THE REGULATION OF RESPIRATION. Part I.

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In two previous articles (1), four respiratory centres were located, namely, the gasping centre at the nœud vital, Fig. 1 (5–6), the expiratory centre just above this, Fig. 1 (4–5), the apneustic centre which gives rise to inspiratory tonus (apneusis) and is placed at the level of the striæ acousticæ, Fig. 1 (3–4), and the pneumotaxic centre in the upper half of the pons, Fig. 1 (1–2), which produces respiration of normal type by periodically inhibiting apneusis. The present paper deals with the chemical, and afferent nervous, influences which regulate the activity of centres 1, 2 and 3.

Gasping. The influences affecting gasping may best be studied after all the higher centres have died, or have been eliminated by section of the brain stem at level 5, Fig. 1.

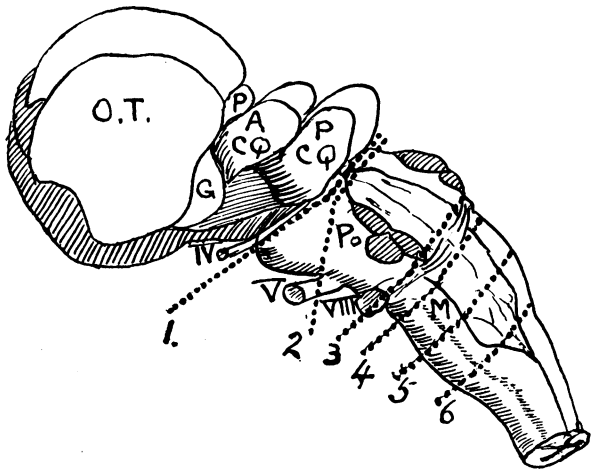

Fig. 1. Diagram of brain stem showing level of crucial sections.

When investigating the chemical influences, it is best to employ continuous ventilation of the lungs with various gases, as indicated in my second article (1). Even so, if the brain stem has been divided at

level 5, the unsatisfactory circulation resulting from this section complicates matters: while if such a section has not been made, it is difficult to be certain that the higher centres are completely out of action. This is a point of essential importance, since vagal stimulation, for instance, produces entirely different results on gasping, according as the higher centres are dead, or are simply in abeyance, so that they still retain some inhibitory power over the gasping centre. A good deal can, however, be learned from the study of gasping as it occurs during apneustic respiration, since the gasping centre is then well nourished, and the normal inhibitory power of the higher centres can be much diminished by vagotomy.

Although even after Section 5, gasping may continue for 15 to 30 minutes, well controlled results are difficult to obtain. The blood-pressure, already low, is steadily falling, and the circulation through the nœud vital is becoming more and more unsatisfactory. There is thus a constant tendency for O_2 to be so seriously lacking, and CO_2 to be so much in excess, that only when gasping is proceeding very briskly can we expect any increase of it by further diminishing O_2, or increasing CO_2. More often, one is compelled to seek evidence by improving, rather than by aggravating the condition of the blood. Further, the activity of gasping often varies more in accordance with the vitality of the centre, than with anything we can do to stimulate it. Hence it is only by very frequently repeating experiments in similar conditions, and by careful interpretation of the results, that conclusions of any cogency can be drawn. Some illustrative experiments may be given.

When a dog whose brain stem had been severed at level 5, was made to breathe into a small closed space (football bladder) the rate though not the height of the gasping was markedly increased (from 8 to $10\frac{1}{2}$ per minute). When oxygen alone was lacking (the animal breathing N_2 through valves), again the gasping became rapid, but to a less degree (9 per minute). In each case the effect took about a minute to come on, and to pass off. The blood-pressure gradually fell when O_2 was diminished, and rose again slightly when air was supplied, but it never exceeded 30 mm. Hg. The experiment indicates, that O_2 lack, even without excess of CO_2, stimulates the gasping centre, an observation strongly supported by a number of other facts. The stimulation was stronger when CO_2 was at the same time in excess, but the more active state of the centre at the beginning of the experiment would to some extent account for this.

In an experiment on a cat whose brain stem was divided between levels 4 and 5 (Fig. 1) the gasping centre was in good condition; here the

addition by continuous ventilation of 12½ p.c. of CO_2 and a further 2 p.c. of O_2 to the 73 p.c. of O_2 previously employed immediately increased the rate of gasping 50 p.c., from 6 to 9 per minute. Later, the response of the centre to various gases was negligible, which emphasises the remarks above made on the care with which conclusions must be drawn. When only 10 p.c. of oxygen was perfused through the lungs, the gasps did not quicken as might be expected, they simply began to fail from the lessening vitality of the centre, which somewhat improved again on 73 p.c. O_2, so that the gasping became more brisk and frequent.

In a cat which died by circulatory failure due to excess of ether, though the heart could not be re-started, yet by constantly massaging it, sufficient circulation was kept going to re-awaken gasping after it had ceased for 13 minutes. At first artificial respiration with the pump and later continuous ventilation with CO_2 18 p.c., O_2 30 p.c. was carried out and gasping continued for half an hour. If during this period the cardiac massage was stopped gasping doubled in rate within 10 seconds and resumed its normal rate the instant massage was recommenced. This effect must have been due to lack of O_2, since CO_2 was in any case in great excess. The experiment also indicates the very rapid response of the gasping centre to changes in the circulation.

Another observation of interest was made on a cat during recovery of respiration after compression of the vertebral arteries, one carotid being left open. Gasping had given place to apneuses with gasps superimposed (the vagi had been cut previously) and later, respiration of normal type had been resumed, but with here and there a gasp superimposed on the inspiration. The animal was next made to breathe my expired air from a large bag (*i.e.* CO_2 5 p.c., O_2 16 p.c.), the gasps increased markedly. Pure oxygen was now supplied, the superimposed gasps ceased within half a minute, leaving the respiration normal (Fig. 2).

The rate of gasping lessens during and after artificial respiration, which confirms the evidence adduced above that the centre is influenced to some extent by the chemical composition of the blood. I have never been able to produce apnœa when the higher respiratory centres were dead. It is found that even when in a fresh and healthy animal, the first cut is made at level 5, gasping occurs instantaneously, although there could have been no great impurity of the blood either in the way of O_2 lack or CO_2 excess. Both these observations point to the gasping centre being when uninhibited either highly automatic or else sensitive to even moderate lack of O_2 and excess of CO_2.

During apneustic respiration when gasps are superimposed on the

apneuses, they can be made to lessen or disappear by supplying plenty of oxygen, and they increase again if oxygen is withheld. Here part of

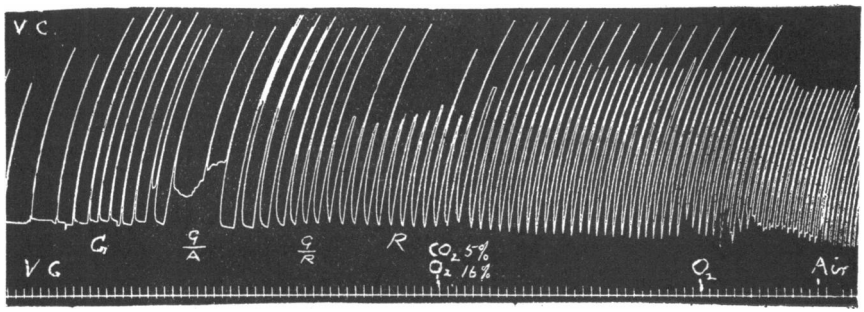

Fig. 2. Cat. In this and the following figures, the upward line is inspiration, and the time tracing 5 sec.

the effect is probably due to the increased or lessened inhibition of gasping by the strengthening or weakening of the apneustic centre as the result of the free supply of oxygen or lack of it. In a particular instance of this sort the blood-pressure remained high, though gradually falling from 200 mm. to 160 mm. The gasps on the apneusis occurred on air breathing at a rate of 5 per minute at first; as oxygenation lessened this rate gradually rose to 8. When pure oxygen was supplied the rate lowered to 6, while when H_2 was breathed the rate rose to 10 and the apneusis ended.

It is known that in man sudden powerful stimulation of almost any afferent nerve, especially if it causes pain, may evoke a typical gasp. Electrical stimuli applied to the nœud vital have a similar effect, so that the above results may depend partly on cerebral inhibition of the higher respiratory centres and partly on direct stimulation of the gasping centre.

The only nerve which, so far as I have seen, has any specific action on gasping is the vagus; the nature of this action is not easy to investigate. Since Section 5 cuts off the main part of the vagal nucleus and its afferent fibres from the gasping centre, we are compelled to judge of the vagal effects in experiments in which a higher section has been made and when it appears from the blood-pressure and type of breathing that the gasping centre alone survives. Out of a great many experiments only half a dozen or so seemed to me at all worthy of consideration. One may instance a cat in which, while pure gasping was occurring, the vagi were frozen, two convulsions occurred and then gasping continued at a

markedly increased rate, during the minute before freezing the rate was 10, in the minute after 16.

In Fig. 3 *c*, a section had been made through the level of the striæ,

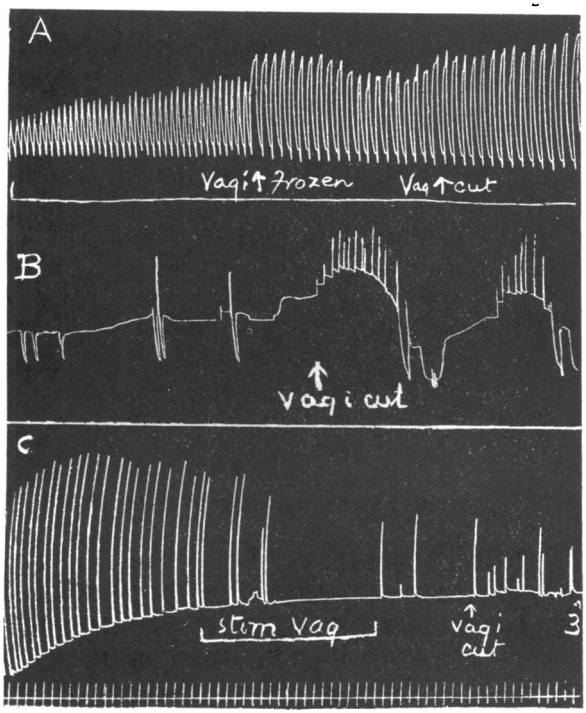

Fig. 3. Cat. Effect of vagotomy during *A.* respiration; *B.* apneusis; *C.* gasping.

a convulsion resulted, and this was followed by pure gasping; stimulation of the vagi very definitely inhibited the gasping (cf. Fig. 4 *c*) subsequent section of the vagi at once stopped this inhibition and gasping recommenced, though somewhat irregularly. In all cases where the higher centres were really dead, inhibition of gasping both in height and rate was the result of moderate vagal stimulation if it had any effect at all. On the other hand, if the apneustic centre was still alive and was inhibiting gasping, then vagal stimulation by inhibiting this centre released gasps, *i.e.* by inhibition of an inhibition (Fig. 4 *b*).

If the vagal stimulation lowers the blood-pressure, this also will tend to increase gasping, just as stopping cardiac massage did in the experiment described above at p. 83.

In confirmation of the releasing effect of vagotomy on gasping is the fact that if during an apneusis, the vagi are cut, the effect is generally

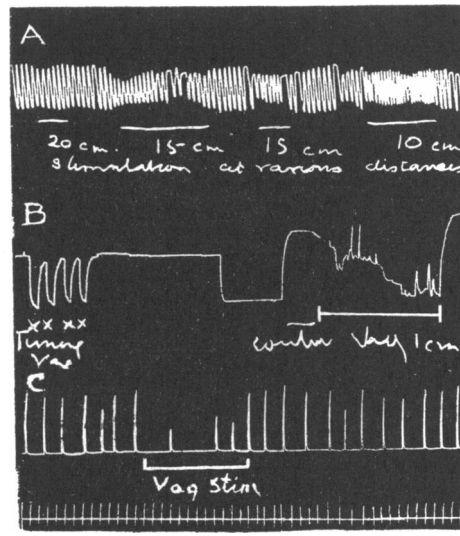

Fig. 4. Cat. Effect of vagal stimulation during *A.* respiration; *B.* apneusis; *C.* gasping.

to heighten and lengthen the apneuses and to release gasps upon them (Fig. 3 *b*). The factors which may conduce towards this result are the direct effect of vagotomy on the gasping centre above mentioned and the increased chemical stimulation of gasping due to the prolongation of the apneusis. It is also a possibility that it is in response to vagal messages that the apneustic centre normally inhibits gasping. Indeed, whenever apneuses have gasps superimposed on them at regular intervals it may be concluded that either the vagi have been cut or that they are more or less out of action for the time being.

It appears then that vagal impulses when acting directly on the gasping centre tend to inhibit gasps, while vagotomy releases them. As long as the apneustic centre is alive, however, these direct effects are obscured by the facts that the vagus acts most powerfully on the apneustic and expiratory centres and that the former of these has a stronger direct effect on gasping than the vagus has. Further, chemical stimulation of the gasping centre is more effective than vagal stimulation of it. Hence in the intact animal vagal stimulation may release gasps in spite of the fact that the direct specific effect of vagal stimulation on the gasping centre is inhibitory.

Apneustic respiration and expiration. In Fig. 5 it will be noticed that when a rabbit was made to breathe CO_2 14 p.c. O_2 28 p.c. the succeeding

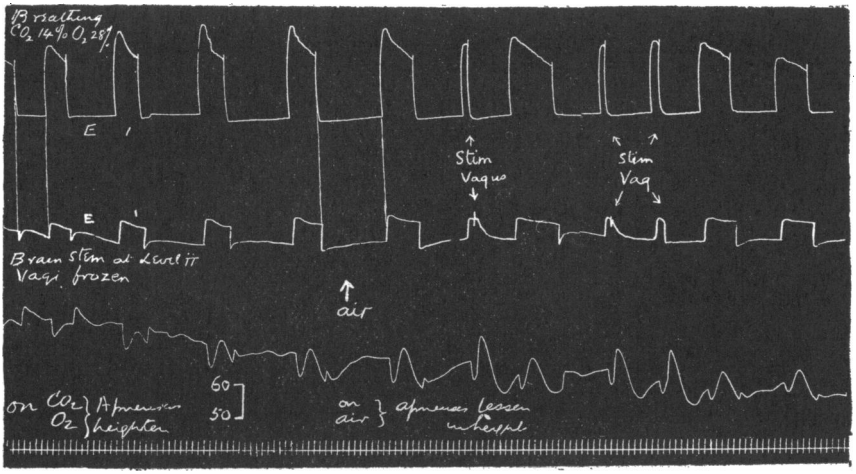

Fig. 5. Rabbit. Effect of breathing excess of CO_2 during apneustic respiration. Upper tracing from thorax, middle from abdomen. Lowest tracing = blood-pressure.

apneuses heightened considerably above the base line (about 25 p.c. increase) and when air breathing was resumed the apneuses diminished again gradually, the length of the apneuses was not much affected. Another noticeable effect was that the expiratory spasms increased markedly in intensity and slightly in duration (see Fig. 2 of my second paper(1)). This and many similar experiments indicate that excess of CO_2 increases the excitability of (stimulates) both the apneustic and the expiration centres; it does not materially influence the duration of the apneusis. That variation in the duration of apneusis and not of expiration is the factor which chiefly determines the rhythm of breathing is shown very clearly in Fig. 6 from the same rabbit. Here vagal stimulation during either phase at once caused its inhibition, but while by periodical stimulation as soon as apneusis was resumed (timing expiration) the whole cycle of movements could be accelerated so that a very good copy of normal respiration could be produced, periodical stimulation as soon as expiration had occurred (timing inspiration) merely eliminated the prolonged expiratory spasms; it did not accelerate the whole cycle, and the result was a series of prolonged apneuses with only momentary pauses between them. These observations confirm the view that apneusis is the natural tonic position, periodical inhibition of which produces normal respiration. The

active expiratory spasms are not tonic but tetanic; they are incidental and are not the basis upon which respiration is normally built up.

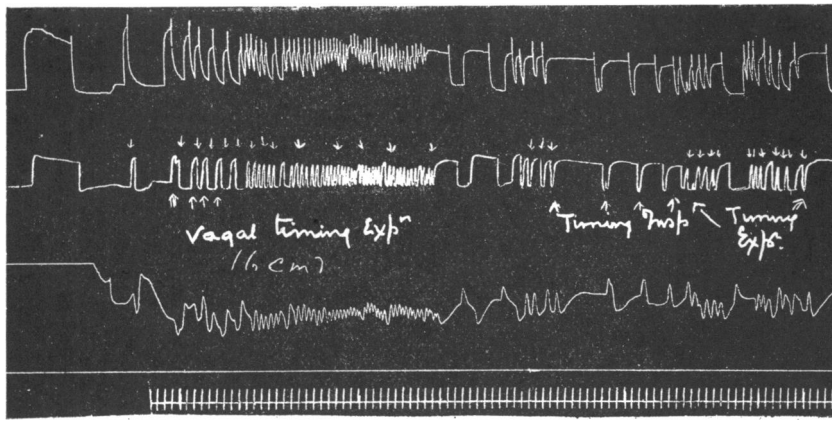

Fig. 6. Continuation of Fig. 5. Effect of vagal stimulation during apneustic respiration.

The increase of the height of apneuses and depth of expiration due to CO_2 excess is important since it explains the increased extent of the respiratory movements which occurs when CO_2 is present in too great amount during breathing of normal type.

If during apneustic respiration oxygenation of the blood is slightly or moderately diminished, for instance when air is breathed through valves instead of pure O_2, there is an increase in height and a decrease in length of apneuses which disappear when the pure O_2 is given again. The outstanding effect of marked or intense oxygen lack is however due

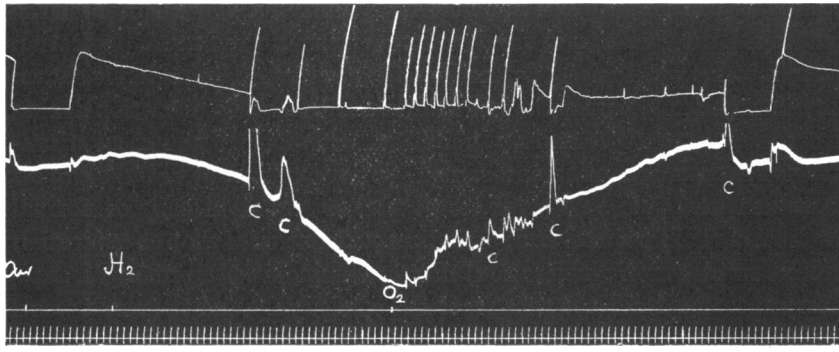

Fig. 7. Cat. Failure and revival of apneusis. Upper tracing from thorax. Lower tracing = blood-pressure.

to the resulting damage to the vitality of the centre. Fig. 7 shows how when H_2 was breathed the inspiratory tonus failed, giving place first to short feeble apneuses and soon convulsive expiratory spasms, and finally to gasps, the blood-pressure sank rapidly and death was only prevented by supplying O_2 again, when recovery took place in the reverse order.

The only effect of O_2 lack on the expiratory centre is to lower its vitality, it has no stimulant effect on expiration.

I do not propose to review the very extensive literature on the effect of the vagus. It is sufficient to state that the views of Hering and Breuer (2), supported by Head (3) and others, are those generally accepted, namely that the vagi contain both inspiratory and expiratory fibres, stimulation of which gives rise to inspiration and expiration respectively. With the view so expressed I differ because I regard, as Gad (4) did, the afferent vagus as essentially inhibitory in its effects on respiration.

CO_2 appears to increase the excitability of all the respiratory centres, and if, during breathing of apneustic type, it is administered with enough O_2 to preserve the vitality of the centres, it stimulates both inspiration and expiration, increasing the height of apneusis and the depth of expiration. It seems likely, therefore, that if the vagi contained excitatory fibres for both inspiration and expiration, continuous stimulation of it would produce the same results as administration of excess of CO_2. This is not at all the case; momentary (or periodically repeated) stimulation of the vagi definitely cuts short (inhibits) both the inspiratory and expiratory phases of apneustic respiration; thus accelerating the rhythm but diminishing the amplitude of the respiratory movements (Figs. 4 *a* and 6). Excess of CO_2 has just the reverse effect—increasing the amplitude and if anything slowing the rhythm of this type of breathing.

Continuous stimulation of the vagus produces inhibition of apneustic phenomena, and since the tonic phase of this type of respiration is inspiratory, the vagal arrest shows itself in apnœa at the base line level. To obtain such an effect, it is necessary to employ continuous ventilation, otherwise the chemical calls become so strong as to overcome the vagal inhibition and short apneuses or gasps appear (Fig. 4 *b*).

The only conclusion which seems possible is that, while CO_2 acts by exciting the respiratory centres, the vagus has the reverse action and inhibits such of them as it acts upon.

Vagotomy during apneustic respiration (Fig. 3 *b*) lengthens and heightens apneusis and releases gasps so that they become superimposed on the inspiratory tonus. From a ventilation point of view this is

advantageous, so that while an apneusis without gasps lasts in the absence of continuous ventilation only for one to three minutes, an apneusis with gasps superadded was in one instance continued, for 13 minutes, and, indeed, it only ceased when H_2 instead of O_2 was supplied. This does not indicate that vagal control of apneusis and gasping is a retrograde function, but rather that it is only a transitional stage towards respiration of normal type which in the unnatural conditions under consideration does not happen to be advantageous.

Vagotomy also releases and lengthens the expiratory phase of apneustic breathing, and expiration becomes spastic until the centre tires, as it generally does in five or ten minutes.

If during apneusis the abdominal or thoracic parietes or contents are interfered with or irritated, inhibition and expiration result, and expiration may be similarly inhibited. This observation raises the possibility that deep sensibility has considerable respiratory importance. The trigeminus has no tonic action on respiration. If stimulated momentarily by blowing into, or irritation of, the nostrils or by electrical stimulation of the nerve or its cut cerebral end, the effect is immediate inhibition of apneusis. If the stimulus is intense or is continued for some time sneezing may result. Irritant gases if passed through the nose cause arrest of breathing till the chemical calls for aeration become irresistible. Section of the trigemini does not affect respiration if managed without injury to the pons.

Conclusions.

The factors which regulate the three lower respiratory centres are partly chemical (lack of O_2 and excess of CO_2) and partly nervous (vagal and trigeminal impulses mainly).

(1) The gasping centre is stimulated by lack of O_2, by excess of CO_2, and stimulation is most powerful when both these factors coexist. The specific effect of vagal impulses on this centre is inhibitory. Yet vagal stimulation may release gasps on certain occasions by inhibiting the apneustic centre's tonic inhibition of the gasping centre. Vagotomy invariably tends to liberate gasps.

(2) The expiratory centre is stimulated by excess of CO_2. Oxygen lack has no effect on it except to impair its vitality. Vagal stimulation inhibits expiration while vagotomy releases and prolongs active expiratory movements.

(3) The apneustic centre is stimulated by excess of CO_2 and much less effectively by moderate lack of O_2. Severe lack of O_2 causes the tonic apneusis to fail and hence indirectly as well as directly liberates gasping.

Vagal stimulation inhibits apneusis as it does expiration. Thus, during either phase of the apneustic type of respiration, vagal stimulation inhibits the existing phase and releases the reverse phase. In this way vagal impulses accelerate the rhythm of respiration and diminish the extent of the respiratory movements in both directions. This is a tonic effect and hence vagotomy invariably slows and deepens respiration.

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