not so evanescent as the very temporary effect on the arterial pressure would lead one to suppose.

The method can also be applied where there has been an actual fall of arterial pressure. But here a standard velocity for each internal pressure has to be first obtained for purposes of comparison. For this purpose acetyl-choline, which has been shown by DALE and RICHARDS to dilate arteries, readily lends itself, as its effect is very evanescent. By
its use the blood-pressure may be reduced to any required degree, and a
curve may be obtained for the velocities at each internal pressure and
under conditions under which the arteries are known to be dilated.

Now it will be realised that if the arterial pressure fall from any
reason other than arteriole dilatation—such as cardiac failure, or
diminished output of the heart—then the arteries must be constricted, as
under such circumstances the vasomotor centre is stimulated by the fall
of blood-pressure which results. The velocity of the pulse-wave for
a given internal pressure brought about by any procedure is an in-
dication when compared with the acetyl-choline standard as to whether
or not the blood-pressure has fallen as a result of arterial dilatation.

The accompanying protocol gives the result of an experiment on the
effects of severe haemorrhage and acetyl-choline on the blood-pressure.
It will be readily seen that for any given internal pressure the velocity
after haemorrhage is appreciably greater than that after acetyl-choline.
We may, then, conclude that in haemorrhage there has not been a relaxa-
tion of arteries, and as there has been a fall of internal pressure, we
can assume that there has been an arterial constriction. A self-evident
example has been taken in this instance.

Protocol of an Actual Experiment.

Distance of carotid at point of section from aortic arch 9.5 cms.
Distance of femoral at point of section from the heart
where the carotid arises from the arch 31.5 "
Length of vessel under investigation therefore 22 "
Normal blood-pressure of cat under chloralose 170 mm. Hg.
Difference in times of arrival of pulse-waves at the two
points (mean of 13 observations), i.e. time taken
in travelling 22 cms. 0.024 sec.
Therefore normal velocity of pulse-wave = 9.16 metres per sec.

The subsequent effects of acetyl-choline and of haemorrhage are
given in tabular form.

<table>
<thead>
<tr>
<th>Pressure</th>
<th>Observations</th>
<th>Time difference</th>
<th>Velocity</th>
</tr>
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<tbody>
<tr>
<td>Normal</td>
<td>170</td>
<td>13</td>
<td>0.024 sec.</td>
</tr>
<tr>
<td>Slight hæm.</td>
<td>160–170</td>
<td>13</td>
<td>0.021</td>
</tr>
<tr>
<td>More hæm.</td>
<td>140–150</td>
<td>10</td>
<td>0.022</td>
</tr>
<tr>
<td>Severe hæm.</td>
<td>100–110</td>
<td>13</td>
<td>0.029</td>
</tr>
<tr>
<td>Acetyl-choline</td>
<td>120–130</td>
<td>12</td>
<td>0.032</td>
</tr>
<tr>
<td></td>
<td>100–110</td>
<td>9</td>
<td>0.037</td>
</tr>
</tbody>
</table>

The acetyl-choline observations were, of course, taken prior to
those after haemorrhage. Note the increase in the velocity after
haemorrhage, even when the internal pressure is appreciably reduced. Note that with acetyl-choline for the same blood-pressure, or even 20 millimetres higher, there is a marked reduction of velocity.

If, however, the blood-pressure is lowered by histamine injection, the action of which is not so clear, a similar result obtains. We can say then that the fall of pressure after histamine is not due to arterial relaxation. Amyl nitrite, on the other hand, gives velocities like those of acetyl-choline, and we can say it brings about a loss of arterial tone.

This method obviously lends itself to investigation of the exact nature of the causes of fall in blood-pressure.

Reaction to Acetyl-Choline.—Reid Hunt (4) observed that certain substances enhanced the action of this drug. No explanation was put forward for this. Later, however, Dale and Richards (5), working from another aspect, showed that the extent of the reaction to acetylcholine depends on the tone of the arteries and is considerably influenced by section of the vasomotor nerves. It does not, however, appear to have been suggested that the reaction to acetyl-choline may be utilised in investigations of the arterial system. The method has been found to be subject to certain limitations, yet within these limitations it is of considerable value.

The chief limitation is, of course, that where there has been a fall of arterial pressure, the reaction to the drug is reduced. In such circumstances some investigators have considered a fall of pressure as a percentage of the blood-pressure obtaining at the moment before the injection, but this method can scarcely be considered trustworthy.

The advantage in the use of the method suggested is the indication it gives of changes of arterial tone, although there may be no change in arterial pressure. This is well seen where there has been a change in the volume of the circulating blood. It should perhaps be said that the reaction to acetyl-choline is remarkably constant in a series of doses and, as shown by Shanks (6), it is rapidly excreted. By its use it can be shown that, if a fluid such as gum saline is injected into an animal, there is a reduced reaction, indicating that arterial tone is diminished. If, on the other hand, the animal is bled, there is an increased reaction indicating increased arterial tone; that is so long as there is no actual decrease in arterial pressure and the pressure is kept up reflexly. The reflex mechanisms concerned have recently been discussed by the writer (2).

If the capillaries are dilated by histamine and there results a relative loss of blood—that is, the animal as it were bleeds into its capillaries—there is an increase in the reaction to acetyl-choline (see accompanying tracing).

In these experiments a fresh animal is absolutely essential, as shock or previous injection of drugs may readily interfere with the vascular response. It has been noted, too, that after large amounts of histamine the arterial constriction has been so intense that the reaction to
acetyl-choline entirely disappears. This may also be seen immediately after a fall of arterial pressure due to histamine, and is probably due to direct action of the histamine upon the arteries. This factor would not complicate, of course, capillary dilatation brought about in other ways. It has been found also, if there has been a fall of arterial pressure due to histamine dilatation of the capillaries, the arterial constriction does not

pass off immediately, although the blood-pressure is made up to normal with saline. The enormously increased arterial tone in such circumstances is seen by an enormous response to acetyl-choline.

The utilisation of this method, together with that given in the first half of the paper, offers a large field of work and, as indicated, has already given very interesting results.

The expenses of this investigation were in part defrayed by a
grant from the Government Grants Committee of the Royal Society to one of us—R. J. S. M'D.

REFERENCES.

(1) DALE and LAIDLAW, Journ. Physiol., 1918, lii. 335.
(2) M'DOWALL, *ibid.*, 1924, lix. 41.
(5) DALE and RICHARDS, Journ. Physiol., 1918, lii. 110.
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THE REACTIONS OF THE PUPIL IN THE CHLORALOSED ANIMAL. By R. J. S. M'Dowall. From the Department of Physiology, King's College, London.

(Received for publication 2nd February 1925.)

Since the original observations of Biffi (1) in 1846 it has been well known that the pupil is under sympathetic control, and also that the sympathetic exerts a certain degree of tone on the dilator fibres of the sphincter. It is moreover evident, from the action of atropine and from observations on cases where the third nerve is paralysed, that the parasympathetic also exerts a tonic influence. It is therefore obvious that a balance exists between these two sets of nerve fibres.

Further, it has been considered by clinicians that the pupil might be some indication of the general state of the autonomic nervous system, but little or no experimental evidence has been put forward on the point. This has largely been due to experimental difficulty, and especially to the fact that the usual volatile anaesthetics affect the reactions of the pupil according to the depth of the anaesthesia.

It has been observed, however, by the writer that if an animal such as a cat be anaesthetised with chloralose, the pupil remains of normal size but is extremely sensitive and rapid in its reactions. A study has been made of the effects on the pupil of various procedures, and the results are given below. It will be seen that not only do its reactions give an indication of the state of the autonomic nervous system of the animal, but they may be utilised as an index of sensation and as a means of tracing out the paths of afferent impulses in the sympathetic nervous system.

The observations may conveniently be classified under several headings. For purposes of completeness, the better-known reactions which are not interfered with are merely stated, while the newer points are dealt with in more detail.

Increased Action of the Sympathetic causing Dilatation of the Pupil.—
1. Stimulation of the cervical cord in the neck. 2. Intravenous injection of adrenaline. 3. Local instillation of adrenaline.

It is generally stated as the result of the work of Meltzer and Auer (2) that the instillation of adrenaline into the conjunctival sac is ineffective unless the superior cervical ganglion has been excised some
time previously. In the chloralosed animal, however, such instillation causes a well-marked dilatation of the pupil, exactly as in the instillation of atropine. It is, however, slower than atropine, no doubt because the adrenaline, by causing local constriction of vessels, interferes with its own absorption. When full dilatation is obtained the pupil is no longer affected by light. It is clear that the dilatation is due to purely local absorption as the other pupil remains normal in size and reaction. The existence of this reaction appears to throw some light on the so-called sensitisation of the iris after excision of the superior cervical ganglion. It may well be held that if chloroform or ether be used the vessels are so acted upon that absorption is interfered with, but that the interference is removed by excision of the superior cervical ganglion. Certainly the activity of the circulation under chloralose compared with that under the more depressant anaesthetics such as chloroform and ether is very striking. It will be seen below that the reactions given to sensory stimulation under chloralose are similar to those obtained also in the sensitised animal.

Reaction to General Sensory Stimulation.—It is well known that stimulation of a sensory nerve brings about a rise of blood-pressure under ordinary anaesthesia, but so often is there irregularity in blood-pressure that the method is difficult to control when the reactions expected are not very large. In the chloralosed animal, however, very definite results are obtained on the pupil by a degree of stimulation which has little or no effect on the arterial pressure.

Stimulation of the areas supplied by the autonomic nervous system have given extremely interesting results.

In the abdomen scratching the visceral peritoneum causes no dilatation, while scratching the parietal peritoneum gives a marked positive reaction. Cutting into the lumen of the small intestine causes no dilatation. On the other hand, stretching a piece of the gut causes a distinct dilatation. In one instance in which the urinary bladder of the animal was full, compression of the organ between the finger and thumb caused marked pupillary dilatation. It will be noted that the procedures which bring about dilatation are those which are known to cause pain, while those which in man are painless cause no dilatation. In man, for example, if the abdomen is opened under local anaesthesia strictly limited to the abdominal wall, cutting of the abdominal viscera is not accompanied by any sensation of pain.

In the chest a similar state of affairs is observed with regard to the lung. No amount of stimulation of the lung or its pleura gives dilatation, while scratching the pleura lining the chest gives an immediate reaction. In the case of the heart, dilatation is obtained by stretching the pericardium or by pinching the heart. In view of the attention recently drawn to the possibility of relieving the pain of angina pectoris by nerve section, attempts were made to find paths in the neck other than
the cervical sympathetic which would give dilatation of the pupil. Results, however, were very inconstant. Sometimes stimulation of the central end of the vagus or of a separate depressor nerve, when there was one, gave dilatation; at other times no dilatation could be obtained although the pupil reactions were normal to other forms of stimulation.

It was, however, clearly evident that dilatation of the pupil could be obtained when all the nerves in the neck had been cut. This dilatation persisted after removal of the suprarenals, but was abolished by section of the spinal cord in the cervical region. These observations may be taken to indicate that sensory pathways from the heart do not necessarily pass up the nerves of the neck but may pass from the stellate ganglion to the upper thoracic roots. This confirms the finding of Langley (3), who used the reflex response given on stimulation of the central end of the accelerator nerves as an index of the pathway, and supports his contention that section of nerves such as the depressor cannot be expected constantly to relieve pain of cardiac origin.

Reaction to Functional Sympathetic Stimulation.—As an example of such stimulation small degrees of hæmorrhage were used. Under such conditions there is increased rate of heart and vasomotor stimulation. As was expected, hæmorrhage brought about marked dilatation of the pupil. Even if the pressure in the aorta were but reduced momentarily, as by removal of the clip on the washout tube of the ordinary carotid canula, there was a temporary dilatation of the pupil. If the hæmorrhage is larger and the blood-pressure does not recover, the size of the pupil increases step by step as each quantity of blood is removed. Similarly, if histamine, say a hundredth to a tenth of a milligram, is injected, there is a momentary dilatation of the pupil during the brief period of a fall in arterial pressure. This is followed by a long period of constriction lasting from ten to fifteen minutes, which no doubt is a result of the action of histamine on smooth muscle, and may be looked upon as an index of the duration of the action of histamine on the arteries, apart from its dilator action on the capillaries. A fall in blood-pressure due to pilocarpine or acetyl-choline caused only a very small dilatation, if any; here it can be assumed that the well-known action of these drugs on the parasympathetic nerve-endings counteracted the dilatation.

The reaction to a fall of blood-pressure may be considered evidence of afferent impulses distinct from those which are appreciated as pain. It is known that arteries are supplied with sensory nerves and that exquisite pain may be experienced at the moment of puncturing a vessel. A fall of blood-pressure, however, is not associated with pain, and the afferent impulses caused thereby may be considered as analogous to the unconscious afferent impulses from the muscles which pass to the cerebellum in the maintenance of equilibrium.

The Effect of Asphyxia.—Asphyxia was induced by stoppage of the artificial respiration after the chest had been freely opened. A profound
dilatation of the pupil resulted, which became permanent at the point of death.

Relationship to the Suprarenal.—The possibility that the dilatation on stimulation of various parts might be due to the secretion of adrenaline was considered. It is found, however, that the reaction is still plain after tying off both glands. It is evident, then, that the dilatation is produced through nervous paths, although possibly augmented by adrenaline.

Sympathetic Exhaustion from Over-stimulation of the Sympathetic.—This is well seen after the intravenous injection of a large dose of adrenaline. After such a dose, as is known, there is a depression of arterial pressure following the classical rise, and this depression may be temporary or permanent according to the dose of adrenaline administered. Large doses may even bring about a condition of shock. When, after a dose of adrenaline, the arterial pressure returns to normal or is further depressed, the pupillary dilatation, so evident during the depressor action of the adrenaline, is succeeded by a marked constriction, the duration of which varies according to the dose. Such a constriction must be considered analogous to the exhaustion which is seen in a perfused heart after the addition of a large amount of adrenaline to the perfusion fluid.

The Effect of Section of the Cervical Nerves.—Section of the cervical sympathetic gives a typical constriction from overaction of the third nerve. It is interesting to note that the paradoxical phenomenon described by Sharpey-Schafer (4) was seen if the section was done on one side an hour before the other. Under such circumstances the pupil on the side the more recently cut was smaller than on the opposite side which had been cut earlier, while the latter was larger than normal.

SUMMARY.

The reactions of the pupil in the chloralosed animal are described, and evidence is put forward which indicates that they may be used as an index of sensation not only from areas supplied by the spinal nerves, but also from those supplied by the autonomic nervous system. Light is thrown on the so-called sensitisation of the pupil by removal of the superior cervical sympathetic ganglion. The afferent impulses from the heart are shown to pass, at least partly, by way of the spinal cord.

REFERENCES.

(1) Biffi, Inaug. Diss. Pavia, 1846.
(3) Langley, Lancet, 1924, ii. 995.
CONTRIBUTORS are requested to place their bibliographical references at the end of their articles, drawing attention to each by a bracketed number in the text, and avoiding footnotes as much as possible. Each reference should appear as follows:—

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(Received for publication 30th September 1925.)

In a previous paper (1) it was pointed out that records of left auricular pressure were very liable to be rendered fallacious by the accidental production of mitral incompetence during the necessary manipulation in introducing the auricular cannula. Several previous workers, especially Wiggers (2), Straub (3), and their pupils, have investigated this subject and the effect of mitral incompetence on the circulation in general. These observers appear, however, to have contented themselves with recording at one time only one or two pressures in the vessels entering or leaving the heart, and with piecing together the evidence. It is evident, however, that although a great deal of information may be obtained in this way, as the conditions of individual experiments vary, it is more satisfactory to investigate the pressures in all these vessels simultaneously and the effect of an artificially produced lesion upon them.

The present experiments were carried out on cats anæsthetised with chloralose. The carotid pressure was recorded in the ordinary way with a mercury manometer, venous and left auricular pressures by water manometers in a manner described elsewhere (4), and pulmonary pressure by the method of Sharpey-Schafer (5), methods which, although individually comparatively easy, require somewhat complicated technique for their simultaneous execution. Coincident points were obtained by stopping the kymograph, and by moving it up and down on its main supporting screw. In addition to the production of mitral incompetence produced by dragging on the valve with the auricular cannula, the pressures were varied further at different stages in the experiment by stimulation of the peripheral end of the vagus. Some objection to this method of producing mitral incompetence might be taken on the ground that there was no actual evidence of mitral incompetence when the heart was examined post-
mortem; but it will be evident that when the normal left auricular pressure is sent up enormously by dragging on the valve in this way, there can be no possible doubt that a functional incompetence is produced, just as we know that in aortic disease with dilatation of the left ventricle mitral incompetence may occur as a result of stretching the auriculo-ventricular opening.

In fig. 1 is seen the result of stimulation of the vagus upon these four pressures recorded as above. It will be seen, as would be expected, that there is a banking-up of the blood entering the heart, causing a rise of venous and left auricular pressures with a fall in both arterial pressures. In this particular experiment, of which records are shown because it chances to belong to this special consecutive series, the arterial pressures are appreciably lower than normal from the inevitable primary shock of the experiment.

In fig. 2 is seen the effect of mitral incompetence. Carotid pressure is not appreciably changed, indeed has improved slightly because of the general improvement in the condition of the animal, but the left auricular pressure is almost double its normal height. The striking feature of the left auricular pressure now is that it is very dependent on aortic pressure, which it follows in every detail and even exaggerates. A very small change of less than 10 per cent. in the aortic pressure will

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**Fig. 1.**—Cat. Carotid pressure in mm. Hg; pulmonary pressure 1 mm. equal to 2 mm. H₂O; left auricular and venous pressures in mm. H₂O. Vagus stimulation shown by fall of arterial pressure. Time 10 seconds. The normal effect of vagus stimulation on these four pressures is clearly seen.
cause a change amounting to over 100 per cent. in left auricular pressure. No doubt it was this observation which has led some distinguished physiologists to believe that the height of left auricular pressure usually varies with the height of the aortic pressure. The more efficient the ventricles, as indicated by the height of the carotid and pulmonary pressures, the better this left auricular change is seen (fig. 3). The cause of the enormous change in left auricular pressure is readily understood when it is realised that normally the aortic pressure is some fifty times greater than that of left auricular pressure. The slightest leak

then in the valve not only allows the passage of blood, but blood at a high pressure is transmitted to the auricle, especially in conditions of stress such as is seen at the end of vagus stimulation when the blood which has been banked-up in the veins has to be dealt with. In these latter circumstances there is an enormously increased output of the right ventricle into the pulmonary circulation, as indicated by the fall of venous pressure, and this still further adds to the abnormal pressure in the left auricle. It is easy to understand therefore why in mitral disease an individual may be comparatively comfortable at rest and yet intensely breathless on taking exercise, in which circumstance a very large change in the pressure in the pulmonary circuit must occur. It has been shown that in such an individual the actual vital capacity of the chest is appreciably reduced (Peabody and Went-
and the lungs cannot fully expand. That this, however, may not be the sole cause of breathlessness is indicated by the fact that in some cases of mitral disease there is an actual fall in the alveolar CO₂, which suggests that the respiratory centre has been over-stimulated. Experiments such as those of Shaw-Dunn suggest that the pressure in the pulmonary circuit may irritate the vagus endings and thus stimulate the centre.

It will be obvious that the effect of vagus stimulation on left auricular pressure is of considerable general experimental interest, since it may be used as a test of the competency of the mitral valve, which, as has been already said, may be rendered incompetent accidentally, and there can
be little doubt that this has vitiates many results alleged to have been brought about through the action of drugs. In all cases where the left auricular pressure is above 45 mm. of water, incompetence should be suspected, and the vagus stimulation test can readily be carried out without any permanent effect on the animal.

The effect of the incompetence on the pressure in the pulmonary artery appears to depend on the state of the right ventricle. Immediately after the production of the incompetence there may even be a fall in pulmonary pressure if the strain has proved too much for the right ventricle, as indicated by an increased venous pressure. When, however, the right ventricle has gained strength, as indicated by normal venous and pulmonary pressures, a change in the left auricular pressure does increase the mean pressure in the pulmonary artery, although not to the extent which might be expected, a fact which suggests that the pulmonary vessels may distend to accommodate the extra blood without much increased pressure. This is seen if figs. 3, 4 and 5 be compared. The improvement of the mitral valve, as indicated by the reduction or absence of the marked fall in left auricular pressure when the vagus is stimulated, has reduced the pulmonary resistance, and the pulmonary pressure has fallen. The general improvement in the heart does not suggest that the right ventricle has been responsible for this reduction.

The pressure in the aorta in a mild degree of mitral incompetence is unaffected, as indeed would be expected, since a fall in the aortic pressure can be prevented in two ways. As pointed out by Straub, the increased left auricular pressure brings about a greater filling of the left ventricle during diastole, and, provided the heart can respond, the output is by the Law of the Heart also increased. Should this compensating mechanism fail, engorgement of the pulmonary circulation occurs; while if the right ventricle fails, as result of a strain, we get dilatation of the auriculo-ventricular orifice, and eventually venous congestion, with which we are familiar in chronic cardiac disease. The aortic pressure is also prevented from falling by increased peripheral resistance, brought about reflexly as a result, no doubt, of a diminution in the normal depressor impulses which pass up from the arch of the aorta. Aveling and M'Dowall (7) have recently found that the operation of this compensatory mechanism can readily be shown in the fall of skin resistance which occurs in association with vaso-constriction. In fig. 2 it is seen that there has been severe breakdown and that the venous pressure is increased. It may here be noted in support of several American observers that the high venous pressure is extremely delicate evidence of cardiac failure. In this instance the venous rise is not great, but in severe cardiac failure it may readily rise to over 100 mm. of water. In fig. 4, where it is seen that the height of the left auricular pressure is still dependent on the aortic pressure, and it may
be assumed that there is still an appreciable degree of mitral incompetency, it is seen that the venous pressure has now returned to normal as the cardiac condition has improved. It may be presumed, however, that there is an increased engorgement of the pulmonary circulation, and we know clinically that after the tricuspid valve fails, patients with

![Diagram](image)

**Fig. 4.**—Same experiment a few minutes later, recovery of the right ventricle is complete but not the left. Description in text.

mitral disease are often more comfortable than when their cardiac condition has improved.

The particular experiment of which the records are given was a particularly fortunate one, as it continued without any appreciable difficulty from accidents, which are frequent in such multiple experiments, for over two hours, during which the mitral incompetence was gradually recovered from. It was therefore possible to follow the changes in the experiment as a whole. At first the right ventricle recovered, as indicated by the fall of venous pressure and rise of
pulmonary pressure, while appreciably later the left ventricle recovered, as indicated by the fall of left auricular pressure and rise of aortic pressure, as seen by the tracings. This is exactly what we know to be the order in which we see recovery from a relative mitral incompetency clinically, and the present experiments therefore may be looked upon as indicating the changes in pressure which actually occur in these areas in disease. It was noted also that at a stage when there was practically no permanent leak through the valve, as indicated by the

![Graph](image_url)

Fig. 5.—Same experiment a few minutes later, recovery almost complete except during stress after vagal stimulation.

low left auricular pressure and the absence of a fall when the vagus was stimulated, there was still a leak during a time of stress on recovery from vagus stimulation (fig. 5). It is, however, possible that this late rise in left auricular pressure (i.e., apart from the main rise which occurred during the vagus stimulation) is due to an inequality of the ventricles, the right ventricle pumping more blood into the pulmonary circulation than the left ventricle can get rid of. The possibility of such an inequality on the part of the ventricle has been referred to by Sharpey-Schafer and Lim (5). It does not, however, appear to apply in this instance, as the absence of any excessive rise in the pulmonary pressure does not indicate any accumulation in the pulmonary
circulation, nor does the height of the arterial pressure suggest any impairment of the left ventricle.

**Summary.**

The effect of mitral incompetence on aortic, left auricular, pulmonary, and venous pressures is investigated simultaneously.

The aortic is seen to be unaffected, and reasons are given why this is so.

Left auricular pressure is found to be enormously increased, especially under conditions of stress.

The pulmonary and venous pressures are seen to be dependent on the state of the right ventricle, which may show impairment.

It is indicated that stimulation of the vagus may be used as a test for the existence of mitral incompetence when the height of the left auricular pressure gives reason for doubt.

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**References.**

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Examples:—

(33) CARNOT and CHASSEVANT, Compt. rend. soc. biol., 1905, lix. 106.
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ON THE NERVOUS CONTROL OF RESPIRATION. By R. J. S. M'Dowall. From the Department of Physiology, King's College, University of London. (With five figures in the text.)
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ON THE NERVOUS CONTROL OF RESPIRATION. By R. J. S. M'Dowall. From the Department of Physiology, King's College, University of London. (With five figures in the text.)

(Received for publication 29th June 1926.)

That respiration may become slower and deeper when the vagi are cut, even in a tracheotomised animal, is one of the best-known facts of physiology. Yet it is quite a common experience to find that this does not always occur, and of recent years the point has been emphasised, particularly by Sharpey-Schafer. No explanation, however, appears to have been put forward; but since it is evident that in order to permit deep breathing under certain normal circumstances, there must be some reduction in the action of the vagi, this investigation has been carried out to determine to what extent the conditions of the experiment may vary the effect of the vagal section.

Method.—In order to determine possible fluctuations, the nerves were blocked from time to time with a constant current of three volts obtained from two nickel-iron accumulators. Ordinary metal electrodes were used; and while it is realised that the use of such electrodes might be open to theoretical objection, the results obtained were of such a uniform character that their use was continued. On checking, it was found that the results given by such a block were the same as those of section, and it was found that the vagi might be applied to the electrodes, provided there was no excessive drying, for three hours without impairment of functional continuity. It appears that any effect of polarisation was negligible, and further, as will be seen below, the actual results are a sufficient check of the efficiency of the method. Cats were used, as in these animals divergent results are commonly obtained. They were anaesthetised with ether or chloroform in the first instance, and subsequently with chloralose. As the anaesthetic was found to influence the results, experiments were also carried out when the animal was decerebrated by a method described recently by the writer. Respiration was recorded by means of tambours.

The Relationship of the Response to Anaesthesia and Decerebration.—Immediately after anaesthetisation with ether, or decerebration, the effect of the vagus block is extremely variable; often it has no effect whatever. Sometimes there is a deepening of respiration without a diminution in rate, so that the block is succeeded by a period
of relative apnoea. In two instances, when the volatile anaesthesia was prolonged, the block actually quickened respiration. The cause of these anomalies is far from clear. If, however, the animal is left undisturbed for an hour or so after decerebration or the administration of chloralose, a marked slowing and deepening of respiration on blocking the vagi is the rule.

The Effect of Asphyxia.—Since respiration becomes deeper in exercise, and presumably the effect of the vagus in such circumstances is reduced, investigation was carried out to ascertain the effect of carbon dioxide with slight oxygen deficiency, such as can be brought about by causing the animal to rebreathe its own expired air from a very thin flexible balloon attached to the trachea. In this way no appreciable resistance is introduced, which we know, especially from the work of SHARPE-SCHAFER, would tend to slow respiration. It may be considered that asphyxia so gently induced is probably the closest simulation of the effect of exercise in an anaesthetised animal. It is seen that during the period when the respiratory rate and depth were increased, vagus block
had little effect (fig. 1). Since during the block the inherent rate of the respiratory centre was being recorded, it is obvious that such results are inconsistent with the view of F. H. Scott that the rate of respiration is not increased by asphyxia if the vagi are cut. The effect of re-breathing with the vagi cut is seen in fig. 2, which shows that the rate of respiration is increased. This is confirmatory of the work of Lumsden at the Lister Institute, who showed that this increase could be brought about by the inhalation of carbon dioxide in the presence of ample oxygen. Lumsden suggests that Scott's experiments were not sufficiently prolonged to show increase; but the present experiments show that the power of the respiratory centre to increase the rate is readily lost. This may be brought about by a repetition of the inhalation or by the previous conditions of the experiment, especially conditions which affect the sympathetic-parasympathetic balance of the animal. The fact that with the vagi intact the animal responds much more readily to increased carbon dioxide is not contradicted.

Under conditions in which the vagus block brings about a marked slowing of respiration, asphyxia frequently brings about some recovery.

The Effect of Adrenaline.—Provided the dose of adrenaline does not exceed a certain amount, it is found that the repeated injection of this drug intravenously results in a reduction of the effect of the block, and eventually in the complete disappearance of the effect, although there is not necessarily any marked change in the rate of respiration prior to the block. The result of the adrenaline injections is sometimes very striking, as in figs. 1 and 3, where it is seen that the block before the adrenaline caused a very marked slowing of respiration, while after it the effect of the block was negligible. So striking, indeed, may be the result that, but for the fact that the reduction of the effect can be

![Fig. 2.—Record of respiration and time as before. Between the arrows the animal re-breathed its own expired air from a thin balloon which offered no practical resistance to respiration. Note not only the increased depth but also the increased rate of respiration.](image-url)
Fig. 3.—Record of respiration and time as before. From V to V' a block was applied simultaneously in each instance to both vagi, the interval between each period of blocking being approximately fifteen minutes. Note the increasing effect of the block in 1–5. In the interval between 5 and 6 two injections, each of $\frac{1}{2}$ mg. adrenaline, were given. Note the marked reduction in the effects of the block although there was no appreciable change in the respiration prior to the application of the constant current. The pupil (prior to the block) at the beginning of the experiment was dilated, and gradually became markedly constricted. After the adrenaline the pupil again became partly dilated, apart from the extreme dilatation immediately after the adrenaline injection.
checked by actual section of the nerves, the efficiency of the block might be doubted.

Large doses of adrenaline appear to have the opposite effect, apparently for two reasons: (1) the high cerebral pressure brought about, which causes a central stimulation of the vagus; and later, (2) on account of what appears to be sympathetic exhaustion. It is known that a profound fall of blood-pressure is liable to succeed the rise brought about by a large dose of adrenaline, and a similar change due to exhaustion is caused by a large dose on the perfused mammalian heart.

**Lactic Acid.**—The injection, intravenously and repeatedly, of 1 c.c. of a 10 per cent. solution of this acid, brings about a similar reduction in the effect of the vagus block.

**Sensory Stimulation.**—The association between sensory stimulation and sympathetic activity has already been pointed out in a previous paper (M'Dowall), and may be of significance in relation to respiration. It is seen that such stimulation brings about a reduction in the effect of the block, but if the hyperpnoea is prolonged, the effect of the sensory stimulation is the opposite, presumably from washing out the carbon dioxide.

**Atropine and Pilocarpine.**—Although it was hardly anticipated that atropine would have any effect, it is found that an injection of 2 to 4 milligrammes brings about a very temporary reduction in the effect of the vagus block; and when the vagus has been cut previously and the respiration has recovered almost entirely, the injection of pilocarpine brings about the typical vagus slowing. An animal whose vagi have been cut is apparently much more sensitive to pilocarpine than a normal animal; this may in part be due to circulatory effects.

**Sodium Bicarbonate.**—Here a double action has to be considered. It was shown by Collip that sodium bicarbonate stimulates respiration, and that this effect may be looked upon as being due to the bicarbonate ion. The fact, however, that the immediate result of the injection of an 11 per cent. solution brings about a stimulation of respiration and of the vaso-motor system, resulting in a rise of blood-pressure which is evanescent and is succeeded by a period of slowed respiration, suggests that it is the temporary concentration or the breaking up of the bicarbonate and the increased pressure in the blood of carbon dioxide thus produced which is responsible for the stimulation. The effect of the bicarbonate on the vagus block is clear. In the stimulating stage there is a reduction or a disappearance of the effect of the block, but when this stage has worn off there is a marked increase in the effect; indeed, there is frequently complete cessation of respiration for over a minute (figs. 1 and 3), some recovery occurring when the animal became partly asphyxiated. A certain amount of variation was evident, however, in different animals. For example, if the animal had been previously injected with adrenaline, it appeared to be specially resistant to the
effect of alkali. It is suggested that this action of alkali is responsible for the fact noted by earlier observers, that the effect of section of the vagi in rabbits (Luciani), which are herbivorous animals, is much more marked than in cats.

Ergotamine.—The actual preparation used was a 1 per cent. solution of ergotamine methyl-sulphonate in doses of 0.5 c.c. to 1 c.c.; this is found to have a paralysing action on the sympathetic, as indicated by constriction of the pupil, slowing of the heart, and reversal of the pressor action of adrenaline which it brings about. It is found that while normal animals appear to stand a dose of several cubic centimetres of this solution, on the injection of 0.5 c.c. in an animal in which the vagi are cut, the result is death from failure of respiration. Sometimes vagus section after the injection brings about excessive breathing of vagal type, which ends in death, but in others there is merely a gradual failure of respiration. It would seem that after ergotamine the general control of respiration is considerably upset.

The most striking effects are brought about by an injection of ergotamine after bicarbonate. Here the continuance of respiration appears to depend entirely on the impulses passing up the vagi, since complete cessation of respiration is brought about when the vagi nerves are cut or blocked (fig. 4). Artificial rhythmic inflation of the lungs may cause resumption of apparently normal respiration, which again ceases if the vagi are cut or blocked. This effect of ergotamine and bicarbonate together is very constant, and quite independent of changes in the vascular system. It would seem that the ergotamine prevents the stimulating action of the CO₂ during cessation of respiration.

Acapnia.—The effect of washing out CO₂ is frequently seen to follow the hyperpnoea of asphyxia, after which the effect of the block is much more marked than before. Of special interest, however, is the acapnia which is common in decerebrate animals, as to which there has been considerable controversy. The fact that such animals may cease to breathe altogether after vagus section has frequently been observed by the writer and others. In 1888 Markwalder, and subsequently Loewi, suggested that this is due to the loss of sensory impulses from...
the other cranial nerves, although no evidence was forthcoming. It appears, however, that the condition is brought about by the hyperpnea caused by the stimulation which results from the decerebration and the washing out of carbon dioxide (fig. 5), since it is found that such acapnia and the fall of blood-pressure associated with it can be prevented by simply attaching a long tube to the trachea. The vagi may then be cut with impunity. The writer frequently makes use of this expedient in practical classes in which decerebrate preparations are used.

![Graph](image_url)

**Fig. 5.**—Record of respiration and blood-pressure. Time as before. From V to V a block was applied to both vagi, from S to S the animal was stimulated by hard rhythmical compression of a paw. At 1 a marked effect of vagus block is seen; at 2 (during the sensory stimulation) the effect of the block was appreciably less marked and, as will be seen, the return to a normal rate of respiration began before the block was removed. Note also the effect of the sensory stimulation on respiration and the bringing about of a fall of blood-pressure due to acapnia, which, however, is temporarily recovered from during the periods of block when respiration was inadequate. Subsequent block during the acapnia shows the typically increased effect. The increased inspiratory tone in 2 appears to be characteristic of vagus block or section during sensory stimulation.

**DISCUSSION.**

It is evident from the results that the effect of blocking the vagi with a galvanic current is by no means constant, even in the same animal, and may be affected by various conditions. Under conditions when the block has little or no effect, section also has no effect; while when the block causes a marked slowing or cessation of respiration, section has a similar effect. It will be evident, then, that the effect of the section will depend on the condition of the respiratory centre obtaining at the time of the section; this appears to be the explanation of the many diverse results which are commonly observed. Thus in the experiments of Sharpey-Schafer the absence of the slowing of respiration which he observed may have been due to stimulation of afferent nerves. This might have been caused by the operation, or the anaesthetic, or by interference produced by previous section of one vagus.
On the other hand, the explanation of the results obtained by MARKWALDER and LOEWI, as indicated above, may well be that acapnia was probably present in their animals. The frequent absence of marked slowing of respiration on section of the vagi in tracheotomised cats under ether is explicable as being due to the stimulating effect of ether on mucous membranes, since in animals which have been deeply anaesthetised with chloralose or decerebrated for an hour or so, and have been allowed to lie undisturbed during that period, a slowing of respiration is always obtained on section of the vagi.

It remains to discuss the nature of the change in the respiratory centre. At first sight it would appear that any procedure which stimulates the respiratory centre causes the effect of vagus section to disappear, and that any procedure which depresses respiration tends to exaggerate the effect of the section. While it is true that in a fresh animal various procedures may influence respiration as stated, it is evident, as indeed some of the tracings in the present paper show, that the actual state of the respiratory centre, as indicated by the rate of respiration, is no guide to the effect which may be anticipated. This point has also been noted by SHARPEY-SCHAFER. For example, the respiration in an acapnic animal in which the effect of the block or section is marked, is not excessively slow prior to the section. Nor is the respiration necessarily increased in rate fifteen minutes after the intravenous injection of adrenaline. Now the rate of respiration may be looked upon as being dependent normally (1) on the sensitivity of the centre to the chemical state of the blood, and (2) on impulses passing up the vagi. What has been really altered in these experiments is the relative amount to which the respiratory centre is stimulated by each of these. The nervous impulses, we have every reason to believe, pass to the vagus centre and thence to the respiratory centre or centres, after the manner suggested by LUMSDEN, thereby restraining the extent of the activity of the respiratory muscles.

The appreciation of the fact that the restraint of respiration through the vagus may be readily altered by a variety of conditions draws attention to the similarity of the restraint of the heart, which is also subject to considerable variation under somewhat similar circumstances. Normally, for example, in exercise and in emotion there is a reduction both in the restraint of respiration and of the heart. Both are also reduced by moderate doses of adrenaline. But our present knowledge of the autonomic nervous system does not appear to permit the suggestion that respiration is under autonomic control.

Variation in the vagus restraint of respiration may readily, however, account for the excessive respiration, under certain conditions, which has hitherto been unexplained.

In diabetes there is reduction in the carbon dioxide of the alveolar air, indicating over-ventilation, a fact which as yet, according to the
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SEASONAL VARIATIONS IN CATS. By E. Armitage, R. J. S. M'Dowall, and S. N. Mathur.

NOTE ON THE PRECEDING PAPER "ON SEASONAL VARIATION IN CATS." By E. Sharpey-Schafer, Edinburgh.
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SEASONAL VARIATIONS IN CATS. By E. Armitage, R. J. S. McDowall, and S. N. Mathur.

(Received for publication 20th December 1931.)

From time to time it has been observed more or less casually that there is some seasonal variation in the response of the circulation of cats to various procedures. The present investigation was carried out with a view to collecting accurate data on the subject, as it appears that it might be a source of discrepancy in results of different investigators.

METHOD.

Two series of cats were compared and contrasted, one series was examined in the winter (November and December) and the other in the early spring (January and February). As far as possible the cats were examined under the same conditions; in every case the cat was anaesthetised with the minimum quantity of ether, followed by chloralose —65 mg. per kilo body-weight being injected intravenously. The cat was allowed to settle for half an hour before the readings were made. The variable factors were the length of time for which the cats had been in the animal house and the external temperature.

The condition, sex, weight, and colour of each cat were noted, and also the size of the pupil and the presence or absence of the eye and whisker reflexes, to give the depth of the anaesthesia. The whisker reflex is convenient, this is the movement of the whiskers, when the inside of the auricle is stimulated by scratching. The blood-pressure, heart-rate, respiratory rate, and oxygen consumption were measured half an hour after chloralose and at intervals of two hours throughout the day, and in each series of readings the response of the circulation to the stimulation of the central end of the sciatic nerve and to asphyxia were recorded. In many cases the effect of stimulation of the central end of the right vagus was also recorded.

The oxygen consumption was measured by making the cat breathe from a Krogh's recording spirometer containing oxygen, and soda lime to remove the expired carbon dioxide. The cat was allowed to breathe the oxygen for two minutes. The results were then converted into the number of cubic centimetres of oxygen used per kilogram body-weight in one hour.
The response to sensory stimulation was found by stimulating the central end of the sciatic nerve with an ordinary faradic current and recording the rise in blood-pressure.

After an interval of fifteen minutes, when the blood-pressure was steady, a piece of gas tubing, 6 mm. bore and 12 ft. long, was attached to the trachea for two minutes, so that the animal re-breathed its own expired air and was asphyxiated without the mechanical disadvantage involved by the use of a balloon. This length of tube was found by experiment to give the best result. The changes in blood-pressure and heart-rate were recorded.

The cat was then rested for about an hour, and after two hours from the beginning of the first series of readings a second series was made. Three or four series were made during the day, and at the end a post-mortem examination was carried out.

Sensory Stimulation and Asphyxia, (a) in Winter; (b) in Spring.
To find the relation between the weight and the surface of the cats, the skins were removed, stretched on squared paper and measured. Allowance was made for the contraction of the skin after its removal, and the area in sq. cm. per kilo was calculated and the average oxygen consumption of spring and winter converted into c.c. per hour per 1000 sq. cm. surface.

**Results.**

From the results (shown in the appended table) it can be seen that taking the averages:

1. The **blood-pressure** rises in the spring and this does not depend on the external temperature. In winter no cat had a blood-pressure of 200 mm. Hg; in the spring several of the cats in good condition had a blood-pressure of 200 mm. Hg or more.
2. The **heart-rate** shows no appreciable change.
3. The **respiratory rate** is somewhat slower in the spring, while the depth of breathing is rather deeper. This suggests that the vagus is less active in spring.
4. The **oxygen consumption** is lower in the spring, whether it is calculated per kilo body-weight or per 1000 sq. cm. skin area.
5. The response to **sensory stimulation** increases in spring. This increase is true for the absolute rise in blood-pressure and the percentage rise on the blood-pressure.
6. The average rise in blood-pressure caused by **asphyxia** also shows an increase in spring.

On mathematical analysis, however, it does not appear that these results are all significant. Calculating the significant differences, using the formula \( \frac{x_1 - x_2}{\sqrt{\sigma_1^2 + \sigma_2^2}} \) where \( x_1 \) and \( x_2 \) are the winter and spring averages and \( \sigma_1 \) and \( \sigma_2 \) are the corresponding standard deviations, the results appear as follows:

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<th>( x_1 - x_2 )</th>
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<td>Blood-pressure in mm. Hg.</td>
<td>Winter</td>
<td>Spring</td>
<td>Winter</td>
<td>Spring</td>
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<tr>
<td>148 ± 6.3</td>
<td>178 ± 7.2</td>
<td>3.1</td>
<td>157 ± 9</td>
<td>208 ± 10.1</td>
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<td>Heart-rate per min.</td>
<td>174 ± 6.5</td>
<td>170 ± 7.9</td>
<td>175 ± 10.3</td>
<td>178 ± 13.7</td>
</tr>
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<td>15 ± 0.9</td>
<td>13 ± 1.8</td>
<td>1.4</td>
<td>16 ± 1.3</td>
<td>14 ± 1.8</td>
</tr>
<tr>
<td>Respirations per min.</td>
<td>627 ± 42</td>
<td>492 ± 29</td>
<td>690 ± 65</td>
<td>574 ± 36</td>
</tr>
<tr>
<td>Oxygen consumption c.c./hr.</td>
<td>34 ± 8.1</td>
<td>41 ± 4.8</td>
<td>39 ± 11</td>
<td>46 ± 10.6</td>
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<td>Blood-pressure rise with sensory stimulation</td>
<td>33 ± 4.7</td>
<td>36 ± 5.1</td>
<td>29 ± 4.8</td>
<td>39 ± 10.9</td>
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The significant difference is 3 or more, so that the only results which are significant are those for the blood-pressure. The oxygen consumption result for all the cats and the asphyxia number for the ten best cats are given in the table and are fairly near to the significant figure. Special investigations were made on the results of the ten best cats in each series, as a check on the results for all cats.

It has already been pointed out by M'Dowall (1) that in spring it is difficult to obtain any marked reflex slowing of the heart by stimulating the central end of the vagus. A result such as that shown in fig. 2 of his paper cannot be obtained in February. This has been pointed out also by Ettinger (2) in the frog and by Swale Vincent (3) in relation to the action of pilocarpine. Similar observations have been recorded by Cori (4), who found difficulty in obtaining cardiac slowing on stimulation of the vagus in summer frogs. This he attributed to increased sympathetic activity associated with the onset of the mating season. In addition, it has been noted by us that the pupil was more constricted in the winter.

**DISCUSSION.**

Although only the resting blood-pressure alters to a significant extent in spring, when we come to discuss why the blood-pressure of cats is higher in spring it would seem justifiable to consider the less significant results; the more so as all the evidence points in one direction and to the fact that the nervous system is more sensitive during spring. The developmental association of the posterior roots with the sympathetic and the larger pupil suggests further that the sympathetic rather than the parasympathetic is concerned. That the parasympathetic is in reduced activity is suggested by the deeper respiration, the constricted pupil, and the difficulty in obtaining reflex slowing of the heart in stimulation of the central end of the vagus in spring-time.

It is interesting to remark that this seasonal increased sympathetic sensitivity has been recently noted by Ettinger in relation to the action of adrenaline on the bronchi, while it has been noted by Gillespie and Thornton (in experiments not yet published) that to obtain contraction of isolated bronchi of guinea-pigs, double the calcium is necessary in winter compared with summer. Hogben (4) has also observed that there are seasonal variations in the amount of calcium in the blood of the South African toad.

**SUMMARY.**

It is shown that the blood-pressure in cats is higher in spring than in winter to an extent which is mathematically significant.

Evidence is given which suggests that this increased pressure is due to an increased activity of the sympathetic part of the autonomic nervous system.
REFERENCES.

(3) Vincent, S., Private communication.
(4) Cori, K., Arch. exper. path. Pharm., 1921, xci. 130.

NOTE ON THE PRECEDING PAPER "ON SEASONAL VARIATION IN CATS." By E. Sharpey-Schafer, Edinburgh.

When I came to Edinburgh from London, in 1899, and proceeded to demonstrate to my class the fundamental experiments in Physiology, I was surprised to find that certain results upon cats which I obtained with regularity in London were difficult to obtain in Edinburgh. In particular I often failed to get cardiac inhibition on vagal stimulation which I had always previously been able easily to show. I was at first inclined to put this down to the difference in climate, but as there is little to choose in this respect between London and Edinburgh I concluded there must be some other cause. I remember that I had been in the habit in London of demonstrating this particular experiment during the autumn term, whereas in Edinburgh it was customary to show it in the spring term. I am therefore inclined to regard the difference as seasonal. The observations on cats recorded in the preceding paper, as well as those of Ettinger on the guinea-pig, lately published in this Journal (vol. xxi. p. 77), render this the probable explanation of my own results.
BIBLIOGRAPHICAL REFERENCES.

Contributors are requested to place their bibliographical references at the end of their articles, drawing attention to each by a bracketed number in the text, and avoiding footnotes as much as possible. Each reference should appear as follows:

1. Number.
2. Name of author.
3. Title of book (or article if wanted).
4. Title of journal (abbreviated).
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6. Number of volume (in small Roman numerals).
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A CHEMICAL CONTROL OF THE HEART-RATE. By R. J. S. M`DOWALL. From the Department of Physiology, King's College, University of London. (With seven figures in the text.)

While a great deal of attention has been paid to the chemical control of respiration, comparatively little work has been done on the corresponding control of the heart. Moreover, what results are available in the literature are confusing, in that they suggest for the most part that the easily produced oxygen want and the accumulation of carbon dioxide have opposite effects on the heart and on respiration, in that while stimulating the latter, they depress the former, facts which are at complete variance with the obvious physiological interrelation of the two systems. Many of the observations have been made on the isolated heart or the heart-lung preparation, results from which are not always applicable to the intact animal. The present experiments indicate that in the intact animal the respiratory and cardiac mechanism respond essentially in the same sense to similar agencies, and that the difference in response is merely one of quantity, not of quality.

The experiments were carried out in cats anaesthetised with chloralose, administered intravenously during a preliminary ether anaesthesia in doses of approximately 65 mg. per kilo. This amount is best given in at least two doses, for it is found that different animals require different quantities of anaesthetic, irrespective of their weight, to produce the same amount of anaesthesia. Thin animals require a relatively small degree of anaesthesia. The depth of the anaesthesia may be conveniently judged by the presence of a constricted pupil, which dilates on sensory stimulation (M`DOWALL, 1925), and by the presence of the eye and ear-whisker reflexes. The experiments were carried out in winter cats, in which the sympathetic is less active than in spring cats (ARMITAGE, M`DOWALL, and MATHUR, 1932). For reasons explained in a previous paper (M`DOWALL, 1931), a slow heart is most commonly found or easily produced in winter cats. The heart-rate was recorded from a specially wide carotid cannula and a mercurial manometer with a period of natural oscillation, which on being checked against a membrane manometer was found to give an accurate record of the heart-rate.

The experiments consisted in the production of general and cerebral asphyxia in different ways, and subsequently the differentiation between the effect of oxygen want and excess of carbon dioxide.
GENERAL ASPHYXIA.

This was brought about by causing the animal to rebreathe its own expired air. This may be conveniently carried out by simply attaching several feet of gas tubing or a small rubber balloon to the trachea. This method avoids any complications due to respiratory effects, which Sharpey-Schafer (1920) has shown to influence the pulmonary circulation so markedly.

In fig. 1 is shown the result of such an experiment. The well-known cardiac slowing in an animal prepared as described is invariably preceded by this cardiac acceleration.

![Fig. 1](image)

Fig. 1.—The animal was asphyxiated between the points A and B.

CEREBRAL ASPHYXIA.

This was produced in a variety of ways.

(a) Cerebral Compression.—It is well known since the work of Leonard Hill (1896) that cerebral compression causes cardiac slowing from stimulation of the vagus. If, however, the animal is allowed to settle down under chloralose anaesthesia after the operative procedures, it may be demonstrated that the cardiac slowing is preceded by cardiac acceleration. This observation was made by Astley Cooper (1896) in dogs, but this stage in compression has been generally overlooked. In these experiments the compression was produced by fixing into the skull in the temporal region a rubber cork through which passed a tube attached to a pressure bottle containing saline.

Fig. 2 shows the effect of raising the intracranial pressure.

(b) Cross Circulation.—In order to carry out this experiment with a minimum of dissection, which is liable to produce cardiac acceleration, a special clamp (M'Dowall, 1930) was designed to occlude the vertebral arteries through the skin. The head was then supplied through the carotid arteries with blood from another animal. The return was made by means of the external jugular veins. The junction was made by
paraffined-glass cannulae, and coagulation of the blood in the cannulae still further prevented by the injection of heparin. Asphyxia of the head of the donor animal at once caused cardiac acceleration in the animal which was being perfused (fig. 3).
(c) Acute Cerebral Anæmia produced by Occlusion of the Cerebral Arteries.—In view of the ease with which the experiment can be carried out, a special study was made of it. The effects of this procedure have usually been looked upon as being solely due to anæmia, but the present results indicate that the local accumulation of carbon dioxide is also a factor concerned. The occlusion was brought about by applying the vertebral clamp and subsequently clamping the remaining carotid artery, the other carotid artery having been previously tied in the operation for the recording of the heart-rate.

As in the case of cerebral compression, the cardiac slowing produced by such a procedure is well known (Stewart, Pike, and Guthrie (1908), and by Anrep and Starling (1905)). The last authors, however, did observe a cardiac acceleration in one experiment, but apparently did not pay much consideration to a result which was unusual in their experiments, which entailed a considerable operative procedure. In the present experiments the early cardiac acceleration is invariable (fig. 4).

The acceleration, on occlusion of the cerebral arteries, was produced after section of the vagi, removal of the suprarenal glands, and denervation of the carotid sinuses, but not after removal of the stellate ganglia by the anterior method, although this involves only a minimum of dissection and movement of the animal.

The part played by carbon dioxide is also indicated by fig. 5, a record of an experiment in which the animal was overventilated prior to the occlusion. The overventilation caused a marked delay in the onset of the acceleration.

The influence of ergotamine in this series of observations was also observed. Fig. 6 records that while this drug in doses of 1 to 3 mg. abolished the cardiac acceleration, a dose of less than .5 mg., however,
Fig. 5.—Complete cerebral occlusion was brought about by clamping the carotid at the arrows. In B the animal was overventilated prior to the complete occlusion.

Fig. 6.—Procedure as in fig. 5. The record shows the effect of acute cerebral anemia before and after the injection of ergotamine (lower tracing) to paralyse the sympathetic. The suprarenals were also removed.
did not do so, although it slowed the heart. It is interesting to note that the preliminary injection of such a dose is a convenient method of obtaining a slow heart in an animal whose heart is found to be naturally fast.

**Oxygen Want.**

This was brought about by causing the animal to breathe through inlet and outlet Müller valves either from a bag of hydrogen or from a bag of air containing small quantities of carbon monoxide. This work confirms that of many observers—e.g. Green, Pyne, and Siddle (1928), Sands and De Graff (1925), and Kisch and Sakai (1923)—but the results have been attributed solely to oxygen want, although some of the workers did note that the acceleration was reduced or caused to disappear by denervation of the heart.

**Carbon Dioxide.**

It was found that animals vary very much in their sensitivity to carbon dioxide. In a number, however, it has been possible to demonstrate a distinct acceleration with a mixture containing 5 per cent. carbon dioxide and 95 per cent. oxygen (fig. 7). In other experiments a mixture containing 10 per cent. carbon dioxide did not produce cardiac acceleration.

**Discussion.**

The above experiments indicate that in a cat suitably prepared it is possible to demonstrate that asphyxia, general or localised to the brain, causes cardiac acceleration. The results show that the effects are produced both by oxygen want and by excess of carbon dioxide.

The exact method by which the acceleration is brought about has
been studied in several ways. The experiment carried out with the
gloi cut and carotid sinuses denervated and suprarenal glands removed,
suggests that there is a central stimulation of the sympathetic, and this
is supported by the failure to obtain acceleration after complete
denervation of the heart and removal of the suprarenal glands. According
to Cannon (1931), however, it would be expected that since the pro-
cedures adopted also stimulate the vasomotor centre and cause the
smooth muscles of the vessels to contract, an effect from the secretion
of "sympathin" might be expected. So far I have not been able to
show such secretion, but it may be that the conditions of my experi-
ments were not suitable.

How far the cardiac acceleration, when the vagi are intact, is due
to a reduction of vagus activity is a difficult point to decide. It is
obvious that a comparison of the acceleration before and after section
of the vagi, which has been the usual method of approaching the problem,
is not satisfactory, since the heart-rate is increased by the section. The
failure of various procedures to produce cardiac acceleration after the
injection of ergotamine, when the vagus restraint of the heart is well seen,
indicates very definitely that the reduction in vagus action is not an essential
factor in the acceleration. Section of the vagi after the injection of ergo-
tamine causes marked acceleration. Further, I have not been able to
demonstrate any cardiac acceleration after the stellate ganglia and supra-
renal glands have been removed, although the vagus mechanism is intact.
The view that asphyxia does not reduce vagus restraint is further
supported by an investigation of the general activity of the cardio-
inhibitory mechanism (M'Dowell, 1931), which showed that after the
acceleration had passed off there might ensue an increased vagus
restraint; this could only be explained as after-discharge of the vagus,
which, although stimulated, could not show its effect during the period
of acceleration of the heart. Since, however, this phenomenon bears
some relation to the changes observed in exercise in which the vagus
restraint is claimed to be reduced, further work is necessary before
elucidation is complete. It has been pointed out by Sherrington
and Liddell (1929) that it is more difficult to slow the heart by
electrical stimulation of the vagus after a large intravenous dose of
adrenaline; it is possible, then, that peripheral sympathetic activity may
interfere with peripheral vagus activity at a time when the vagus is
being stimulated centrally.

The question arises as to how far central chemical excitation may
be a normal method of causing cardiac acceleration during exercise. In
man asphyxia has to be extreme before cardiac acceleration sets
in, but, on the other hand, the compensatory mechanisms of a normal
man are presumably better than those of an anesthetised cat, and
cardiac acceleration may thereby be prevented. The present experi-
ments indicate, as might be expected, that, as in the case of respiration,
there exists a central chemical control which, although less active in the

case of the heart than in the case of respiration, may be called into

operation in an emergency.

**Summary.**

It is shown that cerebral asphyxia, however produced, causes cardiac

acceleration in cats under a certain degree of chloralose anaesthesia. It is

shown that both oxygen want and excess of carbon dioxide are concerned

in the acceleration.

Evidence is put forward to show that the acceleration is due to a

central stimulation of the sympathetic.

**REFERENCES.**


ARMITAGE, M'DOWALL, and MATHUR, Quart. Journ. Exper. Physiol., 1932,

xxi, 365.

ASTLEY COOPER, Guy's Hospital Reports, 1896, i. 457.


GREEN, PYNE, and SIDDELL, ibid., 1925, lxii. 194.

HILL, L., "The Physiology and Pathology of the Cerebral Circulation,


KISCH and SAKAI, Pflügers Arch., 1923, cxviii. 86.


SHERRINGTON and LIDDELL, "Mammalian Physiology," Oxford University

Press, 1929.

STEWART, Pike, and GUTHRIE, Amer. Journ. Physiol., 1908, xxi. 359; ibid.,

xxii. 51.
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THE PHYSIOLOGY OF THE PSYCHO-GALVANIC REFLEX.
By R. J. S. M'Dowall. From the Department of Physiology,
King's College, London.
THE PHYSIOLOGY OF THE PSYCHO-GALVANIC REFLEX.
By R. J. S. M'Dowall. From the Department of Physiology, King's College, London.

The term psycho-galvanic reflex has been given to the fall of the electrical resistance of the skin which occurs during mental effort or emotion. The phenomenon was first described in 1888 by Féré. It is probable that there occur at the same time other electrical changes; for example, changes in potential as pointed out by Prideaux (1920). It is true that the usual method of demonstrating the reflex, namely, that of passing a current of low voltage through the skin of the hand which is placed in one arm of a Wheatstone bridge, does not differentiate between changes of potential and changes of resistance; but experiments carried out with alternating currents and those of Thouless (1925) show clearly that the alteration in electrical resistance of the skin is by far the greatest change concerned. It is important to observe that in researches into the phenomenon, the only electrodes which may be considered satisfactory are those of silver coated with silver chloride in saline solution at constant temperature, a constant amount of skin being exposed in the saline. This is most conveniently secured by dipping the distal part of a finger into the saline, the upper part of the finger being painted with a material impervious to saline, such as rubber solution.

Another psychic effect was that observed by Mosso, with his arm-plethysmograph (in Ludwig's laboratory), the arm-volume being affected by any sudden emotional stimulus such as the unexpected entrance of the Professor. Commencing with Féré and with Vigouroux (1888), a number of workers such as Sticker (1897) and Radecki (1911) came to the conclusion that the psycho-galvanic reflex is essentially due to changes in the peripheral blood-vessels, but these observations were overridden by Veraguth, who apparently excluded this explanation when he demonstrated that the electrical response persists after the circulation to the part has been cut off. He concluded accordingly that the changes are due to activity of the sweat glands. Since it has become realised, largely as a result of the work of Krogh, that the peripheral vessels contract and relax independently of the blood-supply, such negative evidence carries little weight. The sweat-gland theory, which was originally put forward by Tarchanoff, has been supported by Leva (1913), Fauville (1921), Gildemeister...
(1923), and in part by Richter; but, as will be shown below, it also is untenable.

**The Influence of the Circulation on the Electrical Resistance of the Skin.**

In 1924 Aveling and M'Dowall carried out a series of experiments on the electrical resistance of the skin in chloralosed and in decerebrate cats. They observed that all procedures calculated to bring about constriction of vessels in the skin, e.g. haemorrhage, the intravenous injection of adrenaline, or the application of cold, cause a fall of its electrical resistance, while conditions producing vaso-dilatation cause a rise. They found also that a similar fall could be brought about by sensory stimulation in a decerebrate animal, thus indicating the primitive nature of the reflex. It is useless attempting to elicit the reflex until all the effects of anesthetising and shock of operation have worn off. To obtain the best result the cat should have constricted but reactive pupils and the corneal and whisker reflexes should be present.

This work was further extended on man by Wells (1927), who has demonstrated by a series of simple experiments that any alteration of the circulation through the skin of the hand causes a considerable change in electrical resistance. For example, if the peripheral vessels are dilated by preventing the normal venous return, by compression of the arm with a sphygmomanometer cuff at a pressure of 50–60 mm. mercury, there is a marked rise of resistance. Voluntary overventilation, which depletes the blood of carbon dioxide and causes obvious pallor of the skin, brings about a fall of resistance which may amount to 20–30 per cent. of the original resistance. If the hand is held above the head and the artery compressed by a sphygmomanometer cuff in that position, the resistance is found to be reduced; but the flushing of the hand when the cuff is released results in a rise of the resistance above normal. The haemorrhage of the menstrual period also causes a marked fall of resistance of the hand, presumably as a result of the withdrawal of blood from the skin (Wells). It is also found that the colour of the skin can be taken as an indication of its resistance. Most of the results are easy to confirm and can be made the basis of routine experiments for advanced class-work. Time should always be allowed for the subject of the experiment to become accustomed to the various procedures, otherwise the results are interfered with by psychic causes.

**Evidence that the Electrical Changes are Affected by the Circulation.**

It has long been known that in cold weather it may be very difficult to obtain a psycho-galvanic response; indeed it is a routine procedure
amongst experimental psychologists to wash the hands in warm water in such circumstances. This suggests that the cold abolishes the reflex by constricting the vessels.

Many observers, *e.g.* GREGOR and GORN (1913), have recorded the fact that there is great difficulty in eliciting the response in patients suffering from arterial disease such as arterio-sclerosis. Drugs which cause a marked dilatation or paralysis of the skin vessels, such as alcohol and atropine, abolish the reflex in animals. I have found that in cats even the well-marked response with adrenaline could not be obtained under ether anaesthesia. At the time this was unexplained; but the later work of DUNLOP in my laboratory has shown that ether prevents the action of adrenaline in the skin vessels by paralysing them. This, no doubt, accounts for the failure of many earlier observers to obtain a fall of resistance in anaesthetised animals.

In man it has been found by DENSHAM and WELLS (1927) that the reflex is reduced by asphyxia of the limb which dilates the peripheral vessels. The experiments of VERAGUTH have been repeated and it has been found that, if care is taken to maintain the intensity of the stimulus, cutting off the blood-supply to the arm appreciably reduces the response. The importance of the stimuli used has been emphasised by PRIDEAUX and by GOLLA; neglect of this point no doubt accounts for the negative results of VERAGUTH (1909), MÜLLER (1913), and PETERSON and JUNG (1907). Similarly it has been demonstrated that anything, such as heat, cold, or the injection of adrenaline, which tends to fix the cutaneous vessels, reduces the reflex.

**The Relation of the Reflex to the Sweat Glands.**

The sweat-gland theory is the only theory which needs to be seriously considered since it has received most support. There have been several others still less tenable (LANDIS and DEWICK, 1929). The theory was primarily based on the fact that the reflex is most easily obtainable from the soles of the feet and palms of the hands, and a correlation between the number of sweat glands and the activity of the reflex seemed thereby established (LEVA, WECHSLER). The fact was ignored that in these regions the areas, in virtue of the sweat glands, are specially well endowed with blood-vessels and with thick skin which protects the vessels from pressure of the electrodes. SOMMER, however, did record that the tips of the fingers, which have few sweat glands as compared with the palms, might give a larger reaction than the latter. The sweat-gland theory was apparently supported by the fact that the injection of pilocarpine causes a fall of resistance. That pilocarpine is a sympathetic as well as a parasympathetic stimulant does not appear to have been generally appreciated by workers in this field, although the double action is well recognised by pharmacologists. AVELING
and M'Dowall found that during the initial phase of pallor there is a fall of resistance, but a rise later if the electrodes and skin are sufficiently wet. These results confirm those of A. D. Waller (1919), who demonstrated the same fact on man. Waller also showed that atropine in doses sufficient to abolish sweating does not abolish the reflex. Waller's results were supported by Markbreiter (1919), Aveling and M'Dowall (1924) also found that there is no difficulty in obtaining a response to sensory stimulation in cats after the injection of atropine. In further opposition to the sweat-gland theory it may be stated that Golla (1921) records an example of neurotic hyperidrosis in which sweat literally dripped from the patient, who yet gave a normal psycho-galvanic reflex. It is inconceivable that such activity would not interfere with the reflex were it due to increased glandular activity. That the psycho-galvanic response can be obtained in the absence of the sweat glands has been demonstrated most clearly by Gilchrist (1927), who found a marked response in a patient with complete absence of the glands (confirmed histologically). It will not, however, be denied that sweating when it occurs may cause a diminution in the electrical resistance of the skin by simply moistening the epithelial cells, if care has not been taken to have these cells moistened at the beginning of the experiment. Indeed, the difference in the resistance between pad and fluid electrodes may amount to 40,000 ohms. For example, Wells using saline electrodes obtained regular resistances of the order of 10,000 ohms; but Richter (1927) using pad electrodes obtained normal resistances of the order of 50,000 ohms; and, in a patient in which the sympathetic had been paralysed, resistances of 140,000 to 200,000 ohms were observed on the paralysed side. This effect of moisture in reducing the resistance of the skin from 50,000 to 10,000 ohms is easily confirmed. It cannot then be doubted that the fall of resistance obtained by many observers after the injection of pilocarpine is due to sweating. There is, however, no evidence that this bears any relation whatever to the psycho-galvanic response. Richter suggests that the initial rapid fall of resistance is due to sweating, since it is obtained most readily from the palms of the hands. It should, however, be pointed out that the stratum corneum, wherein lies the resistance of the skin, is thickest in the palm and must be all the more affected by changes of moisture. The actual record published by Richter, of the patient deficient of sweat glands, does show slight indication of the two phases commonly seen in the reflex.

No explanation has hitherto been given of the interruption in the fall of resistance during the early part of the reflex; but it may be suggested that it is due to a sudden filling of the skin with blood—possibly as a result of constriction of the spleen and splanchnic areas; for it has recently been recorded by Barcroft (1930) that the exteriorised spleen of a dog may be observed to constrict under the influence
of psychic stimuli. This view is supported by a record in the paper by Richter (1927) in relation to sweating, in which he shows the galvanic response in a patient after the injection of pilocarpine. Here the resistance is presumably low at the commencement; but at the psychic response a further fall is preceded by a rise in resistance which is unusually large.

It may then be concluded that there is no good evidence that the sweat glands are concerned in the reflex. As we shall see, the magnitude of the reflex is such that it could only be produced by changes in a tissue with a very high resistance, namely, the stratum corneum; indeed there is no reason to believe that the stimuli which cause the reflex necessarily cause sweating. In support of this it may be mentioned that increased activity of the sweat glands greatly reduces the psychic response: the converse would be expected if the sweat theory were true.

**The Immediate Cause of the Fall of the Electrical Resistance.**

The site of the resistance of the skin has been investigated by Peterson and Scripture (1909), but in more detail by Lewis and Zotterman (1927), who found that it was almost entirely confined to the superficial layers of the stratum corneum. They found that when a needle is placed on the skin there is a fall of 80 per cent. in the initial resistance as soon as the superficial layer is pierced. Densham (1927) removed the superficial layers of the skin of his fingers by means of a cantharides blister, then placed them in salt solution electrodes, and confirmed the fact that the resistance of the remaining layers is negligible and the reflex absent.

Of some interest is the extent of the changes produced after removal of the various layers of the skin. In an experiment in which the metrical control resistance of the normal skin was 10,000 ohms, removal of the epidermal layers resulted in a fall to 2000 ohms. Removal of the corium reduced the resistance in saline to 50 ohms. This confirms the results of Lewis and Zotterman that 80 per cent. of the skin resistance is in the non-vascular epidermis and 20 per cent. in the corium. Since it is possible to obtain a reduction of 65 per cent. of the resistance of the whole skin, it is evident that this can only be achieved by changes in the epidermal layers, as Densham has suggested. He carried out a number of control experiments on the effects of changing (a) the rate of blood-flow through the skin, (b) the blood-pressure, (c) the temperature, and (d) the corpuscle-content of the skin.

Densham (1927) further investigated the result of altering the resistance of the skin mechanically on normal skin and also using a piece of skin from a human cadaver. He found that the resistance is reduced by any procedure which tends to deform the superficial cells in any
direction, thus allowing presumably an increased conductivity between the cells. Such a deformation may occur when the limb alters its shape as a result of changes in the blood-vessels underneath.

These facts explain why it is easier to obtain the response in man from the palms of the hands or the soles of the feet, since there the stratum corneum is very thick and the skin very vascular. In other places the pressure of the electrodes deforms the skin and prevents the reflex, as also happens in the palms if the electrodes are too firmly applied. But by the use of liquid electrodes the reflex can be elicited from any part of the skin both in man and in animals.

It is possible that the effect in the epidermis is enhanced by the withdrawal of blood from the deeper layers of the skin; for the resistance of whole blood is higher than that of the tissue fluids generally. This no doubt accounts for the observation made by AVELING and M'DOWALL that a fall occurs in the (small) resistance of the tissues below the skin in circumstances calculated to cause vaso-constriction.

**Correlation of the Electrical and Volume Changes.**

It is evident from the work of Mosso that the stimuli and changes which bring about the volume alterations of a limb are those which cause a variation in the electrical phenomena. Indeed FÉRE, who first described the reflex, pointed out that electrical and plethysmographic changes are coincident. GOLLA (1921) has repeated these experiments and has shown that the two phenomena agree exactly in time of onset. These results have been confirmed by UHLENBRUCK (1924) and by HEMINGWAY and M'DOWALL (1926).

It has also been recorded by KROGH that the slightest unusual sound causes the vessels of the ear of an unanesthetised rabbit to constrict; CARRIER noticed the same during a thunderstorm. HEMINGWAY, using Lombard's method, found that in man there is commonly a closure of capillaries in the circumstances which produce the reflex.

**The Nerve-paths Concerned in the Reflex.**

The suggestion that the galvanic response is related to the sympathetic was made by SCHILF and SCHUBERTH (1922), who found that a fall of electrical resistance was obtained if the sympathetic chain were stimulated, and that the response disappears on cutting the sympathetic. This result is supported by the observation of AVELING and M'DOWALL (1924) that injecting adrenaline, the sympathetic stimulant, brings about a similar result. RICHTER has further found that the response may be absent in one limb if the patient suffers from an ipsilateral sympathetic lesion. Now that sympathectomy is a common operation, further evidence of the same nature will doubtless soon be
available. Foâ and PESERICO (1923) determined, in the anaesthetised cat, that the pathway for the hind paws was by the autonomic fibres in the sciatic nerve. They considered that the effect brought about by stimulation of a sensory nerve depends on a reflex arc through the medulla oblongata.

It has also been shown by WANG and RICHTER (1928) that stimulation of the tuber cinereum causes a fall of resistance of the pad of a cat's foot, but that section of the sympathetic prevents this occurrence. MINOR (1923) found in nine patients that unilateral sympathetic paralysis, as indicated by constricted pupil, was accompanied by increased skin resistance; while two patients with sympathetic irritation had a diminished resistance.

The sympathetic is depressed by an anaesthetic, the skin resistance rises (RICHTER), as occurs also in sleep. This I have confirmed. Mosso noted that in sleep there is a dilatation of limb vessels; more recently HESS (1932) has developed a theory of sleep as a state dependent on sympathetic depression.

Any procedure which causes sympathetic stimulation, provided the anaesthesia is not too deep, causes the skin resistance to fall. This fall in a properly anaesthetised animal (preferably with chloralose or dial) is not confined to any particular area of the skin.

**The Biological Significance of the Response.**

Certain psychic stimuli bring about simultaneously a diminution (a) in the volume of a limb, and (b) in the electrical resistance of the skin; both appear to be due to vaso-constriction. The vaso-constriction depends on sympathetic stimulation and (if the stimulus given is sufficient) makes itself evident also in rise of blood-pressure (L. Hill, 1898). The psycho-reflex is commonly assumed to be due to an effect produced in the higher nerve-centres; but it seems more probable that both it and the accompanying phenomena actually represent protective reflexes due primarily to primitive sensory stimulation (pain). In confirmation of this I have made the following observation with HEMINGWAY. While carrying out experiments on the volume of the limb and the electrical changes in the skin, HEMINGWAY became remarkably unresponsive to ordinary non-painful stimuli. Eventually I pinched his ear severely with a pair of Spencer Wells forceps. Thereafter he became extremely responsive to the sound of instruments moving in the instrument tray. This sound had now by a process of conditioning acquired a significance which demanded defence or stress.

How far all stimuli which bring about the response may be considered from the biological point of view as placing the body in a position of alertness or state of emergency for defence or attack, opens up a psychological problem which is beyond the scope of our present
review, and is adequately dealt with by psychological writers, e.g. Aveling. But, from our knowledge of the apparently trivial stimuli which bring about the reaction, it is evident that the nature of the correlation between such physiological and psychological phenomena may do much to give us a more adequate understanding of the reactions of the body to external influences.

**Summary.**

The various factors concerned in the fall of electrical resistance of the skin, which occurs as a result of psychic and other stimuli, are reviewed.

It is shown that any procedure calculated to cause vaso-constriction causes the fall both in man and animals. Evidence is adduced that the psychic response is influenced by the circulation in the part of the skin led off.

The amount of the fall in resistance is discussed in relation to its possible situation. It is shown to be the stratum corneum which becomes altered in resistance.

Evidence is adduced that under circumstances in which the psychogalvanic response is observed, vaso-constriction also always occurs. The view that the reflex is produced as a result of activity of the sweat glands is discussed and shown not to be in agreement with the facts.

The nervous mechanism and biological significance of the skin constrictor reflex is also discussed.

**References.**

Aveling and M'Dowall, Journ. Physiol., 1924, lx. 316.
Barcroft, Journ. Physiol., 1930, lxviii. 375.
Carrére, quoted by Krogh.
Dunlop, Journ. Physiol., 1929, lxvii. 349.
Fauville, Arch. internat. de physiol., 1921, xvi. 58.
Foà and Pesarico, Arch. di fisiol., 1923, xxi. 119.
Gilchrist, 1927, quoted by Richter.
Gildemeister, Pflügers Arch. f. d. g. Physiol., 1923, cc. 278.
Golla, Croonian Lecture, Lancet, 1921, ii. 215 and 265.
Hemingway, 1926, hitherto unpublished.
Hemingway and M'Dowall, 1926, hitherto unpublished.
The Physiology of the Psycho-galvanic Reflex


Landis and Dewick, Psych. Bull., 1929, xxvi. 64.


Mosso, “Fear,” 1896 (Longmans Green & Co.).

Müller, Monat. f. Psychiat., 1913, xxxiii. 235.

Peterson and Jung, Brain, 1907, xxx. 153.

Peterson and Scripture, Journ. of Nerv. and Ment. Dis., 1909, xxxvi. 426.


Prideaux, Brain, 1920, xliii. 50.

Radecki, Arch. de psych., 1911, xi. 209.

Richter, Brain, 1927, i. 216.


Schiff and Schüchter, Pflügers Arch. f. d. g. Physiol., 1922, excv. 75.

Sommer, Beiträge zur Psychiat. (Wien), 1902–3, i. 143.

Sticker, Wiener klin. Rundschau, 1897, xi. 497.


Vigouroux, Progrés médical, 1888, viii. 45.


Wang and Richter, Chinese Journ. Physiol., 1928, i. 279.


Wechsler, Compt. rend soc. biol., 1921, lxxxv. 1015.
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THE WATER SUPPLY OF THE EGYPTIAN EXPEDITIONARY FORCE, WITH SPECIAL REFERENCE TO THE EFFICIENCY OF MECHANICAL RAPID FILTRATION WITH CHLORINATION.

BY R. J. S. McDOWALL, M.B.

(From the Physiology Department, University of Edinburgh: late S.S.O. in charge of Water Supplies, Palestine L. of C.; and late D.A.D.M.S., E.E.F.)

The provision of an epidemiologically safe water supply to the Egyptian Expeditionary Force, as it fought its way across the Sinai Desert to deliver Palestine from the hand of the Turk, will long be remembered as one of the most remarkable achievements of the war.

The route was already historic, as along it the ancient kings of Egypt and Assyria had led their hosts against each other. Napoleon followed the same route in 1798, and Sir William Willcocks is of opinion that the Israelites also used it. The 17th chapter of Exodus gives us an insight into their difficulties regarding water supply.

For a modern army, however, the problem was more difficult, for even the army of Napoleon was in numbers less than one-tenth that of the Egyptian Expeditionary Force. Along the first part of the route is a chain of wells capable of supplying small numbers of troops, and this sufficed for the needs of the Australian and New Zealand cavalry which formed the advance guard, but it was quite inadequate for the main army. The eastern part of the Sinai Desert is practically waterless, and it was on the other side of this waterless area between Gaza and Beersheba that the Turks had entrenched themselves and actually managed to hold up our advance for over a year. It was therefore necessary to provide the army with water from a source outside Sinai, and the only one was the Fresh Water Canal which takes the water of the Nile to Port Said and the other stations on the Suez Canal.

When it is considered that this canal leaves the Nile near Cairo and flows through some 70 miles of the Delta, where it is exposed to every conceivable pollution, and that in addition to being a veritable cesspool it is also bilharzia-infected, it will be seen that the problem of purifying the water for consumption by troops was no easy one.

The primary question to be solved was whether the slow sand filter or the mechanical rapid filter should be used.

It is interesting to note that at home the Metropolitan Water Board, forced by the exigencies of war which demanded economy of coal and labour, had set
themselves a similar problem. In the thirteenth Research Report, Sir Alexander Houston sums up the question at issue thus:

"Is it permissible to filter stored water so rapidly as to create a material economic gain in the saving of filtration area, yet by the aid of anti-filtration or post-filtration sterilisation processes to produce a water which is epidemiologically safe, innocuous, tasteless and reasonably satisfactory from a physical and sentimental standpoint?"

Rapid filters have been extensively adopted in America. On the other hand British opinion, influenced by the possibly not altogether disinterested advice of engineers and supported by the results of certain chemical analyses, largely adheres to the slow filtration method which "has stood on the whole favourably the test of time."

In Egypt, however, there was no doubt as to the gross contamination of the supply, and it was realised that it was of negligible importance what the results were as regards albuminoid nitrogen, ammonia or oxygen absorbed, so long as a water could be provided which was bacteriologically safe. Moreover at Kantara, which was the base of the advancing force, space had to be economised, as had money and labour, while the occurrence of sand-storms might, it was thought, seriously interfere with the working of slow sand filters. It was therefore decided to adopt the method of sedimentation, rapid filtration and chlorination.

Six similar plants were installed at different military posts of the Suez Canal Defence, and it is interesting to note that when the Turk was driven from the immediate vicinity of the Suez Canal, one of these plants was transferred from a smaller post to Kantara where it was subsequently connected with the historic pipe-line across the Desert. Such an economy would not have been possible had the slow filtration process been adopted.

The type of plant used was a modified "Jewel." In the first instance, the water passed through a strainer of brass wire gauze with a mesh of a sixteenth of an inch to exclude the snails which are the intermediate hosts of worms causing bilharziasis. Thence it was led to a settling tank on the maze principle, on entering which a solution of aluminoferric was added. The water took some ten hours to flow through the tank, and by this treatment alone the transparency was increased four or five times and 40 per cent. to 60 per cent. of the organisms removed. It then passed to the filters.

Each filter consisted of an inner steel cylinder, containing 40 inches of coarse sand supported on gravel, and an outer cylinder which was three feet higher. The water rose between the cylinders at a speed which allowed of a maintenance of a head of 2½ feet above the sand level and after passing through the filter-bed of the internal cylinder, reached the exit pipe through perpendicular strainers of perforated brass. The filters were periodically cleaned by reversing the direction of the flow and raking the surface of the sand. After washing, it was necessary to run to waste for twenty minutes to allow the sand surface to settle. The running to waste occurred automatically, indeed all the
valves were so arranged that the process was quite fool-proof. On leaving the filters, the water was quite clear, and 95 per cent. of the total organisms found to have been removed.

The water was then conducted to storage tanks, at the entrance to which it was chlorinated to the extent of usually 0·75 to 1 part chlorine per million of water. The actual method of chlorination differed at some of the tanks, but, so long as efficient mixing was accomplished, it did not appear to matter which was used. The amount of bleaching powder to be added was gauged by a modified form of the ordinary Horrocks test, a modification of which was also used for the testing of the bleaching powder itself.

From the bacteriological point of view, the process since its installation has given the utmost satisfaction. Samples have been taken weekly and an average series of results is given below.

**Summary table of bacteriological results based on 34 years' experience and the examination of multiple samples.**

<table>
<thead>
<tr>
<th>Source of sample</th>
<th>Colony count per c.c.</th>
<th>Glucose fermentation</th>
<th>Lactose fermentation</th>
<th>&quot;Flavimonas&quot; R. coli</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fresh Water Canal</td>
<td>1200</td>
<td>in 0·05 c.c.</td>
<td>in 0·05 c.c.</td>
<td>in 0·1 c.c.</td>
</tr>
<tr>
<td>After sedimentation</td>
<td>800</td>
<td>not in 0·05 c.c.</td>
<td>not in 0·05 c.c.</td>
<td>often in 0·05 c.c.</td>
</tr>
<tr>
<td>After filtration</td>
<td>50</td>
<td>not in 0·5 c.c.</td>
<td>not in 0·5 c.c.</td>
<td>not in 0·05 c.c.</td>
</tr>
<tr>
<td>After chlorination</td>
<td>20–30°*</td>
<td>not in 10 c.c.</td>
<td>not in 10 c.c.</td>
<td>not in 10 c.c.</td>
</tr>
</tbody>
</table>

* Developed chiefly, if not entirely, from non-pathogenic spores unaffected by the chlorination.

The freedom from bilharzial infection was presumed, as all water was stored snail free in the plant, reservoirs and pipes 36–48 hours before actual consumption.

It was originally laid down that no water which contained *B. coli* in 1 c.c. should be consumed by troops in the E.E.F. As, however, the examination took several days to carry out, for practical purposes a test with quantities varying from 0·5 c.c. to 10 c.c. of water for the presence or absence of acid and gas after 48 hours incubation in lactose McConkey broth was relied upon. It was of course only necessary to test the water as a routine after filtration and after chlorination. The efficiency of the preliminary sedimentation was estimated by a transparency test in which a piece of bright metal was observed through columns of water of different depths. It will be noted that the bacteriological standard is below the usual civil one, but the freedom of the troops from water-borne disease will be accepted even by slow sand filtration enthusiasts as a most convincing proof of the safety of rapid filtration and chlorination methods of treatment. It should also be remembered that the comparative immunity from disease occurred in a sub-tropical climate amidst conditions—concentration of troops on dust swept areas and initially most impure water—most favourable to heavy incidence of water-borne diseases.

It is not the writer's intention to discuss the advantages and disadvantages of the method from the financial point of view. These are fully set out in the
reports of the Metropolitan Water Board and elsewhere. He wishes, however, to place on record the efficiency of a method over which there is much important controversy, and it has been tested, not by laboratory experience, but on such a vital matter as the water supply of an advancing army.

The supply from the filters at Kantara was originally intended to supply 500,000 gallons a day for a small force of three divisions detailed to recapture the Egyptian frontier towns of El Arish and Rafa, to which the water was pumped in stages through a twelve-inch main laid upon the desert sand. It proved so successful, however, that when the conquest of Palestine was contemplated, the pipe-line continued to follow the advancing troops and was subsequently laid on to the Gaza-Beersheba line, a distance of 147 miles from the filter-plant and 220 from the Nile.

The ancient prophecy, that when the waters of Egypt should flow into Palestine that country should be delivered, thus came to be fulfilled as a result of a world-wide war. At the same time, there was carried out physiological experiment on a vast scale which proved that rapid filtration and chlorination methods of treatment can render an initially highly polluted and dangerous water safe for human consumption, and which has substantiated one of the most modern contentions as to the purification of water supplies.

In conclusion, I have to thank Sir Alexander Houston for the interest he has shown in my work, and for the furnishing of the reports of the Metropolitan Water Board and other references. My thanks are also due to the several bacteriologists of the Kantara Military Laboratory who, during the three-and-a-half years under review, were always willing to render assistance in the examination of special samples; and to my friend, Captain Rupert Briercliffe, O.B.E., R.A.M.C., who was associated with me in the work, for placing at my disposal many records to supplement my own.
THE ACTION OF ALCOHOL ON THE CIRCULATION

BY

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THE ACTION OF ALCOHOL ON THE CIRCULATION

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The administration of alcohol as a "circulatory stimulant" is a procedure which the practical physician has been very loath to abandon, in spite of the obscurity of the exact nature of its action. The pharmacology of the drug has been overshadowed by the fact that it does not necessarily cause a rise in blood pressure, and that the rise in the pulse rate which it produces may be due to other factors: e.g., excitement. According to Clark (1), the taking of neat brandy or whisky owes its beneficial effect purely to the stimulation produced of the sensory nerves. It has, however, been pointed out by Dixon (2), that in order to observe the effects of alcohol on an animal the usual volatile anesthetics should not be used as they mask its action, and he finds that in man there is an increase in the pulse rate apart from excitement. A small degree of increased force, but not rate, of the heart itself may be seen on the isolated organ. He does not consider that the existing evidence altogether justifies its use as a therapeutic agent.

Cushny (3) and Clark (1), on the other hand, remark that the fact that there is a dilation of skin vessels, without necessarily a change in blood pressure, obviously indicates some redistribution of the blood in the body and a partial withdrawal of it from the vital organs. The former also suggests the operation of a reflex from the periphery. The present investigation gives definite proof of this conception and indicates, more exactly the nature of this reflex and redistribution.

The evidence given below was, in the first instance, made in an investigation of the evidence of W. T. Porter of the existence
of separate vaso-motor and vaso-tonic centers. One of the two main points of Porter's hypothesis is that on the injection of alcohol there is no change in arterial pressure, but the normal vaso-motor reactions, e.g., the depressor reflex, become impaired or disappear. This he considered evidence that the vaso-motor center has been thrown out of action, while the center responsible for arterial tone is unimpaired. Such an action on the part of a drug such as alcohol seemed unlikely on general pharmacological grounds, and a more probable explanation of Porter's results appeared to be that the depressor reflex could not act owing to interference by some peripheral action of the alcohol. Evidence that this latter explanation is the correct one is forthcoming.

That considerable quantities of alcohol may be injected into a vein without causing an alteration in arterial pressure is well known, and in the experiments quoted above Porter injected several cubic-centimeters of a 75 per cent solution. Such a solution has, however, to be injected extremely slowly, as high concentrations of alcohol rapidly impair the heart as may be seen from the rise of venous pressure and fall of arterial pressure caused thereby. A solution of 50 per cent alcohol may, however, usually be injected with freedom. Differences in the ease with which the hearts of individual animals can be injured are often seen. If 2 cc. of a 50 per cent solution be injected into a cat of 2 to 3 kilos, a marked fall of venous pressure is found to occur (fig. 1). Venous pressure may readily be measured by a water manometer carrying a bell float after the manner described by McDowall (4). In this way a most profound alteration in venous pressure may be recorded, a fall of 50 mm. of water being sometimes brought about with successive doses. If large amounts of alcohol be injected slowly a condition analogous to histamine shock and associated with a profound fall of arterial and venous pressures results. With the smaller doses the arterial pressure is maintained reflexly.

In a recent publication the present writer (5), has shown that as a result of this fall in venous pressure a vago-pressor reflex is called into activity, by means of which the vaso-motor center is
stimulated in an attempt to maintain arterial pressure. There is also an increased rate of the heart which assists in maintaining arterial pressure. Section of the vagi at this stage causes a fall in arterial pressure instead of a rise which occurs normally when such section is made. This reflex is, no doubt, one of the primitive protective mechanisms of the animal against the effects of blood loss. A similar set of phenomena are seen in hemorrhage and after histamine and alcohol injection.

The alcohol may be considered to bring about a condition analagous to that produced by histamine. The capillaries of
The effect of large doses of alcohol is to produce a condition of typical shock which results from excessive dilatation probably of all vessels, to which is added the paralysing effect on the vasomotor centers and the heart. With the onset of cardiac impairment the venous pressure, as would be expected, rises, till at the point of failure it shoots up abruptly.

The importance of these observations lies in the relief which a fall in venous pressure will give to an overtaxed heart. It is further to be noted that the practical physician gives alcohol exactly in those cases where the heart is subjected to a strain, as in pneumonia, or where the heart is unable to do a reasonable amount of work as in septicemia.

It may well be asked, does the amount of alcohol which can be given therapeutically lower venous pressure. The measurement of venous pressure in man is a matter of considerable debate, but, without absolute evidence, the indications are that the answer to the question is in the affirmative. It is known that there is dilation of skin vessels and no change of arterial pressure or possibly a rise. There must, then, be a redistribution of blood. Dixon has satisfied himself that there is an increased rate of the heart after alcohol administration in man apart from the effect of excitement and this increase in rate is not seen on the isolated heart, although there may be an increased contraction. If the blood pressure is not changed and the drug does not increase the heart rate directly, as seen by experiments on the isolated organ, we must assume that the increase is caused reflexly and, so far as we know, no cause exists which would bring this about other than a fall in venous pressure, as would be suggested by the redistribution of blood which, as we have just seen, must occur.

These facts, taken together with the very definite and easily obtained results of animal experiments, justify us in assuming that, even in therapeutic doses, alcohol reduces the venous pressure in man and may relieve the heart in this way.

We can also understand why, on purely physiological grounds, chronic alcoholics are notoriously bad subjects in infectious conditions, especially pneumonia. The hearts of such individuals will be frequently subjected to periods of diminished venous
filing in which it is called upon to do very little work per beat, and as the heart, like any other organ, adapts itself to the amount of work it has to do, it will become gradually less efficient and less capable of dealing with an additional load such as occurs in an emergency like pneumonia. The special liability of chronic alcoholics who take little physical exercise to be subjects of cardiac failure is well known, and no doubt it is for a similar reason that the prognosis in pneumonia becomes increasingly worse as the patient gets older and his heart becomes less efficient.

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EXPERIMENTAL SHOCK
WITH SPECIAL REFERENCE TO ANAESTHESIA*

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The problem of why persons subjected to physical trauma should pass into a condition of shock is one which has long been of interest to surgeons. Nowadays, indeed, shock rivals sepsis in its importance in surgical operations.

During the war the study of the subject received a great deal of attention, and many valuable conclusions were reached, but there still remains, especially on the clinical side, a state of great confusion. The present state may, I think, be indicated by the fact that the College last year divided one of its valuable prizes between two surgeons whose views on the treatment of so-called surgical shock were a direct contradiction one of the other.

Now it happens that shock can be produced with great ease in laboratory animals, and in the time at my disposal I propose to put forward evidence to you which will emphasize that shock is not a single entity, but may be produced experimentally and clinically from a variety of causes, and that any single remedy used without understanding of the case in hand is bound to give most contrary results.

DEFINITION OF SHOCK

We may define shock in an animal as the state which results from a fall of arterial blood pressure, which, if severe, may lead to death from oxygen want. Its onset may, however, be preceded by a compensated or even over-compensated stage in which the body succeeds in maintaining the blood pressure against the forces which would cause it to fall.

From our knowledge of the circulation, then, we must consider that shock may occur from cardiac failure, from
loss of blood, from increased capacity of the circulation—that is, from an undue opening-up of vessels which are normally closed—or from a reduction of the peripheral resistance to the flow of blood from the arterial system. From the point of view of surgery, however, it is probably best to group the various experimental procedures under headings which are indicative of the cause. In dealing with the detail I shall deliberately omit a large number of minor points, because I feel that if there was a clearer understanding of the principles involved the literature would not be in the confused state that we find it in to-day, for I am convinced that much of the excellent clinical literature appears discordant purely because those concerned are writing about a variety of different conditions, but all under the same title of "surgical shock." There is evidence which indicates that the patient who dies from gross tissue damage such as burning, the patient who dies from minor mechanical injuries, and those who die after prolonged surgical operations, may be deaths from distinctly different states. I hope you do not think I dwell too much on patients who die—many recover—but there are still thousands who die annually who might be saved if the subject was more systematically studied.

**Shock from Haemorrhage**

I do not propose to spend much time in discussing this variety of shock, as its cause is obvious. I should, however, like to emphasize that many of the mechanisms by which the body attempts to compensate for haemorrhage are nervous and depend on the carriage of afferent impulses to the vasomotor centres, which in turn send out impulses to constrict the spleen and blood vessels generally. What is particularly important from a surgical point of view is that, being nervous, these mechanisms can be relatively easily anaesthetized, and the effect of the haemorrhage therefore becomes enhanced, and there is abundant evidence that a low blood pressure, say of 60 mm. of mercury, if allowed to persist for half an hour, is liable to bring about permanent changes, which may be fatal. Every attempt should therefore be made to restore the blood pressure before administering an anaesthetic.

**Direct Action of Toxins on Peripheral Vessels**

*Histamine or Toxic Shock.*—Great attention has, since the war, been focused on this variety of shock since the discovery of the dramatic phenomenon of histamine shock by Dale and Laidlaw. By some it has been hailed as the complete solution of the shock problem, but it is only
fair to say that the authors themselves have never made this claim. On the other hand, no one will deny that toxaemia is a most important factor in shock, and probably the most important factor when the onset of the shock is delayed.

The special importance of histamine lies in the fact that it is present in watery extracts of practically all tissues, as it is a simple derivative of the amino-acid histidine, and its effect when injected in minute quantities into the circulation of anaesthetized cats and dogs produces in a few minutes a condition of shock. The shock produced is comparable with that variety of shock in man in which the onset of the symptoms may have been delayed and have apparently depended on the absorption of toxins from damaged tissues.

The skin has been shown to contain relatively large amounts of histamine or its precursor; indeed, there is reason from the work of Lewis to believe that the production of this or a similar substance is a physiological method by which the skin is flushed subsequent to minor injuries. The delayed shock of severe burns is probably produced by the absorption of such a substance.

Dale and Richards showed that histamine acts by dilating the capillaries, and this has been since confirmed by many others. As a result of the capillary dilatation there is a relative insufficiency of blood—the animal, as it were, bleeding into its own capillaries, which have become opened up. The state is like that of haemorrhage, only the animal bleeds into its own vessels. But the capillaries are not necessarily congested, for in becoming dilated they apparently become more permeable, and the blood plasma rapidly passes into the tissues, leaving behind, as shown by many observers, a concentrated blood. The finding of a concentrated blood clinically is strongly suggestive that the case is one due to capillary dilatation.

Now we may ask ourselves, Does this variety of shock occur clinically? The matter was really settled for us by the Shock Committee of the Medical Research Council. There is abundant evidence that this is a common variety of shock, so common indeed that it has almost been allowed to overshadow the other varieties. I can best summarize the evidence that such chemical shock exists. The shock is delayed in its onset; the greater the tissue damage the more liable it is to occur. It may occur acutely if a tourniquet is removed from a severely damaged limb and the products of damaged tissue allowed to enter the circulation. The shock is enhanced by cold and anaesthesia with ether or chloroform. Typically we
see this variety of shock after severe burns and when large masses of tissue are destroyed, the patients going into shock not immediately, but after several hours or even days, when there has been considerable absorption of the products of dead or dying tissues.

It has been pointed out, particularly by Zachary Cope, that clinically this variety of shock is commonly preceded by a rise of blood pressure, and by some this has been considered evidence against it being due to capillary dilatation. On the contrary, this is exactly what might be expected, for I have demonstrated that under suitable conditions this rise of blood pressure can be brought about by histamine exactly as in haemorrhage. It is indeed merely an over-compensation to a circumstance which tends to cause a fall of blood pressure. This over-compensation may be seen both in the response to haemorrhage and to posture, as pointed out by Leonard Hill. In the case of histamine Dale and Burn have shown that an increased secretion of adrenaline is called forth. The arterial constriction which has been noted clinically by Malcolm is part of the ordinary reaction to a loss of blood volume. I have shown that it occurs with small doses of histamine as with small haemorrhages. We see this in the progressive fall of venous pressure which occurs on the injection of non-shock doses of histamine, by the increased velocity of the pulse wave, the decreasing capability of the animal to withstand the maximum dose of histamine which may be recovered from, and the diminution in the volume of a limb which succeeds a histamine dilatation.

The importance of the suprarenals in relation to histamine shock has been now conclusively shown by Dale, and also by Kellaway and Cowell, in that if they are destroyed, histamine shock may be caused in unanaesthetized carnivora, which are otherwise very resistant. Herein no doubt lies the importance of cold in relation to shock, for subsequent experiments by Cramer and by Crowden have demonstrated that cold exhausts the suprarenal glands. The necessity for keeping a shocked patient warm is already so well recognized in surgical practice that I am surprised to learn that operating tables are no longer heated except by hot-water bottles.

The Effect of Anaesthetics.—That brings me to the relation of anaesthetics to histamine shock. Normally animals can withstand histamine in large doses, but carnivora become sensitive to histamine if anaesthetized, as was shown by Dale and Laidlaw. An anaesthetic such as ether probably acts by dilating vessels, by increasing their permeability, and by paralysing the normal
mechanism of compensation. This is undoubtedly a point of enormous practical importance, the more so as the effect of the ether at the time of the operation may be masked by the stimulating action which the ether exerts by irritating the respiratory tract. In a narcotized animal it is easy to demonstrate the vaso-dilator action of ether. We must therefore consider that the individual who administers ether or chloroform to a severely damaged patient is guilty of a crime, but he would probably escape censure as the patient may not die immediately. Probably the anaesthetic has been responsible for many fatal cases of obstruction or strangulated hernia which have been operated upon late. I don't think I am saying too much when I say that many such deaths could have been avoided. May I hope that modern surgeons will not be like their predecessors who continued to remove the thyroid gland for twenty years after physiologists had shown that its total removal led to death from myxoedema. We must not smile. It is already fourteen years since Dale and his colleagues did this work, but although it is mentioned in some surgical books its importance does not yet receive general recognition. If such patients must have a general anaesthetic then nitrous oxide is the anaesthetic of choice, since it has been shown by Dale that this anaesthetic does not render an animal so sensitive to histamine shock as ether. It is, however, not such an easy anaesthetic to administer, nor from the point of view of relaxation so satisfactory as ether or chloroform; indeed, we must frankly state that we are as yet without an ideal anaesthetic. Personally, I believe that we shall see a greatly extended and routine use of local anaesthetics for this class of case in surgery. It will be agreed that spinal anaesthesia does not meet the case, as it interferes with the nervous control of the vessels and also causes vaso-dilatation.

**Loss of Central Control of Blood Vessels**

_Damage to Vasomotor Paths._—All the blood vessels of the body are under the control of the vasomotor centre, and the majority are maintained in a state of partial contraction by its activity. It is evident, then, that interference with the pathway between these centres and the blood vessels must bring about vaso-dilatation and a fall of blood pressure. In this category must come the shock produced by injury to the spinal cord, also fat embolism in the medulla, which has been described as a sequel to fractures. The shock which is liable to occur in high spinal anaesthesia is somewhat similar in that the paths
from the vasomotor centre to the abdomen and lower limbs are blocked and vaso-dilatation results.

I do not propose to spend time on such obvious causes of shock, but to pass on to the very interesting form of shock of nervous origin which results from operation or injury in which the tissue damage is negligible but the shock is profound.

Concussion of the Vasomotor Centre.—I should like, however, to mention that concussion as a cause of shock may be more common clinically than is commonly supposed. It may be produced experimentally by simply jarring the head. In accident cases there is obvious probability that it exists.

We now come to those varieties of shock which depend on afferent impulses.

Acapnic Shock.—The vasomotor centre may be thrown out of action by a loss of carbon dioxide. The fact that the carbon dioxide of the arterial blood was somehow responsible for the arterial blood pressure was first pointed out by Yandell Henderson. Unfortunately, Henderson postulated at the same time a somewhat remarkable veno-pressor mechanism, which made his theory an easy prey for critics, and his views even as late as 1923 received very little attention if we may judge by Cannon's book. Henderson showed that in etherized dogs, as a result of the stimulation of afferent nerves, there might be over-breathing to an extent sufficient to lower blood pressure.

In 1923 the essential fact was confirmed by Dale and Evans, who also showed that the carbon dioxide of the arterial blood was responsible for maintaining the normal activity of the vasomotor centre in the medulla, and that a reduction of the carbon dioxide of the blood in an etherized animal led to a fall of blood pressure. I have since shown that the capability of an animal to adapt its circulation to changes in posture, such as being placed in a vertical position, depends on the presence of carbon dioxide. The fact that the vasomotor centre requires carbon dioxide must now be accepted, and we have to ask ourselves, Can this variety of shock occur clinically? The answer is again "Yes, certainly in etherized persons," for I have shown that in a limited number of animals under chloralose over-ventilation does not bring about a fall of blood pressure; a fall occurs if the animal is etherized. In man, over-breathing sufficient to cause apnoea (thus showing that the CO₂ has been washed out) does not necessarily cause a fall of blood pressure (Densham and Wells), because of compensatory constriction of vessels due to
increased alkalinity. I do not, of course, deny that very violent over-breathing, which often is not followed by apnoea, does cause a fall, because this actually interferes with the circulation through the lungs. Mr. Wakeley has kindly allowed me to look over his records of operation cases, and among them I found many examples of increased respiration being associated with a fall of blood pressure. In further support of the existence of such washing out of carbon dioxide is the common practice for anaesthetists themselves now to administer carbon dioxide with their anaesthetics as advised by Henderson.

How far acapnia may be an important factor in shock in unanaesthetized patients is difficult to say, since any fall of blood pressure might cause over-breathing. The fall due to histamine, however, does not usually cause such breathing, because of the bronchial constriction. What I do want to emphasize, however, is that even if the acapnia is not a primary factor in shock, it cannot be ignored, for the evidence is complete that it reduces the activity of the vasomotor centre by which the body attempts to compensate for a fall of blood pressure. Every effort must be made, therefore, to reduce the effect of sensory stimulation during operation. It seems to me that herein lies the great value of morphine, which many surgeons still use in all accident cases. I shall return to the question of anaesthetics when I have dealt with depressor shock.

The VASOMOTOR CENTRE MAY BE INHIBITED

Depressor Shock.—There is a class of case met with clinically which appears to fit into none of the categories already mentioned. I refer to severe shock from an apparently trivial injury, such as a bullet wound through the hand or, as I saw recorded recently, a snowball on the eye. The amount of tissue damage is negligible, and from what I have said of acapnia, it is difficult to see that acapnia is wholly responsible without the occurrence of obvious over-breathing. Here we must believe that there is definite inhibition of the vasomotor system by afferent impulses. The possibility of this occurrence was first put forward by Guthrie, but he did not have any clear idea where the inhibition took place; Meltzer apparently thought it peripheral and Guthrie thought it psychic.

The possibility that afferent impulses might be concerned in shock was first suggested by Crile, but unfortunately he claimed that all shock was produced in this way. His view was that the afferent impulses stimulated the vasomotor centre, which became exhausted, and
he bolstered up his view by so much erroneous argument that his theory fell into disrepute. The fact, however, is incontrovertible that certain afferent impulses cause shock. Anyone who reads the clinical literature of the subject will see quite easily that the shock which is so well described by Lockhart-Mummery is not the secondary wound shock on which the Wound Shock Committee worked. It is an entirely different entity. For example, Lockhart-Mummery, in his Hunterian Lectures in this place in 1905, emphasized the importance of the less destructive manipulations such as tractions in a pedicle or ligament and nerves. The Shock Committee emphasized the importance of gross destruction of tissue.

When men take the trouble to make observations these are usually true, but the deductions may be false. I think that on the whole Lockhart-Mummery supported Crile's view that the centre was exhausted, but his observations were none the less very valuable. We must, however, remember that the absence of any knowledge of histamine shock in 1905 made the whole problem much more difficult and confused. Actually the centre is remarkably resistant to exhaustion, and Porter and others have shown that the centre is not exhausted in shock, and could often be made to raise the blood pressure afferent by stimulation of an afferent nerve. This fact has caused the Crile-Mummery view to pass into abeyance, and what good there has remained of it has been taken over by the supporters of the acapnic theory. There is now, however, definite evidence that, apart from acapnia, shock may be produced not as a result of exhaustion, but by nervous inhibition of the vasomotor centre by certain afferent stimuli, especially mechanical stimuli. The occurrence of inhibition of the vasomotor centre is well known in physiology. The centre may be inhibited not only by special depressor nerves, but also by stimulation of many mixed nerves at a slow rate. This depression may be counteracted by stimulation of another region with a fast rate of stimulation, which stimulates pressor rather than depressor fibres in a mixed nerve because of the different excitability of the fibres. There is then no real conflict between Porter and Crile or Lockhart-Mummery, but merely a lack of full understanding on both sides. The question naturally arises, however, how far the results of Crile and Lockhart-Mummery might be due to loss of carbon dioxide due to over-ventilation, which commonly occurs at the same time.

It may be shown that this depression of the vasomotor mechanism produced by mechanical stimulation is not due primarily to acapnia, for it can be produced in an
animal with the chest open and under artificial respira-
tion. No doubt, however, acapnia does enhance the
effect, so that from the point of view of prevention we can
take acapnic and depressor shock together. They are
both preventable by deep anaesthesia. This gives support
to the view that the prevention of primary shock is pos-
sible by deep anaesthesia. This has long been claimed,
but the claim did not rest on much experimental data.
It is interesting to remark that in Beattie and Choyce's
Textbook of Surgery, however, I find it stated that some-
times anaesthesia causes improvement in shock cases.
Here we have, then, a great difference between shock
produced by chemical and nervous stimuli, a difference
which has an enormous importance in anaesthesia.

In an experiment under dial, the piercing of the fore-
limb with a sharp instrument caused a profound shock,
which was recovered from under deep ether anaesthesia,
during which no depression could be produced. Electrical
stimulation of an afferent nerve at a fast rate brought
about a temporary recovery of blood during a fall of
blood pressure. I have also obtained a fall of blood
pressure by merely tapping a tibia, while in other animals
shock has been produced by mere dissection of the sciatic
nerve, which would be quite innocuous under deep ether
anaesthesia. In my experiments I have found that
cocainization of the carotid sinuses and the vagi enhances
the depressor responses, but the exact significance of this
point I have not yet made out.

This variety of shock, together with that produced by
loss of carbon dioxide, is probably what has hitherto been
known as primary shock—a state well recognized to be
fundamentally different from secondary wound shocks by
workers such as Cowell, Bayliss, Dale, and Wallace. But
the experiments which I have just quoted suggest that
this variety of shock may be more important in accident
cases and in the operating theatre than is generally sup-
posed. In relation to operations an interesting piece of
work has recently been published by Richet and Dub-
lineau, showing that the vaso-dilator centre seems to
develop a preliminary higher excitability under anaes-
thesics. It seems likely that the pressor mechanisms
become anaesthetized before the depressor mechanisms.

Now a very interesting point is that experimentally,
under apparently similar states of anaesthesia, depressor
shock cannot always be demonstrated. This time last
year I had no difficulty in producing it; indeed, my
attention was drawn to it by the fact that on many
occasions I produced it accidentally by operations which
are usually innocuous. On the ground of these experi-
ments which appeared so certain I decided to give this lecture its present title, but when I began to prepare for it in detail in September and October I found myself totally unable to produce shock in this way. It was rather disconcerting. The results were so clear-cut in February and September that I decided to wait for a few months. Now I am relieved to find that I can produce the depressor shock easily again, but as yet I have not been able to define exactly the circumstances under which it arises. The difference may be due to the seasonal variability in the sympathetic system of cats or may be solely a question of exhaustion by cold. This is, however, by no means solely a purely experimental point, but one of clinical importance, because it is found that some patients are much more easily shocked than others, and that fear, emotion, and cold, which stimulate the sympathetic and may cause exhaustion of the suprarenals, are definitely looked upon as aggravating causes (Fraser).

Mixed Shock.—From what has been said it is almost obvious that in some instances the varieties of shock must overlap—for example, chemical shock may supervene on nervous shock; indeed, it may almost be assumed that it will if a nervous shock is allowed to persist, because oxygen want will of itself lead to tissue death and capillary dilatation.

CONCLUSION

The whole clinical problem now requires to be completely reinvestigated in the light of modern experimental facts, with a view to finding methods for diagnosis of the different varieties. A large amount of the existing literature is completely valueless. I do not pretend that what I have said is in any way final, and a large number of the facts are not new; all I hope is that it may serve as a simple basis from which systematic clinical study may be made. But I think you will agree that a fuller knowledge of the experimental facts makes the general approach to the subject easier.

I have omitted those methods of producing shock which I do not think are related to surgical practice, and (as I said at the beginning of the lecture) I have also deliberately omitted a large number of facts regarding shock. Many are secondary to the fall of blood pressure, acidosis, loss of muscle tone, lowered metabolism, etc. I have done so because I want to make it quite clear that a number of clear-cut varieties of shock exist experimentally. Clinically they have not been differentiated except very crudely as primary and secondary, although, as I have indicated, there is every reason to believe that distinct
varieties exist. To the physiologist and biochemist may be left the problem of how best to deal with histamine, a solution to which is one of the most important requirements of modern surgery. But meantime we also want in relation to shock a better clinical surgery capable of making a more adequate differential diagnosis—not the dramatic surgery of the operating theatre, but the unexciting and unremunerative study of the patient in bed, the work which is too often left to anybody willing to do it, the surgery which involves a careful study of available experimental data, which would be a stepping-stone to a new surgery. If more surgeons came into the physiological laboratories and saw the different varieties of shock for themselves, there would be a much better appreciation of the facts, and soon we should have the clinical investigations which are so desirable.

**SUMMARY**

Experimental shock may be divided into several distinct varieties which, apart from that produced by haemorrhage and cardiac failure, may be divided into chemical and nervous.

The chemical variety is typified by histamine shock experimentally and clinically by a delayed shock associated with gross destruction of tissue. This variety is enhanced by anaesthetics.

The nervous varieties may result from physical damage to the vasomotor centre or its efferent paths, from afferent impulses leading to loss of carbon dioxide (acapnia), or from inhibition of the centre. Acapnia and inhibition account for the shock which follows immediately on injury. Shock dependent on afferent impulses is prevented by deep anaesthesia and reduced by morphine. The chemical and nervous varieties may coexist and enhance each other.