OBSERVATIONS ON THE RESPIRATORY CENTRES.

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In a previous article(1) three respiratory centres dealing with quiet unconscious breathing were located. Improved methods and further investigations, in now over 200 animals (cats, rabbits, dogs and monkeys), while confirming the earlier work as far as it went, have brought new facts to light, some of which are herein reported. It soon became evident, for instance, that none of the above centres could explain the regulation of active expiration, and the present paper deals mainly with the central nervous mechanism of the expiratory movements. One or two observations not exclusively connected therewith, are, however, included so as to confirm and supplement the facts relating to the respiratory centres as a whole.

In man and other animals in which gravity and elasticity act in an expiratory direction, expiration during quiet breathing is mainly of a passive nature and the active participation of the expiratory muscles, internal intercostals, abdominal muscles, etc. is not evident. Circumstances may, however, arise and can be produced at will, in which expiration becomes progressively more and more active. Thus respiration of an atmosphere containing excess of CO_2 gradually evokes active expiratory efforts and stimulation of the 5th or of the 10th cranial nerves gives rise to sudden expulsive action familiar as sneezing or coughing. Until the nature of the reciprocal innervation of opposing muscles was worked out by Sherrington(9), there was much discussion as to whether quiet expiration was an active or a passive act. The truth would appear to be, that, as in other controlled movements, contraction of inspiratory muscles is accompanied by a gradually diminishing tone in the opposing expiratory muscles and *vice versa*. There are, however, also the elastic recoil of the lungs and chest, and the effect of gravity to be considered, and normally therefore quiet expiration is a process involving very little if any actual contraction of the expiratory muscles.

If the conditions determining energetic expiration arise, *e.g.* excess of CO_2, vagal stimulation, etc. active contraction of expiratory muscles

manifestly ensues, and this not only increases in intensity in the muscles first concerned, but spreads to the numerous accessory muscles of expiration which go into active or even tetanic contraction (Fig. 3). Further still, if expiratory calls persist, these tetanic spasms may give place to clonic convulsive movements, vomiting, or even widespread convulsion resulting (Fig. 4). All these muscular movements continue to produce an expiratory effect, which indicates that they are due to "irradiation." Since after complete removal of the pneumotaxic centre, by section of the brain stem between level II and level III in Fig. 1 of my previous article(1), active expiratory efforts may still occur (Fig. 2), it is clear that the mechanism controlling them must be below level III, *i.e.* below the upper limit of the striæ acousticæ.

That the existence of a centre for active expiration must be presumed is no new idea. Marckwald(2) states, "Although on the whole direct stimulation of the medulla oblongata brought forth more inspiratory movements, yet I often saw such plain and active expiration appear, that I could not doubt the existence of an expiratory centre of respiration as well as an inspiratory one." The expiratory centre of respiration is he concludes more difficult to stimulate than the inspiratory, and it only comes into action under exceptional circumstances and never takes part in ordinary respiration. It acts during coughing, sneezing, eructating, vomiting, as well as in certain kinds of dyspnœa. "But to refer rhythmical respiration to the alternate stimulation of the inspiratory and expiratory centre is impossible for this reason, that expiration as a rule is a passive act." V. Aducco(3) found that in dogs he could paralyse inspiration by administering a large dose of chloral; expiratory activity continued. He therefore concluded that a separate expiratory centre must exist. Luciani(4) stated that in dogs expiration under normal conditions is always active, and he like Aducco decided that there must be a special expiratory centre. Luciani mentions that many other investigators, including Hering and Breuer, Mosso, Stefani and Sighicelli, have come to the same general conclusion. I am not aware that any attempt has been made either to locate the expiratory centre or to determine its mode of action and relationships. This neglect of expiration is no doubt in part due to the beguiling attractiveness of Head's(8) method of recording the respiration, by tracing the movements of a slip of the diaphragm. The procedure necessitates the use of rabbits or hares, animals in many ways inferior to cats for experimental purposes, and it misleads by omitting to record the purely expiratory movements. It is therefore unsatisfactory as a routine method of taking a general

respiratory record though valuable when an exclusively inspiratory tracing is required.

Experimental. The previous communication emphasised the existence of a group of nerve cells (apneustic centre) located at the level of the striæ acousticæ which, when cut off from above, gives rise to prolonged tonic contraction of the inspiratory muscles. In the experiments described the tonus was obviously brought to an end by deoxygenation of the blood. The lack of O_2 stimulated the lowest medullary centre sufficiently to occasion a few gasps. These re-oxygenated the blood and revived the striæ region, and a fresh tonus (apneusis) resulted.

In a recent series of 27 experiments asphyxial conditions were prevented by continuous ventilation of the lungs. The chest was laid widely open by removal of the costal cartilages and sternum from the 3rd to the 6th rib. Different mixtures of O_2 and N_2, to which sometimes a varying percentage of CO_2 was added, were forced from a large rubber bag through a tracheal cannula into the lungs, exits being provided by snipping the edges of all the pulmonary lobes. By this means the functions of the different centres and the effects of the respiration of various gases could be studied uncomplicated by asphyxial conditions due directly to the unsatisfactory respiratory movements which might be occurring as the result of section of the brain stem, etc.

It was found that the inspiratory tonus could be made to last 30 minutes or more, and even then, only ending as the result of vagal stimulation, or other experimental interference. Fig. 1 from a cat whose brain stem had been severed at the mid-pons illustrates some of the results obtained in this class of experiments. The lungs were perfused with an atmosphere composed of O_2 60 p.c., N_2 40 p.c. and the vagi were intact, but similar results are obtained also after vagotomy. The top tracing is from a tambour placed on the chest, the middle tracing is from a similar tambour on the abdomen below the level of the ribs, and the lowest tracing is the blood-pressure, the zero of pressure being 25 mm. below the 5 second time tracing. Except when intentionally inhibited by electrical stimulation of the vagus, the inspiratory tonus lasted for some 17 minutes at a time, until indeed from gradual blocking of the exit openings the ventilation became unsatisfactory. If, during this period the trigeminus or vagus was stimulated by blowing air into the nostril or larynx, or electrically, the apneusis was instantly inhibited (Fig. 1). If this was done soon after the apneusis had commenced, the moment stimulation ceased the inhibition was removed and the inspiratory tonus was resumed. It was only necessary to periodically stimulate the 5th

or 10th nerve, or if cut, their central ends, as soon as apneusis had resumed, to simulate the natural respiratory rhythm (Fig. 1). When,

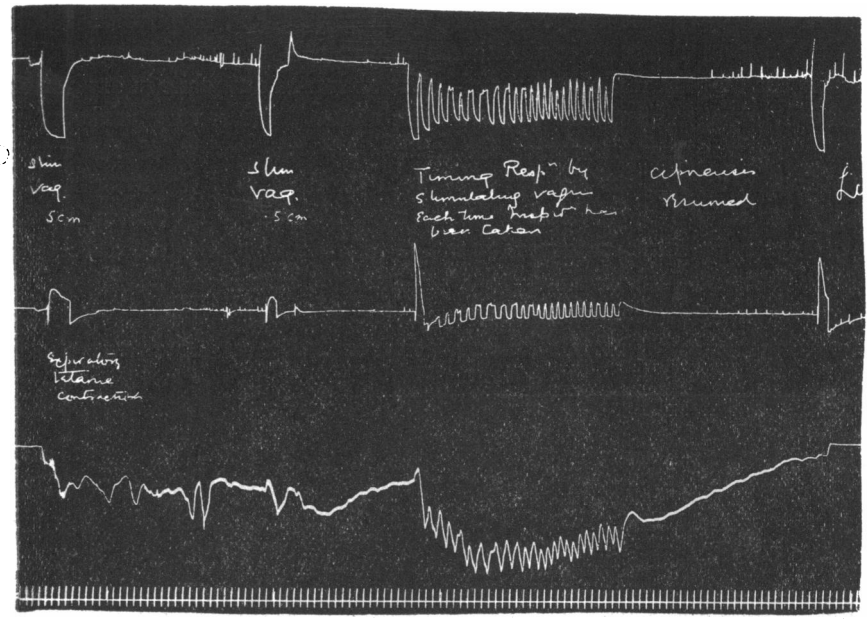

Fig. 1. Cat. See text. Continuous ventilation with O_2 60 p.c. Prolonged inspiratory tonus inhibited periodically by vagal stimulation to simulate respiration of normal rhythmical type. All tracings read from left to right and time in 5 secs. Inspiration is upwards.

on the other hand, inhibition of apneusis was effected at a moment when the apneusis was about to terminate naturally, *i.e.* when the apneustic centre was fatigued or failing, the inspiratory position was not at once resumed but instead an active expiratory spasm occurred (Fig. 1).

The method of recording the respiratory tracings by tambours on the chest and abdomen is not ideal, and some explanation is necessary in order to interpret the records. The tambours, bound to the animal's body, are each connected with recording tambours, which must be arranged to write synchronously. On examining the thoracic tracing it is seen that inspiration writes upwards, expiration downwards. There is, however, one exception; if diaphragmatic relaxation or active abdominal expiration occurs so rapidly that the air cannot get out of the trachea quickly enough, then for an instant the thorax is distended and the writing

point rises abruptly. It falls again immediately and continues to fall as long as expiration persists (Fig. 3). Coughing, or anything approaching it, shows itself in this way. The abdominal tracing tells a rather fuller but more involved story. During quiet respiration, inspiration shows simply as an upstroke, expiration as a down stroke, since during inspiration the diaphragm lowers, pushing the abdomen out while in expiration the diaphragm rises and the abdomen sinks. During very pronounced active expiration, however, the girdle-like constriction of the upper abdomen compresses the contents both upwards and downwards, and a point arrives when this downward pressure over-compensates for the ordinary expiratory compression of the abdominal parietal muscles. After this point has been reached the lower part of the abdomen will be pushed outwards more and more the longer the expiratory spasm lasts. The writing point will in this case first sink and then as expiratory efforts

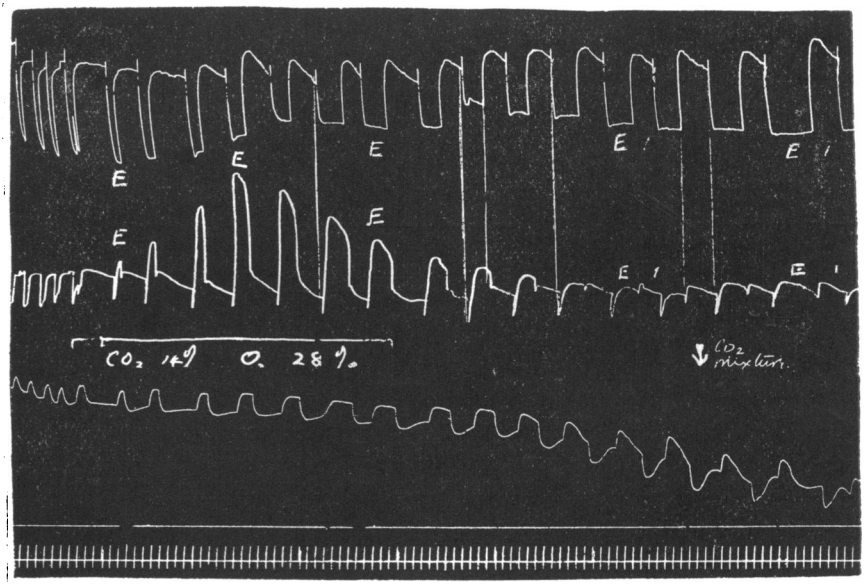

Fig. 2. Rabbit. Final instantaneous rise on thoracic (top) tracing due to sudden relaxation of diaphragm, and rounded expiratory rise on the abdominal (middle) tracing. *E* = expiration; *I* = inspiration. Note how readily the expiratory centre tires when severe spasms are evoked by $+CO_2$. Third tracing blood-pressure. The vertical parallel lines show synchronicity.

increase, it will rise again in a gradual rounded elevation which may even exceed in height the normal inspiratory rise (Figs. 1, 2 and 3).

By comparing the synchronous tracings of the thoracic and abdominal tambours, and by visual and tactile observation the correctness of this

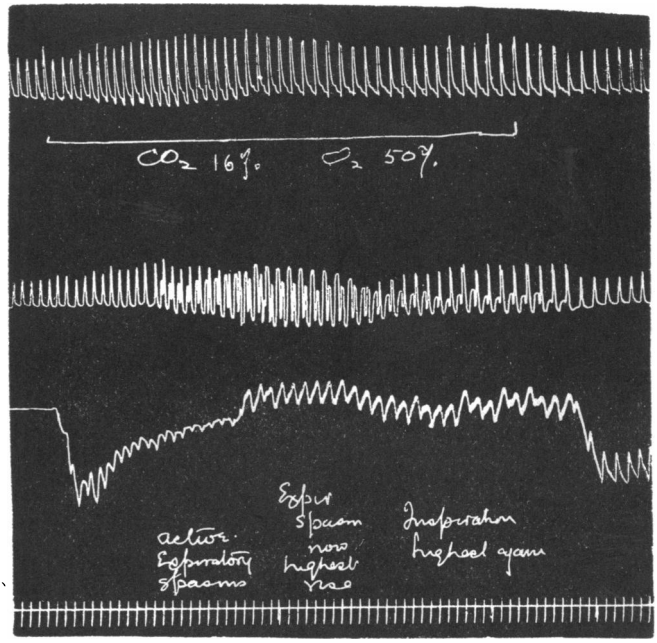

Fig. 3. Cat. Vagus cut. Thoracic (top) tracing—expiration as a depression below the base line. Abdominal (2nd) tracing—expiration as a rounded rise between, and at one period higher than, the inspiratory rises. Active expiration at first thoracic spreads later to the abdominal muscles soon causing fatigue. Third tracing = B.-Pr. Zero 33 mm. below the 5 sec. time tracing.

interpretation was apparent. During respiration of the apneustic type these events occur so deliberately that it is easy to study and understand them (Figs. 1 and 2). Purely expiratory spasms show on the abdominal tracing alone, but when they merge as they sometimes do into convulsions these show on both thoracic and abdominal tracings. This forms a ready and reliable means of differentiating these two processes (Fig. 4).

Another series of experiments confirming the results previously published is illustrated in Fig. 5. Tracings 1 and 2 are from different cats. They show the effects of shutting off the blood supply from the brain and its stem by ligature of both carotids and subsequent compression of both vertebrals. 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,

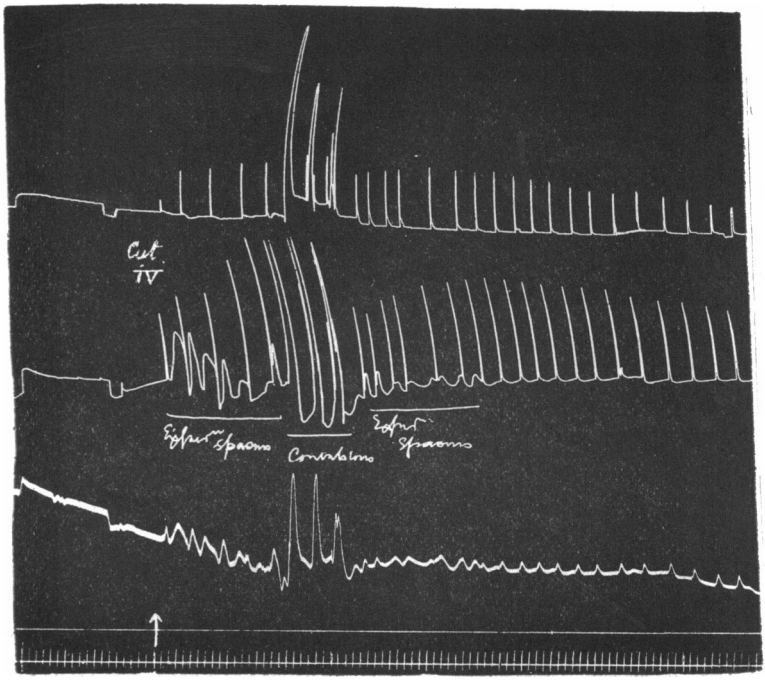

Fig. 4. Cat. Cerebellum removed, the vagi cut and the brain stem severed at level III. At the arrow a further section of the medulla just below the striæ acousticæ (level IV). Apneuses instantly cease. Gasps and expiratory spasms continue, the latter at one stage pass into convulsions and only then show on the top (thoracic) tracing, while all spasms show on the middle (abdominal) tracing. Independence of the rhythms of gasping and expiration.

however, as in the experiment of which Fig. 5 is a record, 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. Active expiratory effects are usually not seen in such experiments on account of the rapidity with which the whole striæ region dies. In Fig. 5 the lowest line of tracings shows at 3 the failure of pneumotaxis from gradually increasing anæmia of the brain stem. It will be noted that the attempts to inhibit inspiratory tonus get progressively weaker till well marked apneuses appear. At 4 the reverse process is seen during recovery

from operative shock; here, apneuses are inhibited more and more successfully till normal breathing is resumed.

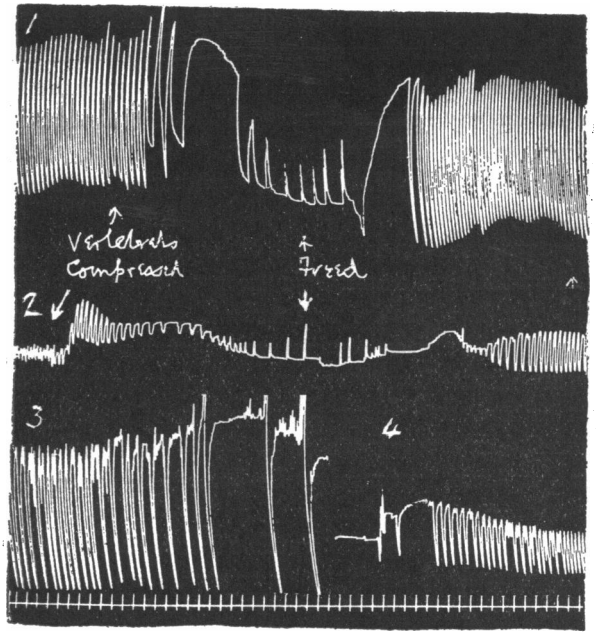

Fig. 5. See Text. Tracings 1 and 2—respiratory failure from anæmia and recovery. 3—gradual failure of pneumotaxis. 4—gradual recovery. 1 and 3 are from one cat, 2 and 4 from different cats.

Both these classes of experiments suggest that the periodicity or rhythm of respiration is normally produced by periodical inhibition of apneusis, supplemented in all but the quietest breathing by stimulation of the expiratory centre. It follows that rapid respiration is an evidence of expiratory activity and not as has been assumed an inspiratory sign. Thus quick breathing must not, for instance when it follows vagal stimulation, be regarded as a proof that the vagi contain inspiratory fibres.

Localisation of the expiratory centre. In a great many experiments in which section of the pons had been carried out it was noticed that when the central nervous system (and with it the various respiratory centres) were dying *gradually* from above downwards, expiratory phenomena invariably outlasted all evidences of the activity of the apneustic centre. When respiratory failure is *rapid* the apneustic and expiratory

centres usually die simultaneously so that in this case no expiratory phase is seen after apneustic failure (Fig. 5). After complete gradual apneustic failure active expiratory spasms continued along with gasping but that these two processes were due to distinct mechanisms was evidenced by the fact that they occurred neither synchronously nor with any regular relation one to the other. Thus the gasps may occur at any phase of the expiratory spasms during their onset, their height, or their recession (Figs. 4 and 6). After a short time (5 to 15 mins.) the expiratory efforts gradually fail and typical spasmodic and purely inspiratory gasping continues alone.

These observations suggested that either the expiratory mechanism was more resistant than the apneustic mechanism or that the former was placed at a lower level in the brain stem. Now it is found that the expiratory mechanism tires readily when constantly stimulated, *e.g.* when CO_2 is in excess (Figs. 2 and 3), while inspiratory tonus is practically tireless as long as the apneustic centre is healthy. It was thus probable that the expiratory centre was not the more resistant of the two and that it would be found to lie below the apneustic centre but above the gasping centre.

Eleven experiments were performed to locate the centre. The method used was that described in my former article up to the point when trephining had been effected. Thereafter most of the occipital bone was removed, hæmorrhage was controlled by local pressure or by pushing wax into the cut surfaces of the bones. The cerebellum was split along the middle line and its peduncles were severed. It was then removed and the brain stem thus exposed was divided just above the striæ (crucial level III). The respiration became immediately of the apneustic type. A further section was next made just below the striæ (level IV), inspiratory tonus at once permanently ceased, and instead powerful tetanic expiratory spasms interspersed with gasps occurred (Fig. 4).

Unfortunately this latter section so seriously interfered with the blood supply to the medulla immediately below that the type of respiration invariably evoked was not long maintained. The expiratory spasms increased in severity for a minute or two (cf. Figs. 2, 3) and reached a climax in which they became clonic and spread as a convulsion widely over the body and even to the limbs. Soon the intensity of the spasms diminished again and in five or six minutes they ceased; the gasping continuing alone. It was noticeable (Figs. 4, 6) that when active expirations and gasping went on concurrently they did so asynchronously each at its own independent rhythm. In some cases before the expiratory

spasms had ceased a further section at crucial level V was made. This at once stopped the spasms, gasping continuing alone. Hemisection at

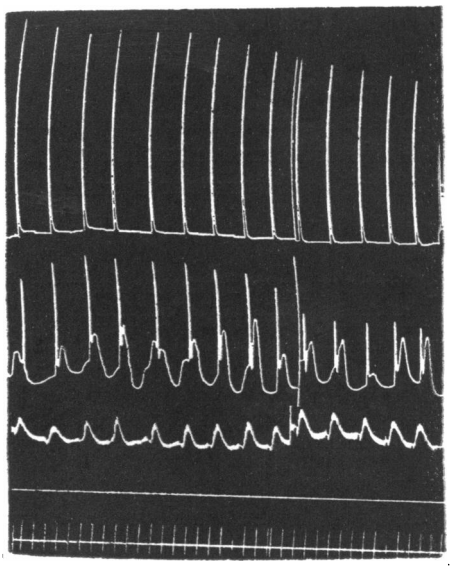

Fig. 6. Cat. Brain stem cut just below the striæ (level IV). Gasping and expiratory spasms occur but are neither synchronous nor correlated. Top tracing, thoracic; middle, abdominal; lower, B.-Pr.

level VI near the apex of the calamus halves the height of the gasps, completing this section causes their immediate cessation and death rapidly supervenes.

These experiments confirm the facts observed in animals whose brain stem is slowly dying from above downwards. They indicate that a special centre for active expiration does exist and that it is placed immediately below the level of the striæ acousticæ but well above the gasping centre or *nœud vital.*

A number of experiments have been carried out in order to show the specific effect on each of the centres, of various afferent nervous impulses and of chemical changes in the blood circulating through them. It is proposed to report later the results obtained.

Discussion.

In describing their observations on the respiration of decerebrate cats, Trevan and Boock(5) mentioned that sometimes the thoracic and

abdominal inspiratory rhythms appeared to be dissociated in time, the thorax rising first and later the abdomen. I think it probable that they mistook the expiratory protrusion of the abdomen for an inspiratory effect. I was myself guilty of this mistake until by taking a tracing direct from an expiratory muscle (external oblique) I learnt, correctly to interpret, the tracings from the abdominal parietes. A glance at Figs. 2 and 3 will show how easily such a mistake may arise. The fact is, however, that diaphragmatic and thoracic inspiratory movements are in all cases synchronous. This is what we would expect since both occur in response to efferent impulses leaving the same (apneustic) inspiratory centre.

Meyer and Meltzer(7) reported that the innermost abdominal muscle in chickens, which is purely expiratory, contracts regularly with each expiration. When the vagus is stimulated the chest becomes quiescent in the inspiratory position; whilst the expiratory muscle remains completely relaxed. This, they pointed out, was an instance of the general law of contrary inhibition or, as Sherrington calls it, reciprocal innervation. Head(8) had previously demonstrated the reverse condition, viz. that during expiration the diaphragm shows compensatory elongation. My own tracings taken separately from inspiratory and expiratory muscles in rabbits, and careful visual observation of the exposed diaphragm and abdominal parietal muscles in cats, confirm the above results. It may I think be concluded that during both inspiration and expiration the inspiratory and expiratory muscles oppose each other reciprocally by a continuous variation of tone upwards and downwards so that neither set of muscles is ever out of action for any length of time. But for such an arrangement each of the processes would be jerky and incoordinated. An example of unopposed inspiration is afforded by gasping such as occurs after section of the brain stem at level V. A sudden spasmodic inspiration is followed at once by collapse of the chest. The breath is not retained long enough to allow full interchange of the gases in the lungs. The process is hence quite unsatisfactory as a permanent respiratory method and has little similarity to controlled normal respiration.

It is certain that the expiratory centre acts quite independently of the gasping centre and it is very doubtful whether even the apneustic centre has any relation to the gasping centre except in the direction of inhibition. My view is that gasping is a relic of some transitory primitive respiratory process half way between gill and lung respiration as a fish gasps when taken out of the water. Yet I have seen so many instances in which gasping has been sufficient to revive animals whose higher

respiratory centres have temporarily failed that I feel no surprise that the faculty has persisted in the evolutional struggle.

From watching the breathing of sea-lions I find that even when on shore their respiration is of a pronounced apneustic type. Periods of prolonged inspiratory tonus are separated by one powerful sudden expiration. When a seal rises for air a sudden violent expiration almost like a cough is instantly followed by a fresh apneusis and the animal sinks again for it may be some minutes.

Tortoises, turtles, alligators and crocodiles sometimes remain under water for an hour at a time and even when on land they retain each breath for 5 to 20 minutes. At the end of this pause the first movement is expiratory. One or two slow breaths may be taken and expelled, a final inspiration then occurs, the nostrils now close until after some minutes expiration determines the onset of the next respiratory cycle. Here, as in mammals, it is the incidence of expiration which settles the respiratory rate by terminating more or less frequently the inspiratory tonus which is in reptiles the position maintained during the prolonged respiratory pause. The reptilian type of breathing is thus purely apneustic and such as occurs in a cat whose pneumotaxic centre has been removed and in which continuous ventilation prevents the rapid onset of asphyxial conditions.

While this apneustic type of breathing suits excellently animals of amphibious habits, it is neither satisfactory nor necessary in the case of purely terrestrial beings. Hence I suggest arose the call for a higher centre automatically and periodically to inhibit apneuses and so produce respiration of normal type. Such is clearly the function of the pneumotaxic centre in the upper part of the pons, for when it is eliminated, *e.g.* by section (at level II), true rhythmical respiration no longer occurs. In rabbits, this centre is less indispensable than it is in cats, monkeys, and probably in man. To some extent a dominant vagus replaces in rabbits the pneumotaxic centre. In these animals removal of the pneumotaxic centre alone does not stop rhythmical respiration, neither does vagotomy if the pontine centre is uninjured, but if the pneumotaxic centre and the vagi are both put out of action then apneustic respiration becomes at once fully developed, and is in every way comparable to that produced in cats and monkeys by destruction of the pneumotaxic centre alone (see Fig. 2). This confirms the results described by Rosenthal(6), Marckwald(2) and others in rabbits.

Expiration during quiet respiration is largely passive and is probably managed by simple inhibition of the apneustic centre by the automatic

activity of the pneumotaxic centre. The expiratory centre is, however, probably involved even in quiet breathing in varying the tone of the expiratory muscles.

During active expiration in any degree there seems no doubt that the expiratory centre is stimulated either directly or indirectly through the pneumotaxic centre. Such stimulation is in response either to excess of CO_2 in the blood or to afferent impulses reaching the centre through the vagi trigemini and possibly the nerves of deep sensation from the thoracic and abdominal viscera and parietes. In most instances several or all of these factors may be at work simultaneously.

The sequence of events during expiration of varying grades appears to be:

1. Inhibition of apneusis with elastic and gravitational collapse of the lungs and chest. This is probably accompanied by an increase of tone in the expiratory muscles.

2. Contraction of the normal expiratory muscles, *e.g.* internal intercostals, serratus posticus inferior, abdominal muscles (Fig. 3, thoracic tracing).

3. Contraction of accessory expiratory muscles and tetanic contraction of the normal expiratory muscles. The contents of the abdomen are compressed and exert pressure both upwards and downwards. The diaphragm is pushed up and the abdomen is pushed out by the girdle-like constriction of the lower ribs (Fig. 3, abdominal tracing).

4. The tetanic spasm noted above may become clonic; vomiting and convulsion may ensue (Fig. 4).

Conclusions.

Rhythmical respiration in the cat and probably in all mammals is managed by an inspiratory mechanism, the apneustic centre, at the level of the striæ acousticæ; by an expiratory centre just below this level; and both these centres are controlled by a higher centre, pneumotaxic centre, in the upper half of the pons.

The gasping centre near the apex of the calamus scriptorius is probably a relic of some previous respiratory mechanism and does not appear to influence true rhythmical breathing of normal type, although it may or may not be a relay in the tract of apneustic impulses to the inspiratory muscles.

I have again to thank Prof. C. J. Martin, F.R.S., for permitting me to continue these investigations in his laboratory, and also for generously aiding me by suggestions and by criticism.

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