THE EFFECTS OF ASPHYXIA UPON MEDULLARY CENTRES. PART I. THE VASO-MOTOR CENTRE.

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CONTENTS.

Introduction. In a former paper(1) I have considered the effects of asphyxia, oxygen lack[1], excess of carbon dioxide and injection of weak acids upon the spinal centres and have shown that, with some reservation in the case of carbon dioxide (see note at end of this article), there is such similarity in the effects produced as to suggest the existence of a common factor underlying the actions of these various agents. In pursuance of this idea I have examined the effect of these agents upon the vaso-motor and the cardio-inhibitory centres. For satisfactory investigation it is obviously necessary to avoid variations due to spontaneous respiratory movements, and for this reason the experiments have been carried out on curarised animals under artificial respiration. Further, for purposes of analysis, it is necessary to investigate the centres one at a time, that is, to eliminate the effect of activity of the cardio-inhibitory centre when the vaso-motor centre is under examination, and *vice versâ*. In order to eliminate the action of higher centres

[1] This term is used to cover the various products resulting from the alterations in metabolism consequent upon lack of oxygen.

and, still more important, to dispense with anæsthetics, animals deprived of the cerebral hemispheres have been employed.

Although the action of asphyxia upon the circulation has been the subject of many investigations, in few has any proper attempt been made to dissociate the factors concerned. Most of the observations have been made on non-curarised animals, frequently with the vagi intact, in which the circulatory changes were profoundly influenced by the respiratory movements. In others, performed with the intention of ascertaining the effect of carbon dioxide, such excessive quantities of this gas were given that it is certain that oxygen lack was also present. The observations made in the early years of the graphic method do not suffer from such defects. In 1863 Traube(2) investigated the action of asphyxia upon curarised rabbits with the vagi cut. He showed that the administration of 21 p.c. carbon dioxide with excess of oxygen produced a rise of pressure with dilatation of the heart, and he ascribed this rise of blood-pressure to the action of carbon dioxide upon the centres for the "musculo-motor system" of the heart(3). Thiry(4) working under Ludwig, demonstrated that the rise of pressure during asphyxia in curarised animals was due to constriction of the small arteries. When he employed a mixture consisting of one part of carbon dioxide with two parts of oxygen, he observed a rise of pressure accompanied by a contraction of the walls of the small arteries (ascertained by direct observation). He clearly stated that the stimulating effect of carbon dioxide was a central one. In some cases on administering hydrogen he obtained a rise of blood-pressure similar to that in asphyxia. In the light of Thiry's results Traube(30) reinvestigated the subject and came to the conclusion that the carbon dioxide carried in the blood was the natural excitant of both respiratory and vaso-motor centres.

The next decade saw the development of the idea that lack of oxygen was the normal stimulus to the respiratory centre and to nerve centres in general—a view strongly championed by Rosenthal(5) and more recently by Verworn(6). The action on the vaso-motor centre has not been investigated as a separate problem by any observer, though Verworn investigated the increased vagus action during asphyxia. Miescher-Rusch(7) and Fredericq(8) regarded carbon dioxide as the normal excitant to respiration, and the latter has always strongly asserted that carbon dioxide is the normal excitant to all medullary centres, respiratory, vaso-motor and cardio-inhibitory, though I have not been able to find upon what experimental evidence this assertion was

based. An account of the conflicting views of numerous observers will be found in an article by Marés(9), who himself obtained a rise of blood-pressure with pure oxygen lack but not with carbon dioxide; he arrived at the erroneous conclusion that the heart was resistant to oxygen lack but was readily poisoned by carbon dioxide. The absence of any rise of blood-pressure in his experiments was due to heart failure produced by the excessive quantities of carbon dioxide which he employed, usually mixtures of 80 p.c. carbon dioxide with less than 20 p.c. oxygen.

The work of Haldane and Priestley(10), establishing the important part played by carbon dioxide in regard to the respiratory centre, directed further inquiry into the question. Hill and Flack(11) paid some attention to the circulatory changes during the administration of excess of carbon dioxide, and during oxygen lack, but their results were complicated by the incomplete dissociation of the two conditions, and by the accompanying changes in respiratory movements. As far as their work went it showed that both carbon dioxide and oxygen lack could excite the vaso-motor centre.

Kaya and Starling(12), examining asphyxia in the spinal animal, made a few observations on the medullary vaso-motor centre and concluded that it was excited by carbon dioxide and probably also by oxygen lack.

The reaction from the views of Rosenthal has been very marked and there is at present a tendency to go to the other extreme, seen, for example, in the writings of Yandell Henderson(13). He not only attributes to carbon dioxide the predominant part in maintaining the activity of nerve centres but repeatedly states that lack of oxygen is not a stimulant but merely paralyses. This statement is not in accordance with the results recently obtained by Hill and Flack(11) and is only in a particular sense supported by the work of Haldane and his colleagues(14, 15) on the regulation of respiratory movements. It will be shown that the results of the present investigation are in opposition to the view that oxygen lack never acts as a stimulant, although it is fully recognised that this stimulant action is not a direct one.

General Methods. The experiments were carried out on curarised decerebrate cats. Under full chloroform anæsthesia the trachea was opened and artificial respiration instituted. The carotid arteries were both ligated and the vagi and cervical sympathetic trunks divided. The skull was trephined over the most prominent part of the parietal bone and decerebration performed by means of a blunt-edged instrument at the level of the anterior border of the bony tentorium, the brain stem

being thus transected about the region of the anterior corpora quadrigemina. No attempt was made to stop bleeding, free escape of blood being permitted in order to avoid any rise of intracranial pressure. The onset of decerebrate rigidity indicated the efficiency of the transection. The moment decerebration was completed the anæsthetic was discontinued. Then 1 c.c. of a 2 p.c. solution of curare diluted with saline was injected either intravenously, or preferably into the central end of the left carotid artery, thus avoiding the heart. The blood-pressure was recorded in a carotid or in the femoral artery and, for investigation of intestinal volume changes, a loop of the lower end of the ileum was enclosed in an oncometer of Edmunds' pattern, which was connected either to a piston recorder or to the volume recorder devised by Maas. The gas mixtures were administered usually by means of Meyer's respiration pump, in a few cases by the method of continuous tracheal insufflation which I described in a former paper(16). For oxygen lack, nitrogen containing usually less than 1 p.c. oxygen was administered. The acid solutions, made up with normal saline, were injected either intravenously or into the central end of the stump of the right carotid artery; in the latter case they reached the aortic arch and were carried on in the blood stream, a portion of the acid thus reaching the medullary centres by way of one or both vertebral arteries.

At the conclusion of each experiment the cranial vault was removed, and the exact level of the transection and the conditions within the cranium were ascertained. If any blood clot was found about the base of the brain affecting the blood supply to the medullary centres, the results of the experiment were rejected.

The Action of Asphyxia.

The action of asphyxia[1] upon the circulation is well known. The changes of blood-pressure occurring as the result of asphyxia and of the various agents examined are shown in Figs. 1–4, which are taken from experiments on the same preparation. Asphyxia, administration of nitrogen, or of 12 p.c. carbon dioxide, or injection of 2 c.c. N/15 lactic acid, all rapidly produced a rise of carotid pressure from about 100 mm. to the neighbourhood of 220 mm. Hg. The administration of 18 p.c. carbon dioxide produced a rise of no greater magnitude, so that it may be concluded that the stimulation of the vaso-motor centre was in all cases about maximal.

[1] Throughout this paper asphyxia signifies asphyxia by cessation of respiration.

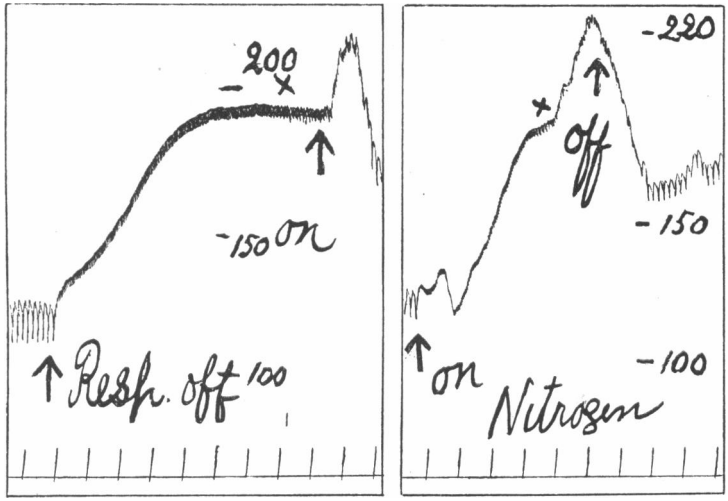

Fig. 1. Cat D 15. Decerebrate at level of anterior corp. quad. Vagi cut. Curarised. Artificial respiration discontinued between the arrows. Slight movements at ×. The same preparation was used in Figs. 1–4. In this and all subsequent tracings the time marker indicates 10 seconds, the upper curve intestinal volume, the lower arterial blood-pressure, the exact height in mm. Hg. being indicated by the inscribed numerals. Synchronous points in volume and pressure curves are indicated by |×. All the animals were decerebrate, curarised and vagotomised.

Fig. 2. Cat D 15. Nitrogen administered by continuous tracheal insufflation between the arrows. At × slight movements.

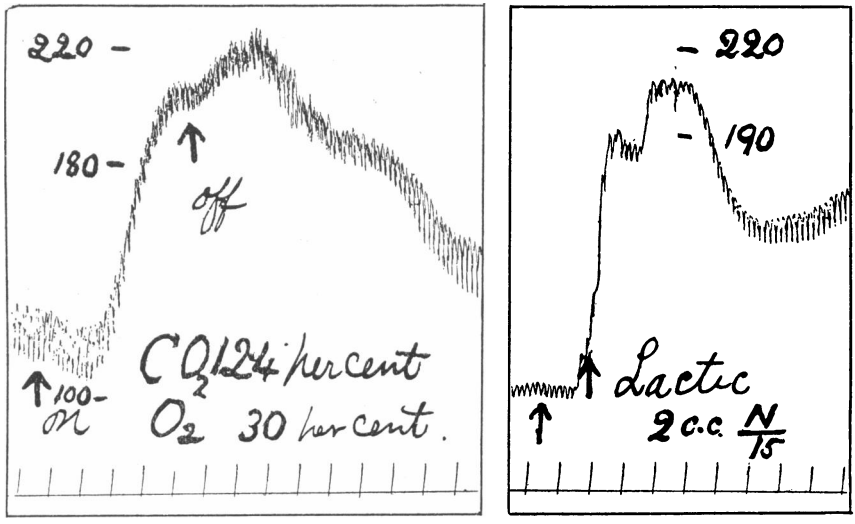

Fig. 3. Cat D 15. CO_2 12·4 p.c. + O_2 30 p.c. administered.

Fig. 4. Cat D 15. Lactic acid, 2 c.c. $\frac{N}{15}$ (=2 c.c. ·6 p.c.) injected into the left external jugular vein.

In several cases the composition of the alveolar air was examined before asphyxia, and at the moment when the asphyxial rise of blood-pressure commenced, or at intervals of one minute or two minutes after the cessation of artificial respiration. The gases were collected by means of a sampling bulb, filled with mercury, which was connected with a side branch in the glass tracheal cannula. The dead space of the apparatus was made as small as possible and by means of a special three way tap at the proximal end of the bulb the first portion of air from the lungs was not drawn into the collecting bulb, into which only alveolar air passed. The gases were estimated by means of Haldane's large gas-analysis apparatus; usually between 25 and 30 c.c. of gas were obtained for analysis.

The following are examples of the values obtained:

	I Percentages of		II Percentages of	
	O_2	CO_2	O_2	CO_2
During artificial respiration	16·7	1·65	15·4	2·1
After 1 min. asphyxia	8·9	3·3	8·8	3·9
After 2 mins. asphyxia	4·3	5·0	2·6	6·0
During artificial respiration	14·9	1·43		
At moment of asphyxial B.P. rise	7·1	2·95		

The carbon dioxide content of the alveolar air was usually very low under the conditions of experiment. It may be that this was due to excessive artificial respiration, but if this were the case it was remarkable, in view of Yandell Henderson's repeated demonstration that a great lowering of blood-pressure is a constant feature of the acapnia resulting from excessive ventilation of the lungs, that the blood-pressure remained at a constant level. The increase in alveolar carbon dioxide during asphyxia is not very great, while there is a great fall in the oxygen percentage. In the light of subsequent experiments the figures obtained indicate that while the stimulation of the vaso-motor centre is due to both oxygen lack and accumulation of carbon dioxide, the failure of the circulation, to which death from asphyxia is directly due, is the result of want of oxygen.

The Effects of Lack of Oxygen.

The blood-pressure changes during the administration of nitrogen are similar to those occurring during asphyxia. The chief difference is that the rise in asphyxia commences almost at once and increases gradually, whilst under nitrogen it does not appear until half a minute

or more has elapsed and is then, as a rule, rather abrupt. This difference is well illustrated in Figs. 5 and 6. It is not markedly apparent in Figs. 1 and 2, perhaps because in the experiment illustrated by Fig. 2 the nitrogen was administered by tracheal insufflation and there may have been a slight accumulation of carbon dioxide. The difference ordinarily observed is due to the increase in carbon dioxide tension during asphyxia, an increase not occurring when nitrogen is given. The subsequent fall of blood-pressure is earlier in onset and more rapid under nitrogen, the available oxygen is washed out from the lungs and tissues with greater rapidity and the heart rapidly fails. If oxygen lack or asphyxia is prolonged for more than a minute, heart block ensues. The effect of oxygen lack on the heart I have described in detail elsewhere(16).

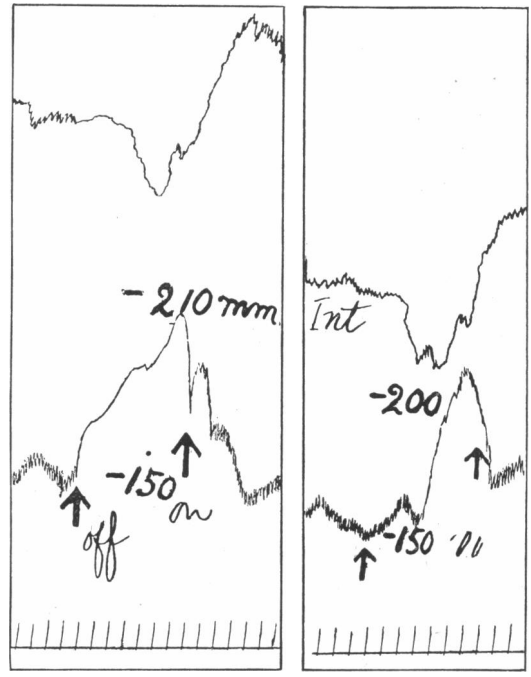

Fig. 5. Cat. Decerebrate above post. corp. quad. Curarised. Artificial respiration stopped between the arrows.

Fig. 6. Same preparation as in Fig. 5. Nitrogen administered between the arrows.

Whether the fall of blood-pressure is entirely due to the failure of the heart or whether there is also paralysis of the vaso-motor centre requires consideration. The initial effect of oxygen lack on the centre is clearly stimulating, a result in opposition to Yandell Henderson's statements. He says, for example, "...it appears that lack of oxygen is not the cause of the symptoms characteristic of asphyxia. Lack of oxygen apart from excess of carbon dioxide is not a stimulus. It merely paralyses(17)." Since in my experiments the alveolar carbon dioxide tension was often under 3 p.c. at the moment of stimulation, it

is impossible for me to agree with the latter part of this statement, a statement which is repeated in other papers by this worker(18).

The excitation of the vaso-motor centre by oxygen lack comes on usually between 30 and 60 seconds after the administration of nitrogen is commenced, in contrast to that of spinal centres which does not occur until two minutes or more have elapsed.

Though there is no doubt that the vaso-motor centre is stimulated as a result of lack of oxygen, results are sometimes seen which suggest that a paralytic action on the centre is in progress at the same time as the stimulation. The fall of blood-pressure is usually attributed entirely to heart failure, and the rise when respiration is resumed is ascribed wholly to the improved action of the heart. Cardiometer records do not always show sufficient decrease in the output of the heart to account for the entire fall of pressure, and intestinal volume curves indicate that there is frequently concomitant vaso-dilatation. A result such as that illustrated in Fig. 7 is not infrequent. If this curve be carefully studied it will be seen that at the same time the intestinal volume decreased and the blood-pressure rose; then with a falling blood-pressure the volume increased, indicating a dilatation of the vessels. About this time respiration was resumed and the blood-pressure at once rose, chiefly, it may be assumed, as a result of the increased cardiac output. It is to be noticed that the vessels again began to constrict with a rising blood-pressure. There is a slight possibility that this was due to a reaction of the arterial wall to increased internal pressure, such as that described by Bayliss(19), but the experiment illustrated in Fig. 8 suggests that it was due to a revival of the vaso-constrictor centre by the new supply of oxygen. This latter experiment was performed on the same animal some time later, when the centres were somewhat fatigued.

The administration of nitrogen for about one minute was followed by a slight fall of pressure and it appeared that the heart was about to fall without any rise of pressure occurring. When the supply of air was resumed the intestinal vessels constricted and the blood-pressure rapidly rose. In this experiment the diminution in intestinal volume came on shortly after the removal of the air supply and the greater portion of the rise of pressure followed later. The course of the phenomena certainly suggested that the stimulation of the vaso-motor centre was not made manifest till a fresh supply of oxygen was acquired.

Results such as these can be explained by assuming that in the case of oxygen lack two factors are at work, one stimulant, the other

paralytic. In accordance with the prevalent views of the action of nerve centres it may be assumed that chemical stimulants do not excite a nerve centre by effecting a change in the metabolism of nerve cell bodies, but by bringing about alterations in the permeability of the synaptic membrane (cf. Sherrington(20)). A substance may excite

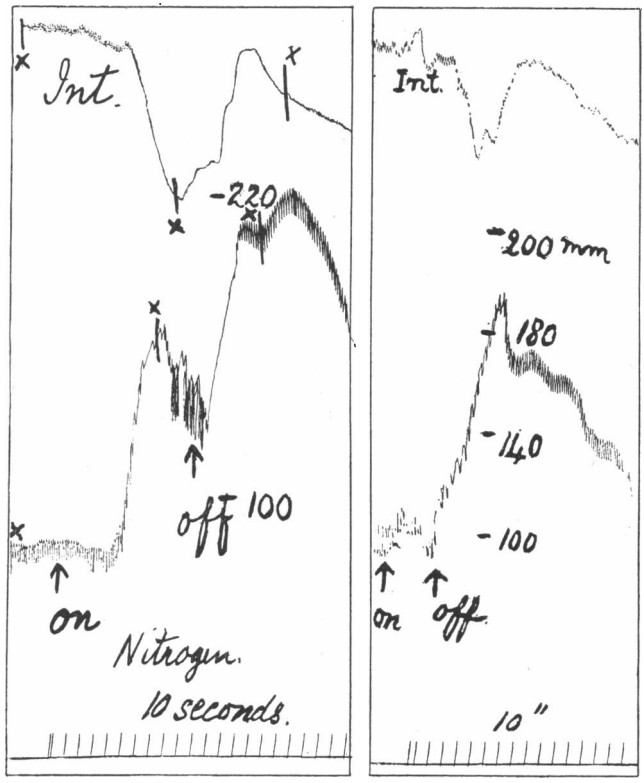

Fig. 7. Cat. Decerebrate above post. corp. quad. Curarised. Nitrogen administered between on and off.

Fig. 8. Same preparation as in Fig. 7, in a somewhat fatigued condition. Nitrogen administered between the arrows. Rise of blood-pressure and constriction of intestinal vessels subsequent to resumption of air supply.

the receptive portion of the cell mechanism, but at the same time paralyse the executive side so that the stimulus elicits no response. This view is well expressed by Yandell Henderson(21): "The function of perikarya is merely nutritive. The lack of oxygen paralyses neurones by starving their cell bodies, while on the contrary the acidosis substances

resulting from partial asphyxia of other tissues are stimulants at synapses." It is quite possible that the acidosis substances themselves may, acting on different portions of the neurone, simultaneously stimulate and paralyse. Certainly the narcosis of nerve centres resulting from injection of acids into the blood stream, seen in the case of spinal centres (cf. Mathison(1)) and also of higher centres, suggests that the acidosis substances are quite capable of this double action, so that in this detail I am not prepared to subscribe to Henderson's statement, though agreeing with the main idea.

The Effect of Excess of Carbon Dioxide.

The rise of blood-pressure in curarised animals supplied with carbon dioxide together with a sufficiency of oxygen was demonstrated by Traube(30) who used mixtures containing 14 p.c. carbon dioxide and excess of oxygen. Most of the succeeding observers used immoderate quantities of carbon dioxide (*see* Mares(9)).

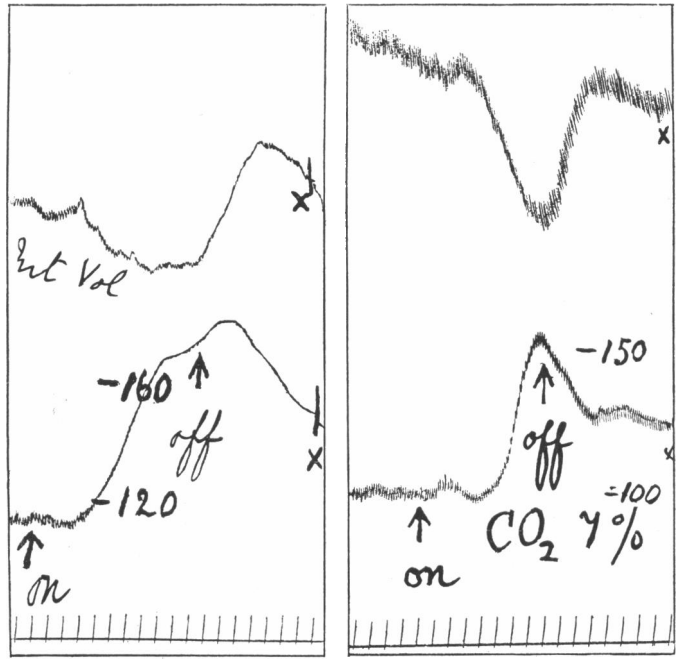

Fig. 9. Same preparation as in Figs. 5 and 6. CO_2 4·7 p.c. + O_2 20 p.c. administered between the arrows.

Fig. 10. Cat. Decerebrate through posterior part of ant. corp. quad. CO_2 7 p.c. + O_2 25 p.c. administered.

The demonstration of the reaction of the respiratory centres to slight excess of carbon dioxide suggests that the reaction of the vaso-motor centre may be similarly sensitive. Kaya and Starling(12), working on curarised animals anæsthetised with urethane, produced marked rise of blood-pressure by administering 7 p.c. carbon dioxide. In animals anæsthetised with chloroform the rise in pressure is infrequent; this accounts for the failure of many workers to produce it.

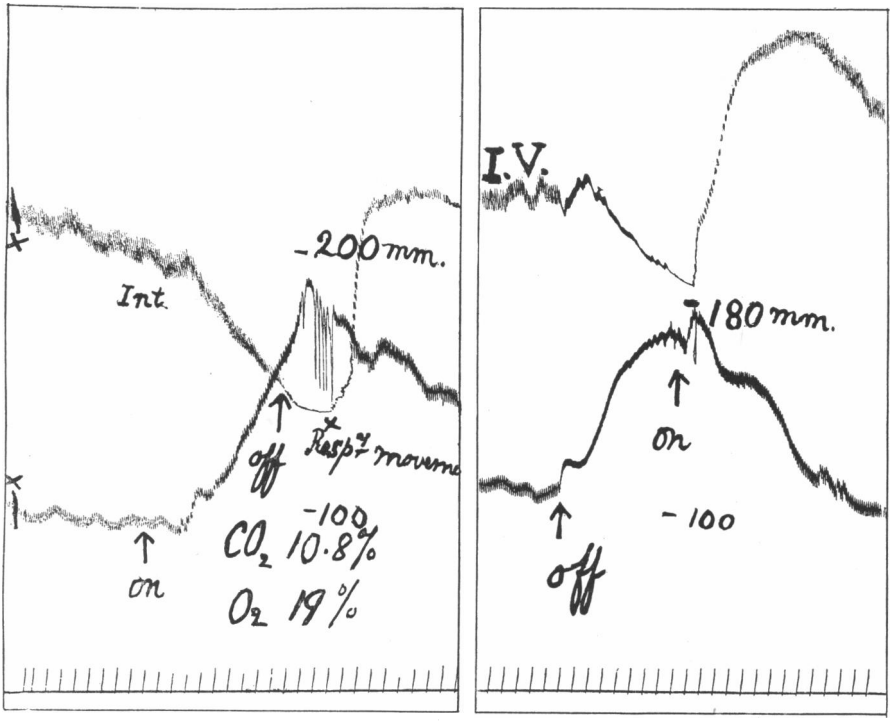

Fig. 11. Same preparation as in Fig. 10. CO_2 10·8 p.c. + O_2 19 p.c. administered. Note eruption of respiratory movements causing large variations in B.-P. tracing; the effect of the curare was becoming inefficient.

Fig. 12. Same preparation as in Figs. 10 and 11. Cessation of artificial respiration between the arrows. Compare with Fig. 11.

The raised blood-pressure may in part be due to the increase in the output of the heart which, as Henderson(17) and Jerusalem and Starling(22) have shown, is produced by small percentages of carbon dioxide. It is always assumed however that the rise is mainly due to vaso-constriction, though I have been unable to find any published record of plethysmograph observations.

In Figs. 9, 10 and 11 are shown the changes in blood-pressure and intestinal volume resulting from administration of quantities of carbon dioxide varying from 4·7 to 10·8 p.c., to be contrasted with Fig. 12 showing the effect of asphyxia upon the same preparation as in Figs. 10 and 11. In all cases the rise in blood-pressure is accompanied by decrease in volume of the intestinal loop. The blood-pressure rose from 100 to about 180 mm. in asphyxia and also under 10 p.c. carbon dioxide. In Figs. 11 and 12 large excursions on the blood-pressure tracing occurred, due to the eruption of spontaneous respiratory movements; the effect of the curare was diminishing and the strong stimulation of the respiratory centre overcome the block in the motor end organs. Fig. 9 is taken from an experiment on the same preparation as Figs. 5 and 6; in this case 4·7 p.c. carbon dioxide produced a rise from 110 to 180 mm., asphyxia or oxygen lack from 150 to about 200 mm.

The medullary vaso-motor centre is readily excited by 5 p.c. carbon dioxide, in marked contrast to the spinal vaso-motor centres which are excited only by mixtures containing 25 p.c. and upwards; the sensitiveness of the vaso-motor centres is greatly increased for carbon dioxide just as it is for oxygen lack. The rise in pressure ensues within half a minute of commencing the administration of the carbon dioxide and proceeds very rapidly but quite steadily,—offering a contrast to the abrupt rise under oxygen lack,—and is maintained for some time; the blood-pressure may remain nearly 100 mm. above its ordinary level for ten minutes or more if the administration of carbon dioxide is sustained. This maintenance of a high blood-pressure is illustrated in Fig. 14; in this experiment 10 p.c. carbon dioxide and 25 p.c. oxygen caused a rise of pressure from 120 to 240 mm. in 40 seconds, and the pressure remained at this level for $2\frac{1}{2}$ minutes, falling only when the carbon dioxide was discontinued. Thus the effect of these small percentages is to stimulate without causing paralysis. A narcotic effect is seen when more than 30 p.c. carbon dioxide is given; it has been fully described by previous workers (*see* Hill and Flack(11)).

The effect of carbon dioxide is very constant; rarely indeed does the vaso-motor centre fail to respond, even when its condition is too bad to permit a response to oxygen lack. This does not necessarily indicate that carbon dioxide is a *specific* stimulant to medullary centres, but certainly shows that it is well adapted to act as the *normal* stimulant.

The Effects of Injection of Organic Acids[1].

The presence of organic acids such as lactic acid in the blood of asphyxiated animals is well established, and the effect of introducing such acids into the blood stream is shown in Fig. 4. The injections have been made with the precautions described in a former paper, sometimes into the central end of the carotid artery, sometimes into one of the jugular veins. Fig. 4 shows the effect of injecting 2 c.c. N/15 lactic acid during a period of 20 seconds into the left external jugular vein. An apparently maximal stimulation of the vaso-motor centre resulted, the blood-pressure rose as high as it did during asphyxia in the same animal.

It might be objected that the acid injected merely raised the carbon dioxide tension of the blood and that this stimulated the centre, but if this were the only effect the excessive tension should have been corrected as the blood passed through the lungs, and the rise of pressure should not have been so lasting as in the illustration. Other organic acids have the same effect. As small a quantity as 2 c.c. N/30 acid is capable of exciting the centre, whilst about 5 c.c. N/6 acid are required to excite spinal cord centres.

The Production of Rhythmic Variations in Blood-Pressure.

Rhythmic waves on the blood-pressure tracing during asphyxia in curarised animals with the vagi cut were described by Traube in 1865(30). In the present experiments waves which answer to Traube's description have been seen under carbon dioxide and during oxygen lack. They fall into two classes: the first includes waves 10 to 25 mm. Hg. in height, recurring about ten times per minute; the second, larger waves up to 60 mm. high recurring about twice per minute. The first class corresponds to the well-known Traube-Hering waves(23). Hering attributed these variations in blood-pressure to overflow from the respiratory centre to the vaso-motor centre. Their rate certainly approximates to that of respiratory movements in a vagotomised animal and Hering's explanation has something to be said in its favour. In the present experiments these waves have been observed with quantities of carbon dioxide as low as 5·9 p.c.; with higher percentages they were

[1] The whole question of the value and significance to be attached to the results of such injection is discussed in a former paper (1).

nearly always present. A high arterial pressure seems to favour, though it is not a necessity for, their production.

The occurrence of the larger waves during oxygen lack and during administration of carbon dioxide is illustrated in Figs. 13 and 14. In Fig. 13 the changes in intestinal volume are also shown, and as these did not correspond exactly to the blood-pressure changes, it appears probable that all parts of the vaso-motor centre were not in the same phase simultaneously, but first one portion, then another, was active. These large waves were accurately described by Traube, but were re-described by Mayer(24) and are thus frequently called Mayer's waves.

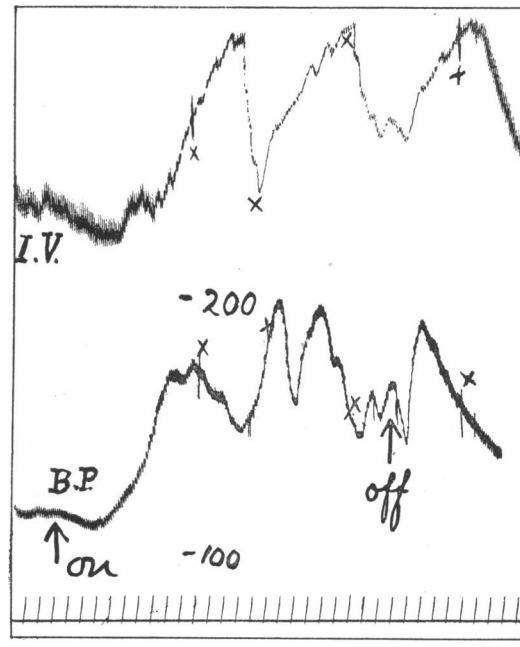

Fig. 13. Same preparation as Figs. 10–12. Rhythmical waves during the administration of nitrogen.

There has been much discussion as to the causation of these rhythmic pressure variations, and many attempts have been made to differentiate between them (see for example Morawitz(25)). Their origin is usually attributed to irradiation from the respiratory centre, but since rhythmic variations in blood-pressure are frequently seen in the spinal animal, which possesses no respiratory centre, there is no necessity to postulate the participation of this centre in their production.

From experimental results there appears to be no sufficient reason for departing either from Traube's original description of the waves or from his explanation that they are due to varying conditions of activity and fatigue in the vaso-motor centre, save to add that such conditions may also exist in spinal vaso-motor centres, a point which Traube did not acknowledge.

Absence of Response to Asphyxia.

In the foregoing account of experimental results only the positive results have been discussed. In some cases asphyxia, oxygen lack, carbon dioxide and injection of acid one and all failed to stimulate the vaso-motor centre. Where carbon dioxide fails to excite the centre oxygen lack also fails, but on the other hand cases are met with where carbon dioxide causes a rise of blood-pressure and oxygen lack does not. This is probably due to the dual action of oxygen lack discussed in a former section.

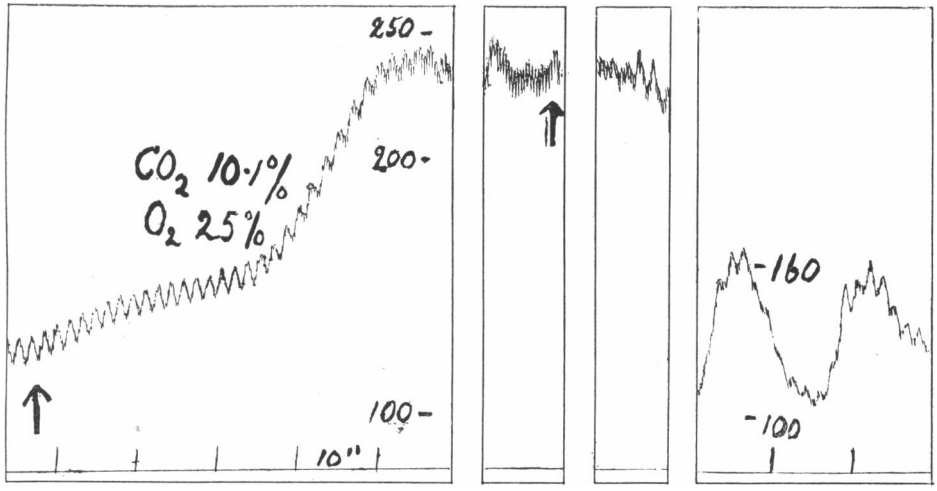

Fig. 14. Cat. Decerebrate. Curarised. Vagi cut. Rhythmical waves subsequent to the administration of CO_2 10·1 p.c. + O_2 25 p.c. between the arrows. Gaps in tracing =90, 30 and 30 seconds.

The phenomena of narcosis, which were discussed in detail in connection with spinal centres, show themselves even more markedly in the case of medullary centres. The narcosis comes on more quickly, probably owing to the more active katabolism of the cells of the medullary centres. My observations agree with those of the various observers who have at one time or another seen this narcosis during oxygen lack, after prolonged administration of large percentages—30 p.c. and upwards—of carbon dioxide and after the repeated injection of acids.

Discussion of Results.

The results of these investigations show that oxygen lack, excess of carbon dioxide or injection of weak acids all excite the vaso-motor centre. To excite the spinal vaso-motor centres requires oxygen lack of at least two minutes' duration, the administration of 25 p.c. carbon dioxide, or the injection of about 5 c.c. N/6 lactic acid. The medullary vaso-motor centre is readily excited by oxygen lack of about 40 seconds' duration, by 5 p.c. carbon dioxide, or by 2 c.c. N/20 lactic acid. Thus, these higher centres show a great increase of sensitiveness not only to nervous but also to chemical stimuli. There appears to be no reason for regarding the respiratory centre as a particular mechanism alone possessing the property of responding to small changes in the carbon dioxide tension of the blood.

The hypothesis that there exists a common factor underlying the action of the various agencies at work in asphyxia receives some support from these experiments, as it did from those on asphyxia in the spinal animal. Recent work tends to show that this common factor is the increased acidity, or hydrogen ion concentration, of the blood. To account for the excitatory effect of lack of oxygen upon the respiratory movements the view was put forward first by Hermann in 1870(26), more recently by Haldane and his colleagues(14)(15)(29), that oxygen lack lowers the threshold of the respiratory centre for carbon dioxide. It is well established that oxygen lack results in the production of acid substances other than carbon dioxide, and there is evidence that any acid is capable of exciting the respiratory centre. Winterstein(27) has shown that when the brain of a young rabbit is perfused with Ringer's solution free from carbonates, the addition of sufficient hydrochloric acid to bring the acidity of the fluid up to N/1000 HCl evokes respiratory movements. It appears reasonable to assume that the hydrogen ion concentration is the factor conditioning the excitation of the respiratory centre, and, the results of my experiments suggest, of the vaso-motor centre. Since the animal has developed a mechanism by means of which changes in the reaction of the blood can be readily and rapidly adjusted by varying the excretion of carbon dioxide, whilst the mechanism for excreting other acids is a slow one, as is shown for example in Ward's results on Monte Rosa(28), carbon dioxide can be regarded as the *normal* respiratory hormone. The acid substances produced during oxygen lack are not of lower potency as hormones

than carbon dioxide, but for several reasons they are not normally employed. Their production is not a steady process like that of carbon dioxide but commences suddenly at a time when the executive side of the nerve cell is feeling the effect of oxygen starvation, so that the cell may be too much disorganised to respond to stimulation. The broad margin of safety protecting the organism against paralysis of its cells by oxygen starvation is assured by the sensitiveness of the medullary centres to hydrogen ion concentration, and therefore to carbon dioxide in common with other acids.

SUMMARY.

1. Oxygen lack, administration of small percentages of carbon dioxide, and injection into the blood stream of weak organic acids all cause rise of blood-pressure by stimulating the vaso-motor centre. In the production of the asphyxial rise of blood-pressure both increase of carbon dioxide and deficiency of oxygen are factors.

2. Prolonged oxygen lack, administration of 30 p.c. and upwards of carbon dioxide, and repeated injections of acids produce a condition of narcosis.

3. Traube waves are seen during both oxygen lack and administration of carbon dioxide.

4. The results obtained suggest the existence of a common factor, probably the hydrogen ion content of the blood, underlying the action of oxygen lack and of excess of carbon dioxide upon nerve centres.

APPENDIX.

Note on the Action of Carbon Dioxide on the Spinal Cord.

In a former paper I stated that the effect of carbon dioxide administered by artificial respiration upon the skeletal muscle centres of the spinal cord was rather anomalous, since no movements were produced, in marked contrast to the action of oxygen lack or injection of acids(1). I have since found that this is largely a matter of concentration. The injection into the central end of the carotid artery of a spinal cat of defibrinated blood saturated with a mixture containing 25 p.c. carbon dioxide and excess of oxygen produces not only rise of blood-pressure but also vigorous scratch movements, and even slight convulsions. The action of carbon dioxide is thus brought into line

with those of oxygen lack and of injection of other weak organic acids, though a consideration of my remarks on p. 447 of the former paper will show that it affords only a partial explanation of the absence of response to carbon dioxide when given by the lungs.

The results afford evidence that the action of carbon dioxide on skeletal muscle centres is not confined to the respiratory centre, but is also capable of affecting the spinal cord; the action differs only in the respect that the medullary centre is much more sensitive.

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