THE EFFECT OF CEREBRAL ANÆMIA UPON BLOOD-PRESSURE AND RESPIRATION.

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In a previous communication (*This Journ.* 55. p. 346, 1921) it was shown incidentally and in confirmation of earlier workers that in the anæsthetised animal the sudden stoppage of the blood-supply to the brain by clamping the four arteries or by rapid bleeding from the abdominal aorta resulted in an immediate stoppage of respiration; the main effects of acute anæmia upon the respiratory centre was paralysis. In this paper are presented in more detail the effects of anæmia upon the medullary functions. Although a great amount of work has already been performed upon this subject it has been concerned almost entirely with the results immediate and remote of complete occlusion of the four main arteries. Even those such as Hürthle who have studied the effects of varying degrees of anæmia have confined their attention to the changes in blood-pressure and have neglected to enquire how far such changes as they observed were due to the action of the vaso-motor centre and how far to the action of the cardiac centre.

The principle followed in the experiments here described has been to subject the brain to a diminishing blood-supply by clamping the arteries supplying it, a record being taken where possible of the pressure of blood in the Circle of Willis, that is to say the pressure at which blood passes to the cerebral arterioles. The experiments were all performed upon rabbits and cats with exception of two upon dogs. The cats and rabbits were anæsthetised with urethane (1 gm. per kgm. body-weight), and some very lightly with C.E. mixture. For the dogs morphia was used. The experiments as performed upon the rabbit were as follows. A tracheotomy tube having been inserted, the subclavian artery was dissected out on each side so as to expose the origin of its branches. Of these the vertebral is the most proximal. The main artery was ligatured at a point just distal to its branches and a loose ligature passed round the artery proximal to the origin of the vertebral. In these pages the expression "clamping the subclavian" means clamping it at this point, a procedure which blocks all the branches without causing any indirect effects from the sudden stoppage of blood to the upper limb since the

main blood-supply to this part of the body has been permanently closed. The common carotid is then dissected out on each side and the thyroid and external carotid branches ligatured. Into one of the common carotids two cannulae are inserted, one pointing downwards in the usual way and used to record the aortic pressure, the other pointing upwards into the brain. The tube connecting this one with the mercury manometer is filled with normal saline since magnesium sulphate and the citrates are not without effect upon the vaso-motor and respiratory centres and would of course reach the medulla from the manometer, whenever the cerebral pressure were to fall. The other common carotid is prepared for subsequent compression by passing a loose ligature round it. For clamping the arteries small bull-dog clamps are employed of a strength just sufficient to ensure complete occlusion without causing damage to the vessels with subsequent thrombosis.

For recording respiration two methods were adopted. The one more generally adopted was to connect one limb of the Y-shaped tracheotomy tube with a tambour of the thinnest rubber. This method has the merit of giving a very sensitive though not standardised record of the rate and depth of respiration but it has the disadvantage of not recording the actual respiratory movements or the state of the chest at any given moment. When it was desired to record these the movement of the abdominal wall was registered by a lever connected to the abdominal wall.

The two essentials in experiments of this sort are that the method of registration should be sufficiently sensitive to record the smallest changes and that the medullary centres should not be depressed by the anæsthetic or by the preceding operative procedures. That these conditions were fulfilled was shown by the fact that when the animal was made to re-breathe its own expired air there was recorded after 30 seconds a well-marked and after 60 seconds a violent dyspnœa. That the centres were in a healthy condition was further shown by the good blood-pressure which was always obtained and by the presence of the usual reflexes characteristic of light anæsthesia.

The upper blood-pressure record gives, I believe, fairly accurately the existing pressure in the Circle of Willis except possibly when this pressure is very low. It responds readily to changes in the aortic pressure. In amount it averages, as Hürthle who was the first to use this method found, about two-thirds of the aortic pressure but it may as in Fig. 3 be much more. This is of course less than the normal since one artery is already tied. What the normal Circle pressure is, is not known. It cannot be determined, as Hürthle states, by taking a record from the

ophthalmic artery since this artery itself contributes blood to the Circle. It is probably not far below the aortic pressure.

The method of experimentation here adopted has several merits including those of simplicity and of rapidity in preparation, the animal being in a good state when the observations are being made. But the greatest merit is the unmistakeable origin of any phenomena observed. When the blood-supply is altered this is done in such a way that only the brain is involved for the blood-supply to the rest of the body is not interfered with except for the very small rise of pressure passively produced. The first changes in circulation and respiration must therefore be the direct results of ischæmia or anæmia of the brain and cannot be due to anything else. Later effects will of course have a more complicated causation. If, for instance, respiration is stopped by anæmia for some time, the effects which follow the re-admission of blood to the brain will be referable partly to the altered condition of the respiratory centre and partly to the altered condition of the blood. Such effects must therefore be interpreted with caution.

I believe that this method of experiment is superior for my purposes to the method of crossed-circulation. In the latter method there is a serious fallacy especially when it is applied to the dog. In the dog occlusion of the four main arteries to the brain does not lead to asphyxia owing, as L. Hill has pointed out, to the very free anastomosis which exists by way of the intercostal and anterior spinal arteries. The brain of the "fed" animal is therefore not exclusively supplied by the "feeder" but by both animals. It follows therefore that when the blood from the "feeder" is reduced the "fed" dog receives a proportionally larger amount of its own blood which will be at a different $H^{\cdot}$ ion concentration from that of the "feeder." To a lesser extent this objection applies also to the cat and rabbit for as will be seen later in these animals although occlusion of the four arteries produces violent disturbances of medullary function there is often a tendency to recover even while the arteries remain closed. In the rabbit too the quadruple ligature does not annul the Circle pressure.

I. *The circulatory effect.*

Clamping the carotid on the side not already blocked. When the opposite carotid is clamped there is in general a rise in aortic pressure. But this is not constant as Gaskell and Shore(1) state and in different animals it is very variable in amount being anything up to about 30 mm. (see Fig. 2). Sometimes in the cat there is a fall in pressure. The rise when it occurs is doubtless due partly to a passive

effect but not entirely. This is shown by the fact that the rise exceeds that which is produced on clamping an artery of equal size which does

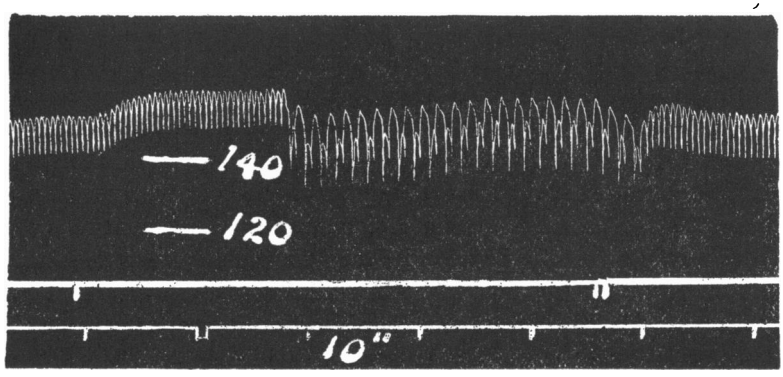

Fig. 1. Cat. Blood-pressure from femoral artery. Between the signals one of the carotids was clamped.

not supply the brain and also by the effect recorded below of cutting the vagi. Part and probably the greater part is to be attributed to the well-known sensitiveness of the vaso-motor centre to its own blood-supply. Whether this response is to the pressure or to the quantity of blood is a question not yet answered. What is the cause of the individual differences found? Those who have studied the reaction of blood-pressure to changes in posture have ascribed the individual differences to differences in the sensitiveness of the vaso-motor centre. The degree of anæsthesia however light no doubt is also partly responsible. But there is another factor which has never been taken into account and that is the concurrent effect upon the cardio-inhibitory centre. In the cat when a fall occurs there is obvious slowing of the heart (Fig. 1) and in the

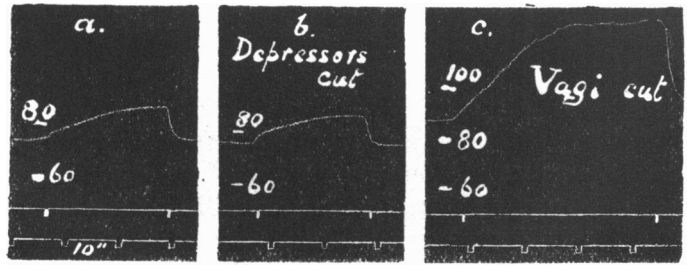

Fig. 2. Rabbit. Between the signals the carotid was clamped.

rise which usually occurs there is also some slowing. Thus slight anæmia sets in action the cardio-inhibitory as well as the vaso-motor centre and the differences shown by different animals may be attributed to the different sensitiveness of these two centres. The considerable effect of the cardio-inhibitory centre in reducing the rise is shown by cutting the vagi and then blocking the remaining carotid. There is then a much greater rise in blood-pressure and it is more uniform in different animals. The fact that in the cat there may be a primary fall of blood-pressure shows that the cardio-inhibitory action is not due to afferent impulses but is a direct action of anæmia upon the centre.

In the rabbit the results are the same except that with intact vagi there is no slowing of the heart. The vagi do however reduce the rise for when they are cut the rise as in the cat is much greater and more uniform in different animals. This reducing action is not due, or only to a small extent, to the depressors, for the rise is not increased after section of these nerves (cf. Fig. 2). It must therefore be due either to afferent depressor fibres in the vagus trunk or to direct stimulation of the cardio-inhibitory centre by the anæmia causing weakening but not slowing of the heart. From the analogy of the results in the cat and from the improbability of afferent fibres being stimulated I consider that the effect is direct. The individual differences which are found must therefore be ascribed chiefly to the varying degree in which the vagus centre is brought into play in different animals. It is well known that the vagus centre is powerfully stimulated when in a state of extreme anæmia or asphyxia but the fact that a slight diminution in blood-supply stimulates both vaso-motor and cardio-inhibitory centres simultaneously is one which if already known is not generally recognised.

This result leads to an interesting corollary. The sensitiveness of the vaso-motor centre to its blood-supply is generally regarded as the chief factor in the compensation of blood-pressure against disturbances due to gravity. The fact that this sensitiveness is also shared by the vagus centre suggests that an animal would compensate better with vagi cut than with vagi intact.

The effect of clamping the opposite carotid upon the pressure in the Circle of Willis has been studied by Corin(2), Hürthle(3), and Gaskell and Shore with inconsistent results. Gaskell and Shore working on the dog found a fall in pressure with no tendency to recover. Hürthle found a fall followed by partial recovery of variable extent. Corin found a fall only of momentary duration followed by a rise sometimes actually to a higher level than that which obtained before the occlusion.

This result is doubted by L. Hill(4) who believes that it could only occur if the original pressure were very low. Hürthle is also sceptical and rightly comments on the inadequate information given by Corin regarding the aortic pressure. In my experience closure of the carotid causes a lowering of Circle pressure which remains at the lower level if the aortic pressure does not rise. But if the aortic pressure does rise the Circle pressure tends to recover slightly and in some cases up to its original level. Rarely however Corin's paradoxical result occurs. Clamping the carotid while producing a rise in aortic pressure causes a rise in Circle pressure to a height well above its previous level, the high pressure remaining until the artery is released (Fig. 3). It is difficult to

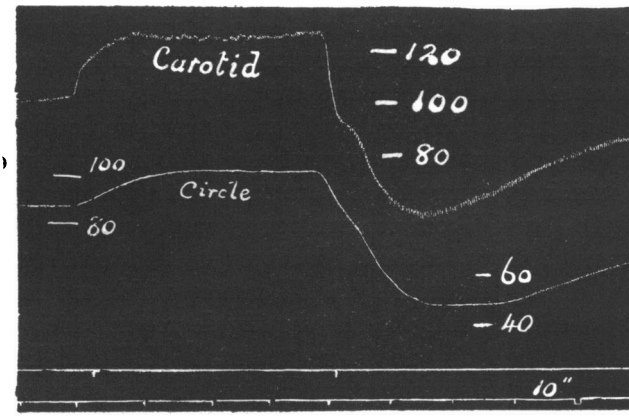

Fig. 3. Rabbit. Between the signals the carotid was clamped. This tracing has been touched up for the purpose of photographic reproduction but the general contour has not been altered.

give an adequate explanation of this phenomenon but it may be that in these cases the supply of blood by the vertebrals was unusually great and that the rise in aortic pressure increases the pressure in the Circle. A very free vertebral contribution is certainly indicated by the remarkably high Circle pressure which obtains in these cases before any of the arteries are closed.

Clamping of one of the subclavians tends to produce in comparison with clamping of the opposite carotid an equivalent fall in Circle pressure but a smaller rise in aortic pressure. This fact also appears from an analysis of Hürthle's figure but he makes no comment on it.

Severe anæmia. In the rabbit with two carotids already clamped, closure of one of the subclavians produces usually a fall in Circle pressure

and a further slight rise in aortic pressure. If now the subclavian of the other side be also closed there occurs a sudden and well-marked rise in aortic pressure together with a profound fall in Circle pressure. A typical example is seen in Fig. 4. The aortic pressure commonly reaches a height of over 180 mm. Vagal inhibition then sets in with well-marked slowing of the heart. This causes a steady fall in pressure until the heart fails, the same picture in fact that is seen in ordinary asphyxia. In those cases in which the pressure was already high, clamping of the fourth artery causes very little further rise for vagal inhibition sets in at once. General muscular spasms and convulsive movements are liable to occur as previous workers on this subject have described but they are by no means constant.

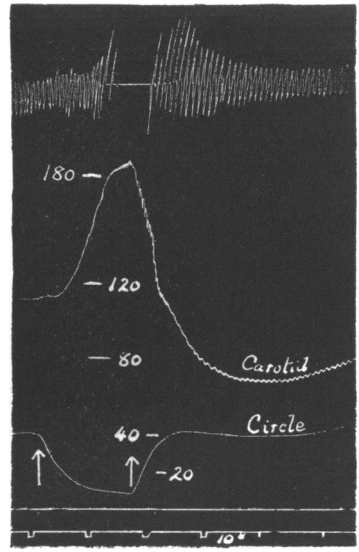

Fig. 4. Rabbit. At the first arrow the R. subclavian was clamped, the other arteries being already closed. At the seond arrow the carotid was opened.

The Circle pressure does not fall to zero. There is, in agreement with the results obtained by Hürthle and by Gaskell and Shore, a residual pressure of between 18 and 6 mm. There is therefore still some blood flowing into the medulla under these circumstances as Gaskell and Shore demonstrated by subsequent injection. Moreover there is evidence which will be shown below that medullary function sometimes recovers though in a modified form while the arteries are still clamped. On the other hand the tendency to recover bears no relation to the height of the residual Circle pressure and such collateral circulation as must persist does not influence the manometric reading of the Circle pressure for the tracing does not show any change even with the most violent changes in aortic pressure.

It is stated by L. Hill(5) that the bulbar centres are first excited and then paralysed but that when the anæmia is slow in onset the excitatory symptoms fail to appear. I have put this to the test by subjecting the brain to a very gradual reduction in its blood-supply by closing the carotid very slowly with a screw-clamp, the other arteries having been closed. When this is done the great rise in pressure which occurs on

sudden clamping is absent but this is due not as Hill thinks to an absence of stimulation of the vaso-motor centre but to the fact that vagal stimulation by the anæmia sets in earlier. After section of both vagi the rise in pressure is just as great whether the fourth artery be clamped suddenly or gradually. The effect of gradual clamping with the vagi intact is shown in Fig. 5. There is therefore no doubt that extreme

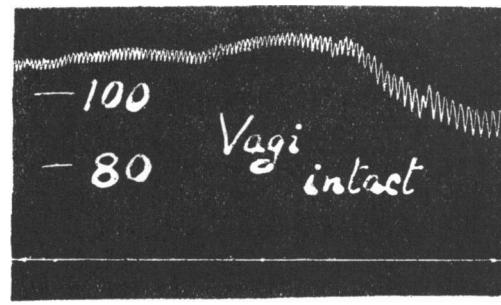

Fig. 5. Cat. This shows the terminal part of gradual clamping of the fourth artery begun three minutes earlier when the pressure was 92 mm.

anæmia is a strong and direct stimulus both to the vaso-motor and to the cardio-inhibitory centre. The rise in pressure when the vagi are cut is not however proportionate to the degree of anæmia. There is a critical Circle pressure of between 18 and 6 mm. at which reduction in blood changes from being a slight to a powerful stimulus.

Recovery. Recovery in blood-pressure is always immediate. When blood is restored after a short occlusion, that is while the pressure is still high, there is a sudden fall in pressure to a subnormal level followed by rise to normal (Fig. 3). When the occlusion has lasted until the pressure is subnormal owing to cardio-inhibition, provided that there is no heart-failure, restoration of blood causes an immediate rise of pressure to the normal partly through the termination of cardio-inhibition (Fig. 10). As a rule the vaso-motor and cardio-inhibitory centres recover simultaneously.

The part played by the suprarenals has not been investigated but the complete absence of any after-effects or delay in the restoration of blood-pressure points to the fact that a possible liberation of adrenalin due to the cerebral anæmia plays very little, if any, part in the rise of pressure.

II. *The respiratory effect.*

Hæmorrhage. Before dealing with the main part of this section a word is necessary on this subject. It is stated by Gesell(6) that

pulmonary ventilation varies inversely as the blood-pressure. Mainly upon this statement he builds a new theory of the regulation of respiration according to which the metabolism of the respiratory centre is a factor to be taken into account under normal as well as under abnormal conditions. The centre according to this view is influenced not only by the blood reaching it but by the products of its own metabolism. These products are two acids, CO_2 and a fixed acid which is probably lactic. The increased respiration which is said to follow anoxæmia is brought about by diminished oxidation leading to increased acid formation there, such acid through delay in its removal playing a part in the stimulation of the centre. On this view the effective stimulus to the centre would appear to be the actual acidity or hydrogen ion concentration of the centre which is the sum of the acidity of the arterial blood plus the acidity contributed by the metabolism of the centre. When the amount of blood supplying the centre is diminished the removal of products of metabolism from the centre is defective with the result that the centre is stimulated to greater activity. Gesell's main evidence for his theory is the fact recorded by Gesell, Capp and Foote(7) that pulmonary ventilation varies inversely as the blood-pressure. The actual observation upon which this assertion is based reads as follows. "The effect of hæmorrhage on pulmonary ventilation...varied considerably. In some instances hæmorrhage had little or no effect on the pulmonary ventilation of room air and in other instances small hæmorrhages markedly increased the ventilation." And again, "Hæmorrhage and injection (of gum-saline) which elicited the usual respiratory responses not infrequently were accompanied by no or small alterations in the mean blood-pressure."

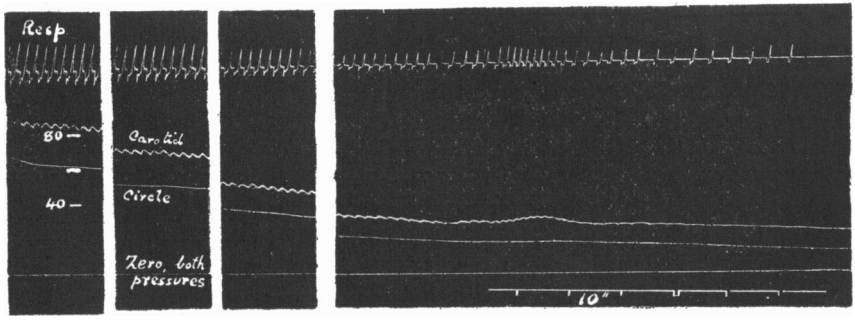

Fig. 6. Rabbit. Hæmorrhage from the abdominal aorta. Between the first and second and between the second and third are intervals of ½ min.; between the third and fourth, 1 minute.

In view of the far-reaching conclusions which Gesell draws and the dubious nature of the experimental evidence upon which they are based I have thought fit to re-investigate the effects of hæmorrhage on respiration. Rabbits and cats were bled into a compensating tube tied into the lower part of the abdominal aorta. Fig. 6 shows the typical result obtained in the rabbit, the hæmorrhage in this case lasting three minutes. It will be seen that so far from there being an increase in respiration there was a decrease both in rate and depth except for a slight transient hyperpnœa which preceded complete apnœa. The hyperpnœa occurred at an aortic pressure of 32 mm. and a Circle pressure of 18 mm. In the cat (Fig. 7) a similar state of things is observed except that the stage of

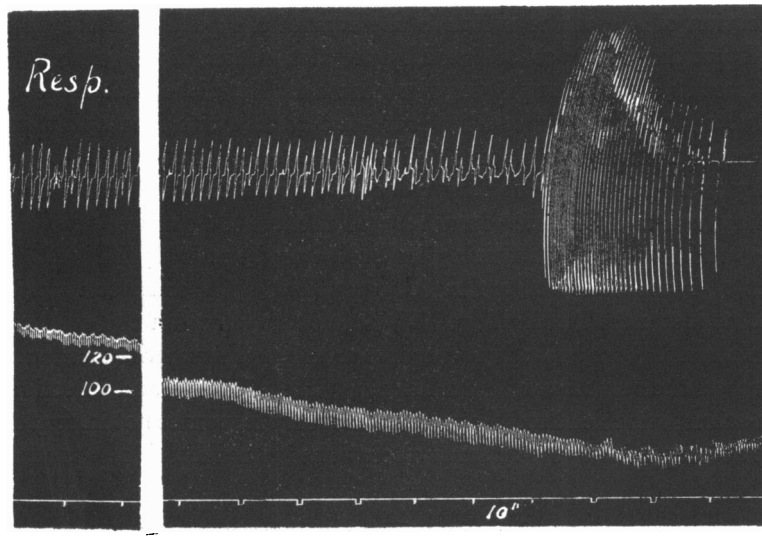

Fig. 7. Cat. Hæmorrhage from the abdominal aorta. Between the sections an interval of one minute.

hyperpnœa is more marked. It occurs however only when the pressure has reached a very low level. On restoring the blood (Fig. 8) respiration is resumed in a staircase manner. From such experiments as these the changes produced by the hæmorrhage are so complex and wide-spread that it would be unjustifiable to refer any respiratory effects to the direct effect of a diminished blood-supply upon the centre. But the fact brought out that pulmonary ventilation does not vary inversely with blood-pressure completely negatives Gesell's assertion and shows that his theory is without experimental foundation.

Occlusion of the vessels. When the respiratory effects are investigated the fact which stands out most prominently is that the respiratory centre

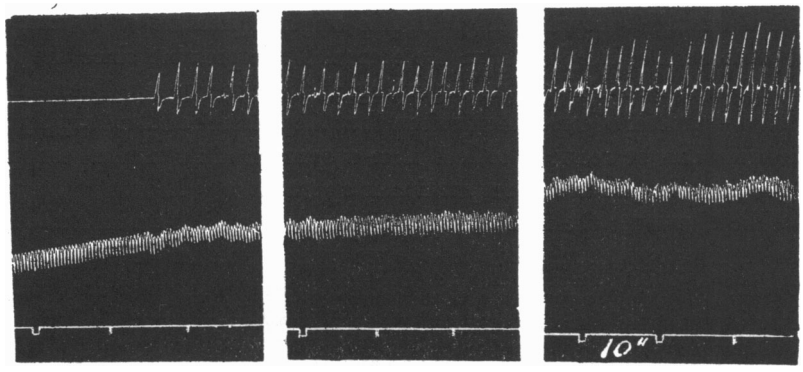

Fig. 8. Cat. Recovery by return of blood. Between the sections intervals of $\frac{1}{2}$ minute.

can withstand, without in the least modifying its action, a very considerable reduction in its blood-supply. When as many as three out of the four arteries are clamped there is no change of any kind in the rate

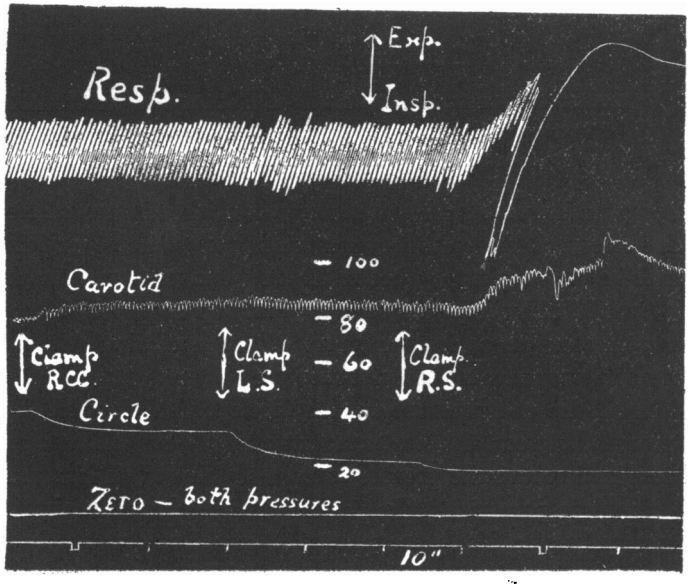

Fig. 9. Rabbit. Description in text.
R.C.C., right common carotid. *L.S.* and *R.S.*, left and right subclavians respectively.

or depth of respiration, whether the artery which remains open is one of the carotids or one of the subclavians. Such reduction in blood-supply brings the Circle pressure down to about 22 mm. as for instance in the typical example shown in Fig. 9. The original pressure of 40 mm. in this case is of course less than the normal Circle pressure since the left carotid had been tied at the beginning of the experiment. The results of a large number of experiments show that the pressure of blood supplying the brain can be reduced to less than a quarter of its normal amount before any disturbance of respiration is apparent.

When however the fourth artery is clamped respiration immediately ceases. The stoppage may be absolutely abrupt (Fig. 4), or the respiratory movements may undergo a rapid reduction in depth with or without reduction in rate. In other cases the respiratory movements may at the

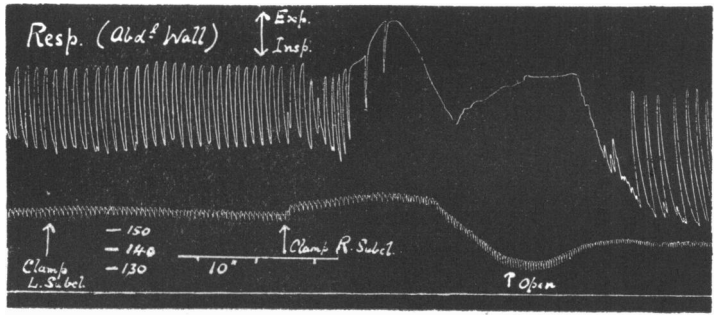

Fig. 10. Cat. Movement of abdominal wall recorded.

last undergo an increase in depth sometimes with diminished frequency but such increase is never more than transitory and never lasts more than six or seven respiratory beats. There is never a well-marked and prolonged period of hyperpnœa, such as would be expected to occur were the respiratory centre as it runs short of oxygen being stimulated by products of its own incomplete metabolism.

To judge from the pressure in the Circle of Willis there is a very narrow margin between the least amount of blood sufficient to maintain normal respiration and the greatest amount which is still insufficient to prevent complete paralysis. Fig. 9 for instance shows respiration continuing normally at a Circle pressure of 22 mm. but completely stopped at a pressure of 18 mm. There is therefore as for the vaso-motor centre a critical pressure below which respiration is violently disturbed. The actual pressure varies slightly in different animals but in any individual

the pressure which is critical for the vaso-motor centre is critical also for the respiratory centre. The effects upon these two centres are simultaneous but opposite, respiration ceasing but blood-pressure rising at the same moment. In Fig. 9 the rise in pressure was counteracted to a considerable extent by cardio-inhibition.

It may of course be said that both centres are in reality affected in the same way, there being a tonic contraction of peripheral muscles in both cases, that is to say the respiratory muscles and the arterioles. Hill for instance speaks of respiratory spasm and vaso-motor spasm. What usually happens is shown in Fig. 10 in which the actual movements of respiration are recorded. Respiration comes to a stop in full expiration. Whether or no this can be described as respiratory spasm the physiological effect is that pulmonary ventilation is completely inhibited.

A word is necessary concerning the hyperpnœa which as we have seen sometimes precedes the apnœa. Since it tends to occur just as the medulla is running short of blood it might be thought to be due to stimulation of the respiratory centre by the acid products of incomplete metabolism. Were this the cause the hyperpnœa should be more marked the more gradually the anæmia is brought about. But the reverse is the case at any rate in the rabbit.

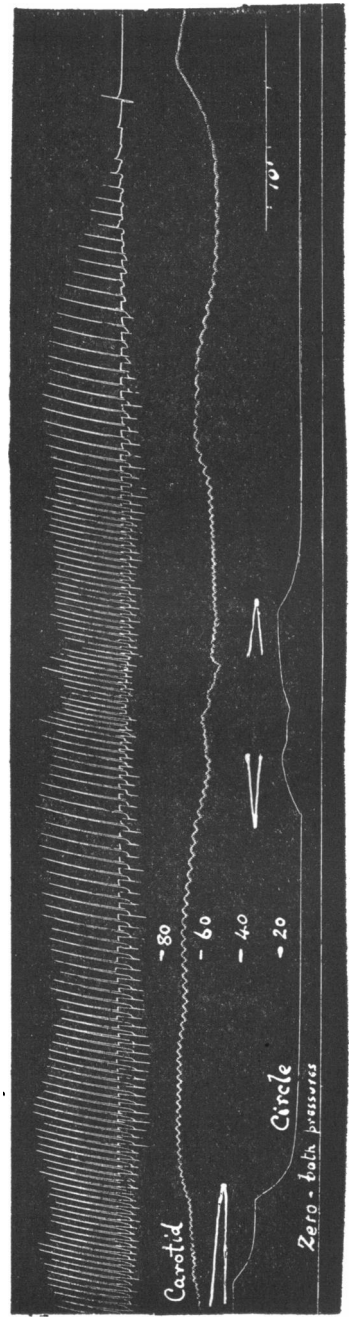

Fig. 11. Rabbit. Description in text.

Fig. 11 shows the result obtained when the fourth artery is closed by a screw-clamp very gradually. Narrowing of the clamp is shown by the mark > and widening by the mark <, the direction of the change being also indicated by the record of Circle pressure. It will be seen that although there may be very slight increase in depth as the blood-supply diminishes the main effect is a well-marked reduction in rate with restoration of rate as blood is re-admitted. The rate of respiration that is to say can be controlled by varying the blood-supply. In other words the respiratory centre is active only inasmuch as it is supplied with a sufficiency of blood. Sudden anæmia therefore produces conditions which gradual anæmia does not. One is reminded here of the effect of sending a current of gradually increasing intensity into a nerve.

Recovery. If the blood has been shut off only for a few seconds then on re-admitting blood respiration re-starts usually abruptly with hyperpnœa which is due probably to the increased hydrogen ion concentration which the blood has undergone during the apnœa. If on the other hand the anæmia has been allowed to continue the apnœa continues while the blood-pressure falls from vagal inhibition and in this way the animal dies with or without the terminal gasps characteristic of asphyxia. More frequently however respiration re-commences even while the arteries are still clamped. This occurs about half a minute after the beginning of complete occlusion and while the blood-pressure is still high. Each respiratory movement consists of a sudden deep inspiration followed directly by expiration and afterwards a pause. One must assume that in these cases there is established a degree of collateral circulation sufficient to allow the respiratory rhythm to be partially restored and at the same time to prevent excessive stimulation from lowering the blood-pressure. In some instances this state of things would appear to be capable of continuing if not indefinitely at any rate for a long time. In others the gradual fall in pressure and the ever-widening intervals between the respiratory movements lead to death. It may be remarked that in successive occlusions and releasing of the fourth artery the respiration starts more and more readily indicating an increasing collateral circulation.

When to a medulla in this state of modified activity blood is re-admitted blood-pressure as a rule immediately falls to normal. Respiration is restored to normal at the same time or shortly after. Of the way in which it is restored I have already given a brief account(14). In some cases there is merely a rapid quickening up to the normal rate. Very frequently recovery takes place as shown in Fig. 12. On opening an

artery there is first a momentary suppression of the previous rhythm as though the first effect of increased blood-supply were an inhibition.

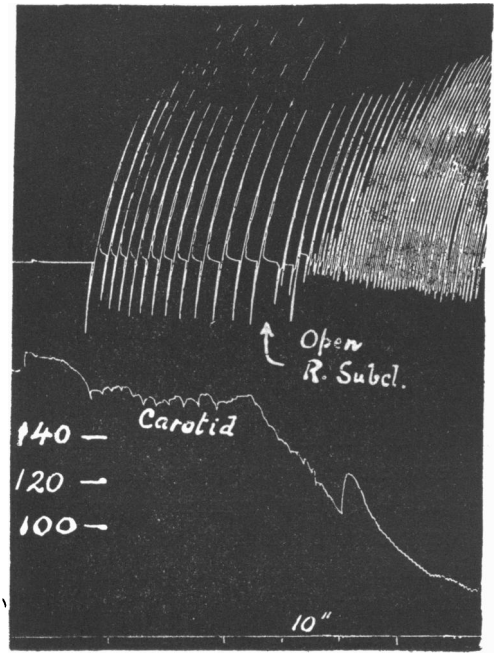

Fig. 12. Rabbit. Description in text.

Then respiration is resumed at a quicker rate. After a couple of breaths there appears an interpolated beat which, beginning as a very weak beat, progressively increases in strength up to that of the original beat. In one case I have noted the sudden suppression of the interpolated beat on again clamping the fourth artery. Sometimes the beat may be approximately doubled in rate suddenly as occurred in the case shown in Fig. 13 when the left vertebral was opened. The slight improvement in the blood-supply which this procedure caused is shown on the tracing of Circle pressure. On subsequent opening of the left carotid an interpolated rhythm set in so that in effect the original beat was first about doubled then about quadrupled. These phenomena appear to me to indicate that the central mechanism of respiration resembles the heart-beat in that it consists of two processes, the initiation and the conduction of a disturbance. In recovery from anæmia we observe in those cases where the rate is progressively quickened a recovery in initiation with normal

conduction and in those cases in which an interpolated rhythm appears gradual recovery in conduction.

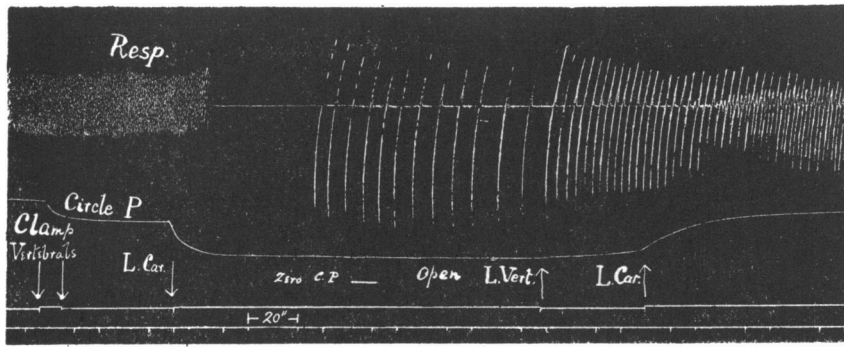

Fig. 13. Rabbit. Description in text.

Lumsden(8) in a recent series of papers has expressed the view that there are three centres concerned in respiration; the lowest or "gasping" centre; above this an "apneustic centre," which when uncontrolled causes respiration to take the form of prolonged inspirations; above this again, in the upper part of the pons, a "pneumotaxic" centre which produces normal respiration by periodic inhibition of the apneustic centre. The effects of occlusion in the cat are according to Lumsden as follows: "About half a minute after the blood is completely shut off the pneumotaxic centre fails, respiration becomes slow and then apneustic in type, a long inspiratory tonus is followed by a few short failing apneuses. Very soon gasps alone occur and death results. If however...the vertebrals are freed before gasping ceases, recovery takes place in the reverse order. Gasps give place to short and then to long apneuses; by periodical inhibition of these, slow respiration and soon normal breathing result." The arteries clamped by Lumsden were the carotids and vertebrals. My experience agrees with that of Hill in that the majority of cats survive the ligature of the arteries owing to the anastomosis which exists or becomes established through the other branches of the subclavians. In my experience too, respiratory effects if they are forthcoming at all always begin to manifest themselves within a second or two of the quadruple ligature. In those cases in which any delay occurred subsequent investigation showed that the occlusion had not been complete. Respiration always ceases and recovers in the ways which I have described. I have never seen either after occlusion or during recovery

a form of breathing which Lumsden calls apneusis. How the chest comes to stop in full expiration has been already described and illustrated in Fig. 10 where the actual movement was recorded. It is true that the return of respiration on re-opening an artery may take the form of sudden gasping inspirations. This fact might at first sight appear to be evidence in favour of a separate gasping centre such as Lumsden postulates. But these gasps instead of giving way to another form of respiration soften down regularly into ordinary quiet breathing. In some instances a more complex phenomenon is seen. Respiration recovers first in the form of deep gasps. On re-opening an artery the gasps quicken and between the gasps appear a normal respiration so that gasping and breathing take place alternately. Then there occur two breaths to a gasp, then three breaths and so on. Meanwhile the gasps diminish in depth progressively and themselves become gradually converted into normal respiration taking their place in the regular sequence. These results, I think, are evidence that gasping is to be regarded as a modification of the normal respiratory beat and not a form of respiration due to the uncontrolled action of a separate centre normally in abeyance. My experiments in fact lend no support to Lumsden's conception of the respiratory mechanism.

The respiratory centre is more readily damaged by anæmia than the vaso-motor. When the respiration has remained in abeyance during prolonged occlusion its resumption when blood is restored is often delayed though the blood-pressure recovers immediately. When the circulation and respiration are so depressed that artificial respiration has to be resorted to blood-pressure is always the first to recover.

Differences in different species. A word is necessary about the differences shown in the rabbit, cat and dog. In the cat it is, in my experience, despite Hürthle's evidence to the contrary, a matter of considerable difficulty to obtain a satisfactory record of the Circle pressure, owing to the extreme fineness of the internal carotid in this animal. I have attempted to take a record from the upper end of the vertebral but the results have not been satisfactory owing, I believe, to the many branches given off by this artery before it terminates in the basilar. I have not succeeded in the cat in controlling the rate of respiration by controlling the medullary blood-supply. As already stated it is more difficult to disturb function in the cat than in the rabbit owing to the freer collateral circulation which the cat possesses. In the dog it is impossible to do so. When in this animal the carotids and subclavians together with all their branches are clamped the Circle pressure is still remarkably high owing

to the very free anastomosis by way of the intercostal and spinal arteries. I see no reason for believing that there is any real difference in the central mechanism of respiration in these three species. Such differences in effects produced are due I believe to differences in blood-supply.

III. *The effect of lactic acid upon the anæmic medulla.*

It has often been stated that under special conditions the respiratory centre can be stimulated by lactic acid arising within it through deficient oxygen supply. Starling(9), for instance, quotes an experiment in which a rabbit was exposed to a low oxygen tension. On subsequently giving oxygen the disappearance of the hyperpnœa was immediate. Since exposure to low oxygen tension for a short time does not cause any lactic acid to appear in the blood the conclusion is drawn that if lactic acid were the cause of the hyperpnœa it must have been produced in the centre. Again, the fact that the rise in alveolar CO_2 after breathing an atmosphere deficient in oxygen was initially rapid suggested to Haldane and Poulton(10) that "most of the lactic acid which excited the centre was formed in the centre itself," and that the acid was either rapidly oxidised or washed away by the more alkaline blood which circulates very rapidly through the centre. Then there is the well-known hypothesis advanced by Douglas and Haldane(11) to explain the Cheyne-Stokes respiration which sometimes follows the apnœa due to excessive breathing. The centre suffering from oxygen want owing to the apnœa is stimulated by the lactic acid formed within it. "It is probable," write Haldane and Poulton, "that when the amount of oxygen is extremely low lactic acid is produced in the centre itself. It is perhaps the formation of lactic acid in the respiratory centre which actually terminates the apnœa after forced breathing." All these statements rest upon two assumptions; first, that lactic acid appears in the centre under the circumstances of the experiments; second, that were lactic acid so produced an anoxæmic centre would be capable of being stimulated by it. Neither of these assumptions has ever been proved. The first rests, apart from the post-mortem formation of acid in the brain, only upon the very dubious experiments of Langendorff(12). That the second assumption is not warranted is shown in Fig. 14. The record is taken from the rabbit prepared in the usual way. As the result of closure of the fourth artery (at *A*) the blood-pressure rose and reached a level of about 110 mm. while respiration stopped, in this case without any preliminary hyperpnœa, except for a few occasional gasps. At *B*, 7 mgms. lactic acid in 0·7 Ringer (previously boiled to exclude oxygen in solution) was injected

brainwards into one of the carotid arteries. There is no doubt that the lactic acid reached the medulla for there occurred the momentary inhibition of the heart which is liable to occur whenever anything is injected into the carotid. This was followed immediately by a further rapid rise of blood-pressure to 140 mm. The obvious super-imposition of this rise upon the first, following as it does directly upon the injection, must point to stimulation of the vaso-motor centre by the acid. Mathison(13) produced vaso-constriction by injection of lactic acid into the carotid, the other arteries being open. He therefore believed that the vaso-motor centre could be stimulated by lactic acid produced within it. My experiments support his contention. At any rate it is clear that an anæmic centre no less than one which has a free blood-supply can be stimulated by lactic acid.

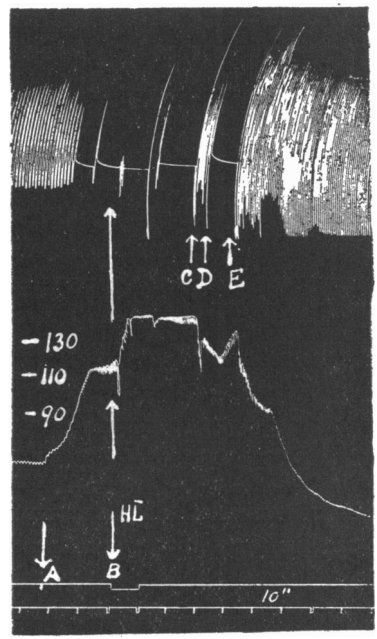

Fig. 14. Rabbit. Description in text.

In striking contrast with the vaso-motor is the respiratory centre. There is no reason to believe that injected substances diffuse with more difficulty into the respiratory centre than into the vaso-motor centre yet the former shows no sign of stimulation. It remains quiescent except for the gasps at regular intervals which had set in before the lactic acid was injected. At *C* the carotid was momentarily opened. Note the sudden fall in pressure and resumption of respiration to be stopped once more upon closure of the artery at *D*. The rapidity of respiration during this period may have been due, in part at least, to the presence of the injected acid in the medulla. At *E* blood was again admitted. This experiment therefore shows that the respiratory centre when quiescent from want of oxygen completely fails to respond to the presence of lactic acid in amount sufficient to stimulate the vaso-motor centre. It is therefore very unlikely that the centre would respond to lactic acid produced within it. This experiment shows incidentally one more point of difference between the respiratory and vaso-motor centres.

Discussion of results.

The experiments described above have some bearing upon three questions affecting the respiratory centre. First, there is the effect of anoxæmia upon it. The balance of opinion upon this much-debated question is in favour of the view that want of oxygen is a stimulus to the centre. This view is based upon the results of experiments in which men and animals have been made to breathe atmospheres deficient in oxygen. Under these conditions, however, the centre is affected not only directly by the anoxæmia but also indirectly by the changed state of the blood due to anoxæmia in the whole body. In the experiments here described the rest of the body apart from the brain is not primarily affected and therefore any respiratory changes noted must be directly produced. The two kinds of experiment further differ in the fact that while in the breathing experiments there is brought about (though only primarily) a pure deficiency in oxygen, in these experiments what is altered is the quantity of blood. It is reasonable however to assume that reduction in quantity of blood produces its effects through insufficient oxygen. The very considerable reduction in blood to which the centre remains indifferent must involve a diminution in oxygen at least equal to if not more than that which obtains in the experiments in which a deficient oxygen supply is breathed. Unless the centre is indifferent towards a much diminished blood-supply at full oxygen saturation, while it is easily influenced by a normal blood-supply at low saturation, we are forced to the conclusion that anoxæmia has no direct effect upon the centre and that such effects as have been observed in the breathing experiments have been indirectly produced. The fact that in my experiments the respiratory centre responded vigorously to re-breathing of the expired air shows that the negative result could not have been due to the anæsthetic, for it is very unlikely that the centre would retain a high sensitiveness to CO_2 while its sensitiveness to oxygen-want was in any degree impaired.

The second point concerns the metabolism of the centre. No direct determination of the metabolism of the central nervous system has yet been satisfactorily performed. The indifference of the respiratory centre to diminution in its blood suggests that the group of cells of which this centre is composed has a comparatively low rate of metabolism.

Thirdly, as regards the nature of the respiratory centre. Those who have postulated that under conditions of defective oxygen supply there is accumulated in the centre an amount of lactic acid sufficient to

stimulate the centre, have argued from analogy with the appearance of lactic acid in muscle stimulated artificially under anaerobic conditions. In doing so they have tacitly assumed that the respiratory centre is a reflex organ, which has activity forced upon it as in the case of muscle in the experiments of Fletcher and Hopkins. But the fact that the main effect of insufficient blood upon the centre is diminished or suppressed function is evidence in favour of the view that the centre is essentially automatic though subject to modification by afferent impulses. The amount of lactic acid which at most could be produced within it would therefore be equivalent not to the amount formed in stimulated muscle but to the extremely small amount found in resting (anaerobic) muscle.

The most striking fact brought out in the above experiments is the contrast between the properties of the respiratory centre and those of the vaso-motor together with the cardio-inhibitory centre. The respiratory centre while very sensitive to the amount of CO_2 or the hydrogen ion concentration of the blood is insensitive to the quantity of blood, while the vaso-motor centre is far more sensitive to the quantity of blood than to the acidity; the respiratory centre is paralysed by extreme anæmia, while the vaso-motor centre is strongly stimulated; finally the respiratory centre when quiescent from extreme anæmia is insensitive to the injection of acid, a procedure which excites the vaso-motor centre to further activity. The two groups of cells which control the two great functions of respiration and circulation behave towards nutritional disturbances in a diametrically opposite manner. This fact is sufficient to show that phenomena relating to the incomplete metabolism of excised muscle are not necessarily the same in the nervous centres.

Conclusions.

1. Both the vaso-motor and cardio-inhibitory centres are directly stimulated by a slight diminution in their blood-supply. The resulting inhibition checks and sometimes annuls the rise of pressure which vascular constriction tends to produce.

2. Rarely the pressure in the Circle of Willis can be raised by the occlusion of a cerebral artery.

3. The respiratory centre is totally insensitive to diminution in its blood-supply until this diminution becomes extreme.

4. There is a certain critical Circle pressure varying between 18 and 6 mm. in different individuals, at which the respiratory centre is paralysed and the vaso-motor centre strongly stimulated. Stimulation of the cardio-inhibitory centre immediately follows.

5. The apnœa is sometimes preceded by transient hyperpnœa but this is not caused by defective oxygenation of the centre since it does not occur when the reduction of blood-supply is gradual.

6. When the reduction in blood-supply is gradual the blood-pressure rises but slightly owing to the fact that the cardio-inhibitory centre is stimulated simultaneously with the vaso-motor centre.

7. At low cerebral pressures the rate of respiration can in the rabbit be controlled by regulating the blood-supply.

8. Evidence is presented which suggests that under conditions of defective nutrition discharges from the respiratory centre may suffer a decrement and be suppressed somewhere on their way to the periphery.

9. Gasping is a modification in the nervous mechanism acting as a whole and is not due to the action of a separate centre.

10. When the medulla is completely or almost completely anæmic, injection of lactic acid directly into a cerebral artery stimulates the vaso-motor centre but is without effect upon the already paralysed respiratory centre.

11. Hæmorrhage is not attended with any increase in breathing until a very low pressure is reached. Hyperpnœa of variable degree then occurs.

12. The differences in the results found in rabbits, cats and dogs are due to differences in blood-supply.

13. The metabolic processes occurring in the respiratory centre play no part in controlling the rate and depth of respiration.

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