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AFFERENT IMPULSES IN THE VAGUS AND THEIR EFFECT ON RESPIRATION.

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In an early paper on sensory nerve impulses [Adrian, 1926] the writer gave a brief account of the discharge in the vagus during respiration. More detailed studies have been made by Keller and Loeser [1929] and lately by Partridge [1933], but neither of them gives records of the discharge in the individual nerve fibres. Without these it is difficult to know whether all the vagal endings are alike, and difficult to compare them with other sense organs. The present work deals with these points and with another question on which there has been some apparent disagreement, that of the existence of sensory endings responding to deflation of the lungs. The results confirm Keller and Loeser in demonstrating such endings, though the deflation needed to excite them can seldom occur in a normal animal. A final section deals with the effects of the vagal discharges on the respiratory centre.

Method.

Most of the experiments on the afferent discharge were made on cats, decerebrated or decapitated under chloroform and left until the effect of the anæsthetic had worn off. Some were made on rabbits anæsthetized with urethane, dial or chloralose, and these anæsthetics were also used in cats when the reflexes were investigated. In all but a few experiments a tracheal cannula was inserted and the movements of the lung were signalled by a rubber tambour leading from a side tube, the main branch being left open or connected temporarily to a 20-litre bottle. A small bottle (3 litres) was used to produce dyspnœa and various gases could be breathed from a Douglas bag. In many experiments artificial respiration was carried out by a pump with a rotary valve producing a known inflation at each stroke (Palmer's "Ideal" model). To study the effect of

increased or diminished external pressure on the thorax the animal was placed in an air-tight tank as in the experiments of Hammouda and Wilson [1932].

Except in the experiments on vagal reflexes the nerve was cut high up in the neck and dissected out for about 4 cm. To obtain the discharge in individual fibres it was subdivided with fine needles after removal of the sheath. Small bundles of nerve fibres are split off the main trunk, and in the cat it is nearly always possible, by further subdivision, to reach a stage at which the impulses form a single series. In the moist atmosphere of the incubator in which the animal is placed the nerve remains in good condition for several hours. Persistent discharges from the cut end seldom occur and can be abolished by further stripping of the sheath. The impulses were recorded in the usual way with a condenser-coupled amplifier, a Matthews oscillograph and a loud speaker. Silver silver-chloride Ringer electrodes were used with worsted leads to the nerve.

Results.

A detailed study of the discharge in single fibres was made only in the cat, for the slower rate of breathing makes it easier to analyse the sequence of events than in the rabbit. The general behaviour of the sensory endings is the same in the rabbit, though the existence of a separate cardiac depressor nerve is an important anatomical difference. Since the cat's vagus contains other afferent fibres besides those concerned in respiration it will be convenient to describe first the various types of afferent discharge which are not purely respiratory.

Discharges without the respiratory rhythm.

The greatest activity in the vagus always occurs at inspiration, and the majority of the fibres which yield measurable action potentials are evidently connected with sense organs which are excited by the expansion of the lungs. But besides these there are groups of impulses occurring at each heart beat, irrespective of the state of the lungs, and there is sometimes a persistent discharge in a few fibres with no sign either of cardiac or respiratory rhythm.

Persistent discharges. The records in Fig. 1 C and D show one continuous series of impulses uninfluenced by the expansion of the lungs together with a respiratory discharge of the usual type in several fibres. The former came from an ending near the trachea or lung root: it was increased in frequency by pulling the trachea slightly upwards and

abolished by pressing it downwards (Fig. 1 D). Similar discharges have been found in three preparations, and in some others there have been persistent discharges arising from within the thorax but not affected by the position of the trachea or the expansion of the lungs. Some of them have changed in frequency when the animal was placed on its side, but with others the factors responsible for stimulation have not been made out. The majority of the endings which give persistent discharges are

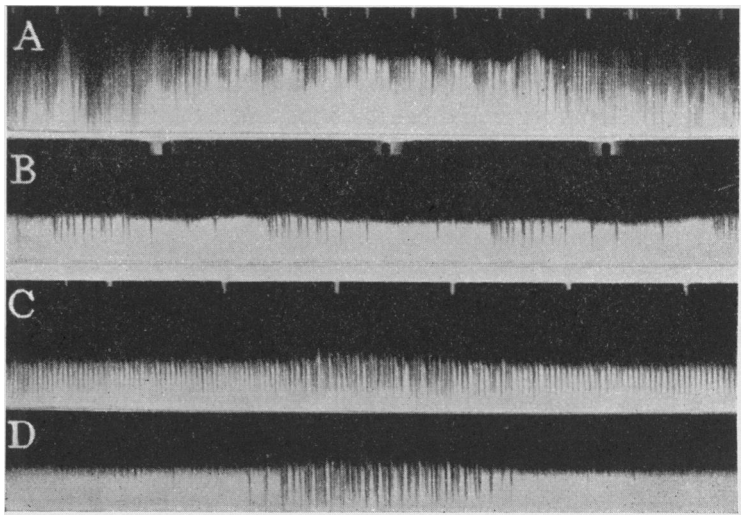

Fig. 1. Records showing afferent discharges in the vagus not influenced by respiration, all from decerebrate cats. A. Preparation with many nerve fibres, some giving cardiac rhythm. The usual respiratory discharge occurs at the beginning and end of the record. B. Record at higher speed showing cardiac discharge in two or three fibres. C. Persistent discharge (frequency 80 per sec.) due to slight traction on trachea. A respiratory discharge occurs in other fibres in the middle of the record. D. Persistent discharge abolished by moving trachea downwards. Time marker (white lines) gives $\frac{1}{4}$ sec. intervals in these and in all records.

evidently receptors of the slowly adapting or postural type stimulated by mechanical deformation but placed in regions which are not affected by the movements of the heart or lungs.

Cardiac discharges. In some cats the cardiac fibres (*i.e.* those giving a pure cardiac rhythm) are grouped into a slender nerve which runs with the vagus but is easily separated from it. In other animals there is no separate sheath, but the cardiac fibres are grouped together, so that if the vagus is split repeatedly cardiac fibres will be present in one or two

of the bundles but absent in the rest. This arrangement is often present in the right vagus although the cardiac fibres are contained in a separate nerve sheath on the left side. Examples of the cardiac type of discharge are shown in Fig. 1 A and B. In Fig. 1 A some of the fibres come from the lung and signal inspiration whilst others give cardiac rhythm. The discharge in each fibre usually consists of three or more impulses at each heart beat: by shunting a fraction of the electrocardiogram into the electrode system it can be shown that the impulses coincide with each systole. The number of impulses at each heart beat is increased by raising the blood-pressure and reduced by lowering it, and in general the discharge agrees very closely with that in the rabbit's cardiac depressor and carotid sinus nerve [cf. Bronk and Stella, 1932].

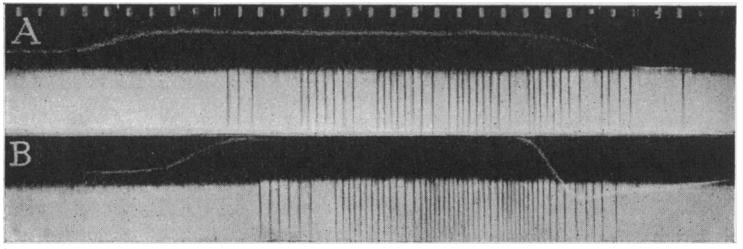

Fig. 2. Record from single fibre of vagus (decerebrate cat) showing discharge with mixed respiratory and cardiac rhythm. A, normal breathing; B, dyspnœa. Signal line moves upwards on inspiration: in these and other records it has been drawn in where it is too faint for reproduction. The duration of each record is 3 secs.

Discharges with mixed respiratory and cardiac rhythm. Since the structures near the root of the lung will be deformed by the pulsation of the heart and great vessels as well as by the movements of respiration we might expect to find some endings which are stimulated by both events. These are often found and the type of discharge they give can be seen from the records in Fig. 2. The cardiac rhythm is less constant than the respiratory and may disappear when the position of the animal is changed. The fibres which give this double rhythm form only a small minority of those in the vagus and in many preparations they have not been detected.

Respiratory discharges: endings stimulated by inflation.

In natural breathing (cat or rabbit) the frequency of the impulses in the vagus rises to a maximum at inspiration and falls to a minimum as the lungs contract. This is true both for quiet breathing and for extreme

dyspnœa induced by CO_2. In the whole nerve there are usually a good many fibres in which the discharge never ceases entirely during the interval between inspirations, though in dyspnœa the number becomes less and less as the deflation of the lungs at expiration becomes more complete. Typical records in which the impulses form a single series are given in Fig. 3 and a record from the rabbit's vagus is included for comparison (Fig. 3 A). Curves of impulse frequency are given in Fig. 4. The frequency rises and falls along a smooth curve as the lungs expand and

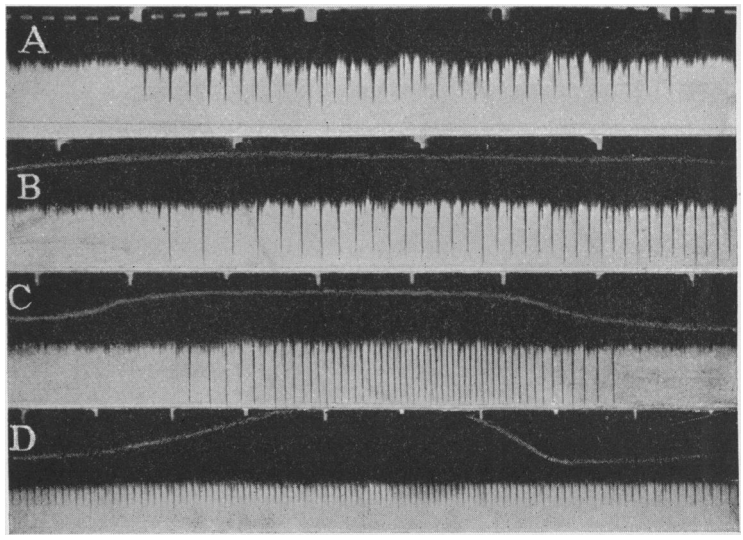

Fig. 3. Normal respiratory discharge in single fibres of the vagus. A, from a rabbit under urethane; B, C and D, from decerebrate cats. White line signals respiration and moves upwards when lungs expand (tambour connected to air reservoir). Time marker gives ½ sec. intervals.

contract, and the records might well have come from the stretch receptors of a muscle extended and relaxed rhythmically. The likeness remains when the expansion of the lungs is controlled by inflating them artificially. In Fig. 5, for instance, it can be seen that the frequency depends on the degree of inflation and falls off very slowly when the inflation is maintained.

We are dealing therefore with an ending which is like the muscle spindle in having a very slow rate of adaptation to the stimulus. The stimulus is evidently the actual deformation (stretching) of the tissues in which the endings are placed. Air currents are not essential, for the

discharge continues when the lungs are held inflated. The pressure of the air in the alveoli is also immaterial (except in so far as it produces

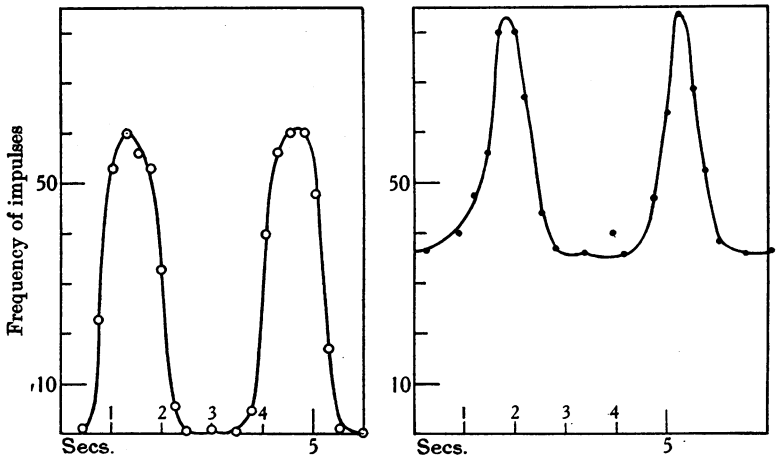

Fig. 4. Frequency of impulses in single fibres of the cat's vagus during normal breathing. Two preparations, both decerebrate.

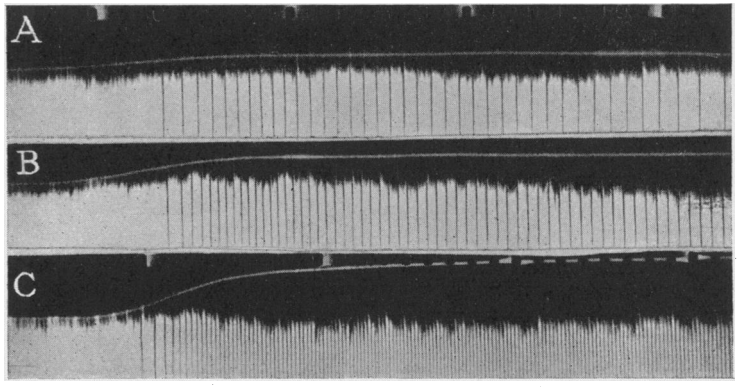

Fig. 5. Spinal cat, single fibre preparation. Inflation of the lungs by pump. Movement of signal line directly proportional to inflation.

A.	Inflation =	65 c.c.	Maximum frequency	80	per sec.
B.	,,	= 115 c.c.	,,	120	,,
C.	,,	= 230 c.c.	,,	250	,,

deformation), for the discharge is the same for a given degree of expansion whether this is produced by blowing air into the trachea or by the natural movement of respiration.

The relation between the degree of inflation and the frequency of the discharge in single fibres is shown in the curves in Fig. 6. It is approximately linear over the range investigated, and in this it agrees with Partridge's findings for the rabbit's vagus (several fibres). It is scarcely possible, however, to compare the form of the stimulus-frequency relation shown by the vagal endings with that of other sense organs, for in no case can we form more than a very rough estimate of the relation between the stimulus which we measure (volume increase of lung, tension

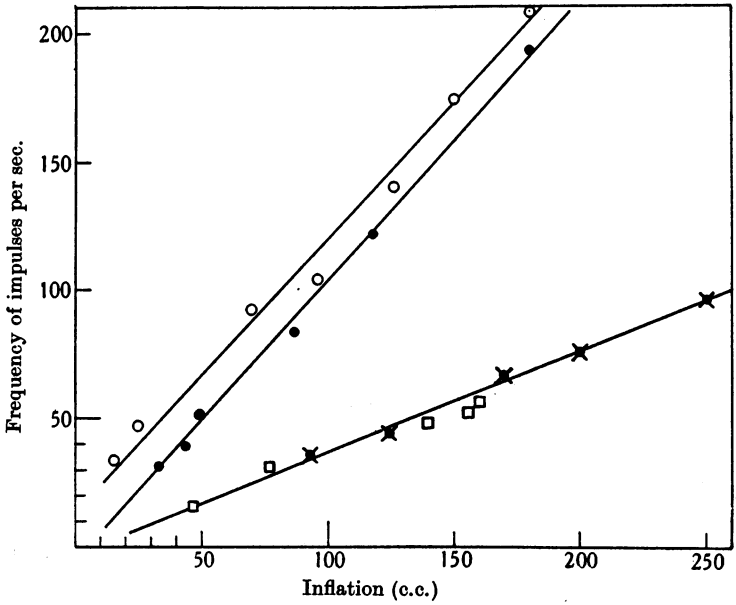

Fig. 6. Maximum discharge frequency in single fibres with varying inflation of lungs. Spinal cats. The two upper curves are from a small animal and show two series of measurements made within 10 min. The lower curve (also two series) is from a larger animal.

on muscle, etc.) and the deformation which it will produce in the sensory endings.

Adaptation. Keller and Loeser [1929] state that the discharge in the rabbit's vagus depends on the rate of inflation of the lungs as well as on the final extent, but Partridge [1933] finds no difference in the maximal frequency whether the inflation is slow or rapid. The discrepancy probably arises from differences in the range of stimuli employed, for in single fibres of the cat's vagus there is evidence of adaptation, but with stimuli of moderate intensity the effect is slight. When the degree of inflation

does not produce a frequency higher than about 50 per sec. there is little difference in the maximal frequency caused by an inflation developing in ½ sec. or 3 sec., and after 10 sec. maintained inflation the frequency has seldom fallen by more than 5 p.c. But with rapid inflations, giving higher frequencies, there is an early decline from the maximum as there is in the discharge from a stretched muscle spindle. Curves illustrating this are given in Fig. 7. It is possible that the initial decline may be due in part to a redistribution of air in the lungs allowing the areas first expanded to contract slightly, but the rate of decline is not appreciably

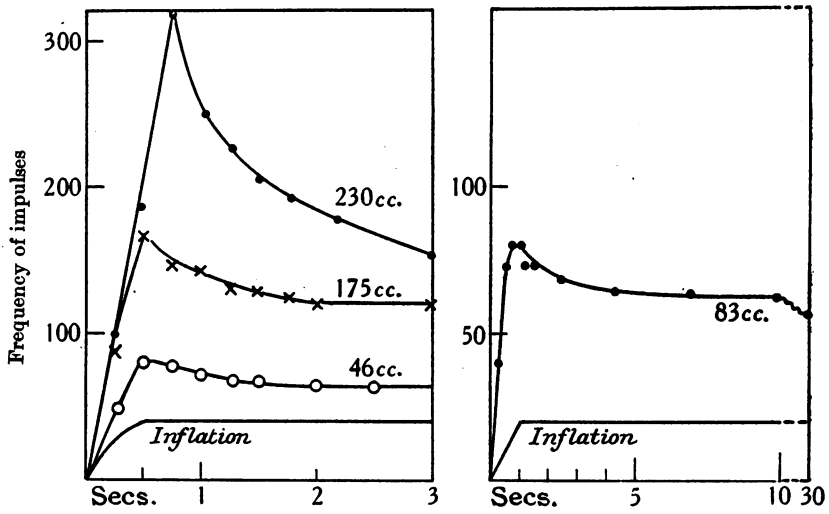

Fig. 7. Frequency curves from single fibres to show adaptation to stimulus. Spinal cat.

changed by binding the abdomen. After the initial decline the rate remains constant or falls slowly provided that the endings are in good condition. The fall is much more rapid when the circulation has failed (see later, p. 341).

Wedensky effect. In a few preparations an interesting result has followed from an extreme inflation of the lungs. The frequency rises to 300 per sec. or more and then falls suddenly, the discharge becoming irregular and finally ceasing altogether (Fig. 8 B). If some of the air is allowed to escape, the regular discharge reappears at a frequency in the neighbourhood of 50–100 per sec. This result is obviously an example of the Wedensky effect, closely resembling that found by Tsai [1931] when impulses from a frog's muscle spindle are recorded in a nerve fibre which has been led through a narcotizing chamber. In Tsai's experi-

ments a discharge of low frequency could pass the narcotic block, but if the frequency was raised by increasing the tension on the muscle conduction failed, either partially or completely, to return again when the tension on the muscle (and therefore the frequency of the incoming discharge) was lowered. In the present experiment it is conceivable that the failure occurred in the region of the nerve ending, but more likely that some impairment of conduction was produced in the nerve fibre by the dissection. Even if the fibre escaped all damage, the cut ends of other fibres might affect it by causing an electrotonic block or by raising the concentration of potassium ions etc. in its neighbourhood.

Variations in threshold, etc. With the circulation intact and the lungs aerated the vagal endings which signal expansion have all agreed in

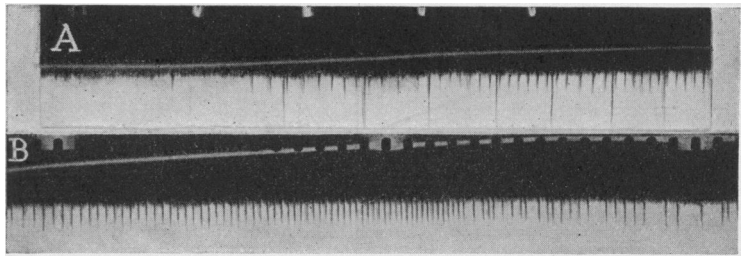

Fig. 8. A. Record from two fibres to show variation in threshold and in discharge frequency for a given stimulus. Spinal cat. The series of small impulses shows a cardiac grouping (as in Fig. 2). B. Wedensky effect. With extreme inflation (250 c.c.) the discharge frequency rises to 300 per sec. and then becomes irregular. Spinal cat.

showing a very slow rate of adaptation. Judged by this criterion all of them are of the same type. There are, however, considerable differences in excitability, or rather in the amount of inflation needed to stimulate the different endings. This may be seen from Fig. 8 A which shows the discharge in two vagal fibres during a gradual inflation.

Whatever its cause, this variation in threshold will evidently increase the range of the signalling mechanism, but it may well depend mainly on the position of the endings, the actual deformation required to excite being the same for all of them. A change in the position of the animal will often produce a change in the response of a single ending to a given inflation. Otherwise the response remains constant over periods of an hour or more.

The effect of CO_2, *and of circulatory failure.* Bronk and Stella [1932] in their study of the stretch receptors in the carotid sinus have shown

that these endings are very little affected by changes in the acidity or gaseous content of the blood. Their function is to signal the expansion of the artery and nothing else. In the same way the stretch receptors in the lungs are extremely insensitive to environmental changes other than mechanical deformation. This was clearly shown in Head's work [1889] where it was found that inflation of the lungs with N_2 or H_2 produced the usual inhibition of inspiration. Keller and Loeser have found that in the rabbit the substitution of N_2 for air or the addition of 5–10 p.c. CO_2 causes no change in the vagal impulses, and Partridge agrees with them. In the cat (spinal curarized preparation) inflation with air containing 10–12½ p.c. CO_2 for several minutes seems to produce a very slight diminution in the discharge. This is shown by a fall of about 5 p.c. in the total number of impulses at each inflation. The change is scarcely large enough to be outside the range of error: it is certainly too small to be the basis of any considerable change in the depth of breathing. But as Keller and Loeser have pointed out, in the intact animal CO_2 may affect the vagal discharge indirectly by causing alterations in the calibre of the bronchioles.

Failure of the oxygen supply is another factor which has remarkably little effect on the vagal endings. The air may be shut off or nitrogen substituted for it until the heart has ceased to beat, without causing any decided change in the response to a measured inflation. In mammalian muscle Matthews [1931] has found that, if the effect of the anæsthetic has worn off, arrest of the circulation leads invariably to a spontaneous discharge of high frequency from all the sensory endings. With the vagal endings the only suggestion of this is a persistent discharge of low frequency (20 per sec.) which develops in some of the fibres when the lungs have been inflated rhythmically with nitrogen. The difference is easily explained, for Matthews found that the discharge from the muscle receptors was caused or greatly favoured by something produced in the muscle fibres and produced much more rapidly if they are made to contract. Since few of the vagal endings are likely to be exposed to metabolites from muscle there is no reason to expect great spontaneous activity in many of them.

The vagal endings cannot, of course, survive indefinitely after the failure of the oxygen supply and they become inactive within half an hour to an hour after the heart has stopped. The first sign of deterioration is a more rapid decline in the frequency of the discharge under a constant stimulus. A series of curves illustrating this are given in Fig. 9. They show the same change as Bronk's curves [1929] for the effect of nitrogen

on the response of a frog's muscle spindle, but it is surprising to find so little evidence of impairment 20 min. after the failure of the heart and the replacement of the air in the lungs by nitrogen.

Chloroform. In animals with the circulation intact very high percentages of chloroform vapour are needed to affect the vagal discharge; when it is affected it is usually abolished rapidly, and there is an immediate recovery as soon as the chloroform is withdrawn.

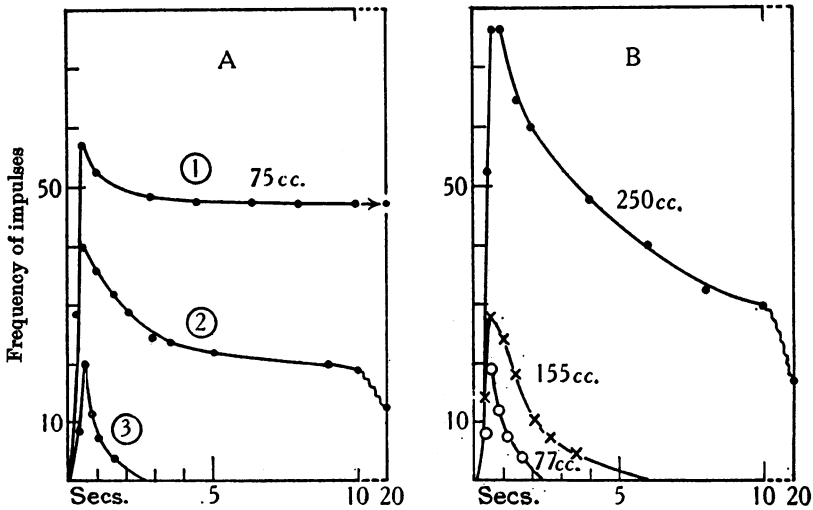

Fig. 9. Frequency curves from single fibre to show the effect of failure of circulation. Spinal cat. Lungs filled with nitrogen after death.

A. (1) Effect of inflation with 75 c.c. air with circulation intact.
(2) „ „ nitrogen 20 min. after heart failure.
(3) „ „ nitrogen 50 min. „

B. 50 min. after heart failure. Varying inflations with nitrogen.

Chloroform mixtures were breathed from a Woolf's bottle or blown into the lungs by a pump. The concentration was estimated roughly by weighing samples of the mixture collected in a 250 c.c. flask [Waller, 1904]. With decerebrate animals breathing a mixture of moderate strength the vagal discharge at each inspiration becomes less and less as the anæsthesia deepens, but this is due simply to the shallower breathing, for the response to a test inflation remains quite unaffected after the stage of complete flaccidity is reached and even after the stage at which respiration fails. With spinal animals under artificial respiration a mixture containing less than 2·5 p.c. of chloroform has no appreciable effect on the vagal discharge, though it abolishes all reflex activity. A mixture of 4 p.c. or more produces an immediate decline in the vagal discharge,

and within a minute or two it fails completely. It must be remembered, however, that during this time the lungs are still being inflated with undiminished force by the pump: the conditions are therefore quite unlike those in a patient breathing naturally. If the chloroform is turned off within a minute or so after complete failure there is an immediate recovery of the vagal discharge and within another minute it is back at its initial value. The rapid failure and recovery are illustrated in the records given in Fig. 10 which show a return almost to normal within

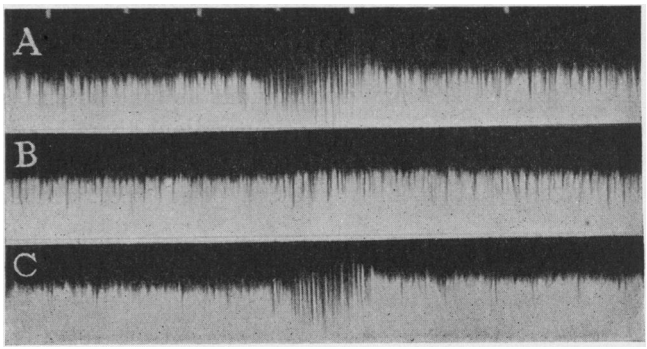

Fig. 10. Rapid failure with strong chloroform vapour (5 p.c.) and rapid recovery with air. Spinal cat. Lungs inflated by pump. A, with air; B, 70 sec. after chloroform has been turned on; C, recovery after 10 sec. inflation with air.

10 sec. Attempts to maintain a partial anæsthesia of the vagal endings were unsuccessful. The lower concentrations of chloroform were too weak to affect them (though amply strong enough to affect the central nervous system) and the higher caused a rapid failure. This may be due to the rate at which the chloroform is absorbed by the blood stream, but it is difficult to produce a graded anæsthesia of a nerve trunk with chloroform vapour, and the action on the vagal endings may be equally abrupt.

The practical outcome of these experiments is to show that the strength of chloroform normally administered to a patient (*i.e.* below about 2·5 p.c.) is without effect on the endings in the lung which respond to mechanical stimulation. Very high percentages may affect them, but a few inflations with air should be enough to give complete recovery.

Endings stimulated by deflation of the lungs.

In the brief account given by the writer in 1926, it was stated that in normal breathing there is no sign of a renewed discharge of impulses at the moment when the lungs are most deflated, and that forcible deflation

of the lungs in a spinal cat does not give rise to a discharge. The forcible deflation referred to was that produced by compressing the thorax by hand, and this, in the cat, is not enough to stimulate the endings which respond to deflation. But Keller and Loeser showed that suction of air from the lungs undoubtedly gives rise to a discharge of nerve impulses. Their experiments were made on rabbits, and in the present work it has been found that the result is equally true of the cat: forcible deflation of this kind does produce a discharge.

In the cat when the thorax is opened the discharge can only be produced by deflating the lungs completely. It then varies rhythmically as each pulsation of the heart moves the collapsed lung. When the thorax is intact the discharge is usually continuous as long as the suction is maintained (Fig. 11), though in some preparations there has been only a short outburst at the beginning. From this it appears that some of the nerve endings are of the more rapidly adapting type, but the majority

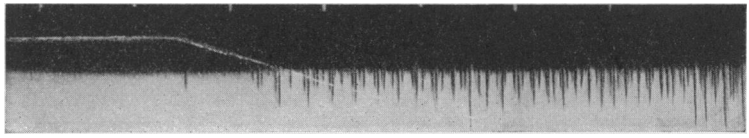

Fig. 11. Afferent discharge produced in several fibres by suction of air from the lungs. Spinal cat.

are like those responding at inspiration. It is possible and indeed likely that some of the endings which react to suction are those which react normally to inflation, for both inflation and extreme deflation might stretch the tissues in which they lie. But there is no doubt that deflation calls a new set of endings into play as well. When only a few fibres are in action the impulses due to inflation and suction can often be distinguished by their size and form; also suction of air from the lungs has a specific effect on the respiratory centre. If the vagi are intact it causes an immediate contraction of the muscles which produce inspiration, whereas an inflation of the lungs has the reverse effect, since it inhibits inspiration. Thus the endings concerned in the response to extreme deflation must form part of a distinct nervous mechanism, though it is a mechanism which must be very rarely called into play.

The rabbit agrees with the cat in showing no expiratory discharge in normal breathing or in dyspnœa [Keller and Loeser, Partridge], but it differs from the cat in that it is usually possible to produce one by increasing the external air pressure on the thorax and abdomen so as to

assist the collapse of the lungs. The animal is placed in a closed chamber with the tracheal tube communicating with the air outside, the arrangement being a copy of that used by Hammouda and Wilson in their study of the vagal reflexes. Raising the air pressure in the chamber assists the collapse of the thorax at expiration and hinders the expansion at inspiration. The records in Fig. 12 were made from the vagus of a rabbit under these conditions, and it will be seen that with increased external pressure the usual discharge at inspiration is greatly reduced and in its place a definite expiratory discharge appears. In the cat this method has always failed to give an expiratory discharge, owing presumably to the greater strength of the body walls.

Whether the endings which are stimulated by collapse play much part in normal breathing is exceedingly doubtful. In the decerebrate or

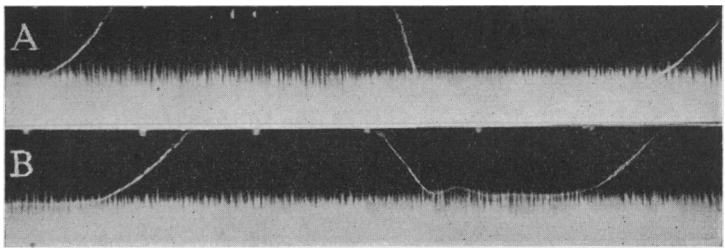

Fig. 12. Afferent discharge at expiration produced by increased external pressure in the rabbit. Rabbit (under urethane) in air-tight chamber with trachea tube leading outside. A. Normal extra-thoracic pressure. Usual inspiratory discharge. B. Increased extra-thoracic pressure. Expiratory discharge and quickened breathing.

anæsthetized animal they play none at all except in conditions which are definitely abnormal. The failure to record a discharge at expiration has not been due to lack of activity in the expiratory muscles, for these have often contracted vigorously. It is possible that the forcible deflation occurring in extreme dyspnœa might stimulate the expiratory endings, but so far this has not been observed. On the other hand it is highly probable that these endings may come into play in various pathological conditions, *e.g.* when portions of the lungs are solidified or tied to the chest wall by adhesions.

It should be noted here that suction of air from the lungs (or breathing into a reservoir containing air at reduced pressure) will not necessarily have the same effects as increased pressure applied outside the thorax. Suction may well stretch some of the endings which are normally stretched at inspiration, but increased external pressure is unlikely to

do so. This difference may explain some of the divergent results which have been reported with the two procedures [cf. Hammouda and Wilson, 1932; Creed and Hertz, 1933].

The stretch receptors and the respiratory centre.

So much has been written about the action of the vagus in respiration that a brief discussion cannot hope to do justice to earlier work. It can only be excused by the fact that a more detailed knowledge of the afferent discharge gives a better foundation for analysing the vagal effect. We know that inflation of the lungs will produce a sustained discharge from the stretch receptors and that the deflation normally occurring will merely put an end to this discharge, though suction of air from the lungs will excite another set of endings. In normal conditions, therefore, the effect of the vagus must depend mainly, if not entirely, on the impulses from the stretch receptors. Persistent discharges unaffected by lung movements have been found in a few preparations and there is always the possibility of action currents too small to detect. But the dominant activity in the vagus is that due to the stretch receptors, and it is worth considering whether their discharges are enough to account for the whole of the vagal effect. In particular, can they account for the fact that more rapid breathing occurs when the vagi are intact than when they are cut? The messages from the stretch receptors have an inhibitory rather than an excitatory effect. Why should more rapid breathing be possible in their presence than in their absence?

The question was discussed by Hammouda and Wilson [1932]. Their evidence, based on the reactions to altered extra-thoracic pressure, led them to a picture of the sensory mechanism of the vagus which agrees in the main with that given here. But to explain the slowing of breathing on division of the vagi they suggest that the vagus has a double influence on the respiratory centre, an inhibitory influence varying in intensity with the lung volume, and besides this an influence which maintains the tone of the centre and augments the frequency of the discharge. The latter is considered to remain in general at a constant level of intensity unaffected by changes in the tension of the lung tissues.

Such an influence might be exerted by impulses in nerve fibres too small to give measurable action currents. It is quite possible, however, that the one sensory mechanism is enough: that the quickening of the rhythm is due to impulses from the stretch receptors and results from their inhibiting each period of inspiratory activity in the brain stem. An explanation on these lines was in fact given in the classical paper

published by Henry Head from Hering's laboratory in 1889, though it appeared then that the expiratory endings might play some part in the effect.

Later evidence has confirmed the main points in Head's theory. In the first place there is now no reason to doubt the power of automatic action by the respiratory centre. We are dealing with a group of neurones in the brain stem which tend to discharge periodically without the need for any periodic inflow of afferent impulses. Winterstein [1911] has shown that a recurrent discharge of motor impulses takes place in the phrenic nerve although the vagi have been cut and all movement has been paralysed by curare (and this has been confirmed in the experiments of Adrian, Bronk and Phillips [1932] as well as in the present work). During complete motor paralysis and a temporary pause in the artificial ventilation afferent impulses will still reach the central nervous sytem from pressure receptors, etc., but there will be no waxing and waning of the incoming stream to determine the period of the phrenic discharge. This is slower than that of normal breathing but no slower than that of breathing after division of the vagi. Thus the respiratory centre (or some part of the brain stem apparatus concerned in respiration) must be capable of beating with its own inherent rhythm. Its cells cannot be regarded as passive agents controlled entirely by afferent messages, for internal changes must be constantly taking place tending to produce a recurrent development of the active state.

Without the vagi the centre usually beats at a slow rate and only small variations of rhythm are possible. The messages from the stretch receptors change this spontaneous beat to the more rapid and flexible rhythm of normal breathing. They are inhibitory, but they can influence the rhythm in either direction because inhibition of the phase of activity will shorten this part of the cycle and tend to hasten its return, but inhibition during the phase of rebuilding will delay it. The dual influence discussed by Hammouda and Wilson depends, on this view, not on a dual afferent mechanism, but on the dual effect of inhibition on the respiratory centre. In Head's words the vagus inhibits inspiratory activity but at the same time raises the vitality of the centre by causing this activity to accumulate.

The maximum inhibitory effect occurs during the phase of activity and therefore the rhythm is usually quicker with intact than with cut vagi. The motor discharge will be curtailed, there will have been a smaller expenditure of active material and it is reasonable to suppose that less time will be taken in preparing for a fresh outburst. Thus a

series of brief inhibitions at each expansion of the lungs should give a cycle consisting of brief motor discharges repeated at short intervals; whereas the absence of all inhibition should give longer discharges spaced at greater intervals. This is the characteristic effect of division of the vagi, for the slowing is usually due to a prolongation of both the active and inactive phases of the cycle.

Fig. 13 illustrates the slowing of the rhythm due to the abolition of the vagal control and the quickening due to recurrent inhibition. The

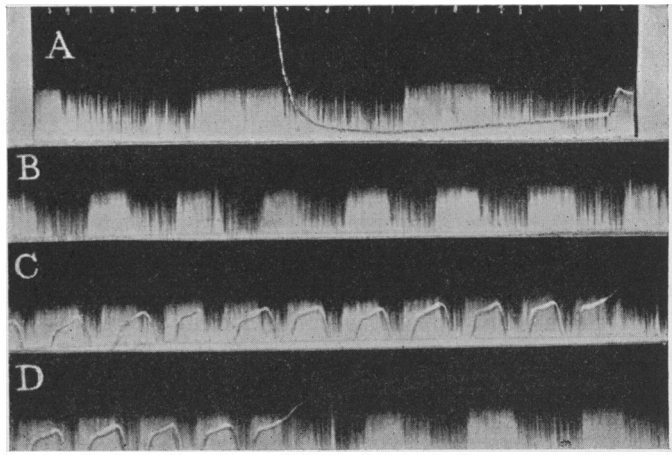

Fig. 13. Discharge of motor impulses in the top root of the phrenic nerve cut distally. Decerebrate cat. All records at same speed. A. Both vagi blocked with novocaine. Slow rhythm (27 per min.) unaffected by sudden inflation of the lungs. Downward movement of signal marks inflation. B. Vagi intact. Normal breathing 58 per min. C. Vagi intact. Periodic inflation of lungs timed so as to inhibit each motor discharge. Downstroke of signal shows inflation. The rate increases to 90 per min. D. After 11 sec. the periodic inflation is stopped. The rate falls at once to 48 per min. Time marker (top record) gives $\frac{1}{4}$ sec. intervals.

records show the discharge of motor impulses in the top root of the phrenic in a decerebrate cat. When the vagi have been temporarily blocked with novocaine the motor discharges recur at 25 per min., each lasts for $1\frac{1}{2}$ sec. and the cycle is quite unaffected by inflation of the lungs. With intact vagi the inhibition normally occurring at each breath cuts short the motor discharge after it has lasted only $\frac{1}{2}$ sec. The rate of breathing is now 58 per min. By blowing air into the lungs at each inspiration the inhibitions are increased in intensity, the motor discharges are shortened still further and the rate rises to 90 per min., falling at once to 48 as soon as the inflations are discontinued. It will

be seen that both parts of the cycle are affected: the change in rate is due mainly to the shortening of the phase of activity, but there is some reduction in the interval between the end of one discharge and the beginning of the next. This is shown more clearly in the records in Fig. 14 which are made at higher speed.

This is little more than an example of the well-known fact that in an animal under artificial respiration the rhythm of the active movements of the diaphragm may come into phase with that of the pump. It shows that an increase in the inhibitory message at each inspiration can produce a quicker rhythm: it is therefore unnecessary to suppose that the vagus exercises its tonic effect on the centre through a distinct set of nerve fibres.

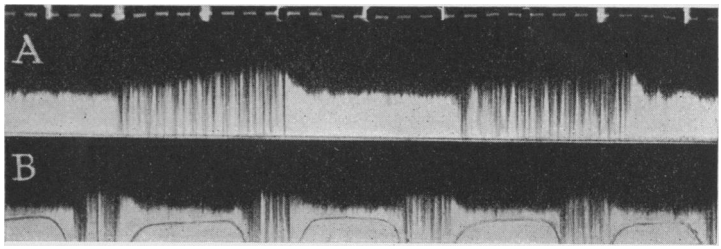

Fig. 14. Same experiment as Fig. 13. Records at higher speed (time marker gives $\frac{1}{4}$ sec.). Signal line drawn in. A. Normal discharge of motor impulses in phrenic root. B. Effect of periodic inflations. Both active and inactive phases are shortened.

The opposite effect will be produced if the inhibitory message acts throughout the period when the centre is recharging, for this will tend to delay the appearance of a fresh discharge. Thus the rhythm, in so far as it is determined by the stretch receptors, will be most rapid when the inhibitory effect rises sharply at each inspiration and falls to zero at expiration (Fig. 15 A) and slowest when the rise is less pronounced and there is some persistent inhibition throughout the cycle (Fig. 15 B). The frequency of the afferent discharge varies with the lung volume (p. 338). Therefore, if we can assume that the inhibitory effect does not much outlast the afferent discharge, the curves in Fig. 15 might relate to lung volumes instead of to inhibitions and the quickest rhythms should occur when the lung volume changes as in Fig. 15 A. The inhibition does no doubt outlast the afferent discharge, but records such as those in Fig. 13 show that it can rise and subside rapidly enough to affect only a limited part of the cycle. The conclusion given above is best illustrated by two

examples, the change in rhythm produced by altering the external pressure on the thorax and that occurring in CO_2 dyspnœa.

Increased pressure on the thorax. The effects of this have been studied in detail by Hammouda and Wilson, using the air-chamber method. They worked on dogs and found that an increase or reduction of pressure in the chamber caused an immediate quickening or slowing of the breathing. The changes only occur with intact vagi and they occur before the change in ventilation can have any effect.

A number of experiments have been made on cats by the same method, the afferent discharges in the vagi being sampled by recording the impulses in a few fibres slit from the side of the nerve. The earlier

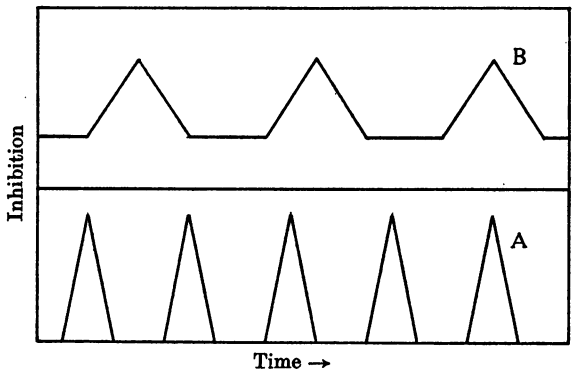

Fig. 15. B. Rise and fall of inhibition likely to give slow breathing.
A. Rise and fall of inhibition likely to give rapid breathing.

experiments failed to show the reaction to increased pressure and it was thought that its occurrence in other animals might depend on the stimulation of expiratory endings. But in later work, with chloralose as anæsthetic, the reaction was found in the cat, although there was never any sign of an afferent discharge produced by the deflation of the lungs. Fig. 16 gives typical curves showing the frequency of the vagal impulses (in several fibres) just before and just after the pressure in the chamber is raised. As might be expected, the whole frequency range is lowered when the thorax is reduced in volume, and in particular the discharge is much briefer and sinks to zero between each inspiration instead of remaining at a moderate level.

The quickening of the breathing is shown in the curves. It is evidently due to the reduced inhibition, but on the scheme outlined above it must be due not so much to the reduction in the peak of the inhibitory

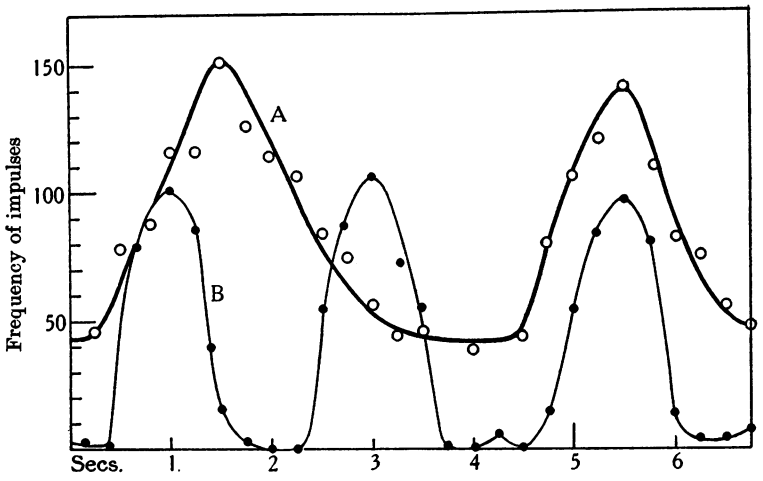

Fig. 16. Afferent vagal discharges in cat anæsthetized with chloralose. One vagus intact. Frequency curves (preparation of several fibres) showing the effect of increased extra-thoracic pressure on the discharge and on the rate of breathing. Curve *A*, normal extra-thoracic pressure. Rate 15 per min. Curve *B*, 5 mm. Hg positive pressure outside thorax. Rate 27 per min.

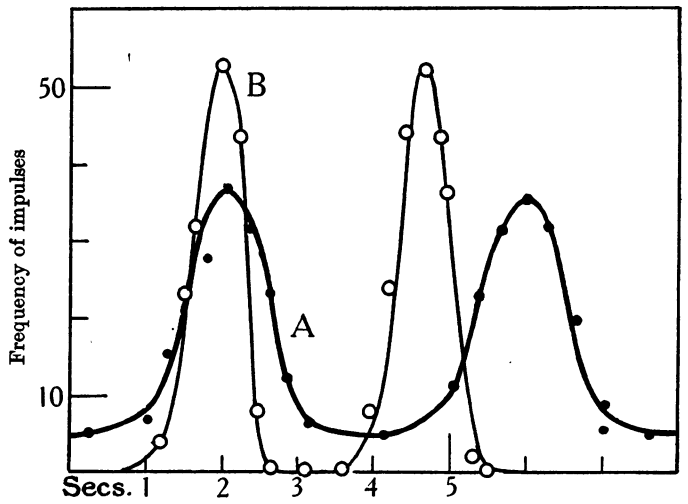

Fig. 17. Afferent vagal discharge in decerebrate cat showing the effect of dyspnœa due to rebreathing. One vagus intact. A. Normal, rate 15 per min. B. Dyspnœa, rate 22 per min. The impulses have been counted in two inspirations only.

effect as to its reduction in the later part of the cycle. By recording the action currents in the intercostals it can be shown that the motor discharges are more powerful and of slightly longer duration when the pressure is increased. This would naturally follow from the smaller inhibitory discharge at each inspiration. The greater motor discharge should tend if anything to lengthen the period required for rebuilding, but as there is less residue of inhibition during this phase the threshold for the discharge will be lower and will be reached earlier. If this is the factor which determines the increase in rate we ought to find that increased pressure on the thorax will have the greatest effect when there is a considerable background of persistent inhibition. This is certainly the case, for the preparations which have shown the quickened rhythm have been those in which the vagal discharge has normally remained at a fairly high level during expiration. Some tonic contraction of the diaphragm and intercostals (as often occurs with chloralose) favours the reaction, since it keeps the lungs slightly expanded; where such tone is absent there is often no increase in rate with increased intrathoracic pressure though there is a considerable slowing when the pressure is reduced. A reaction of this kind is usually found when dial or urethane are used as anæsthetic.

Change of rate in dyspnœa. The quickening of breathing in CO_2 dyspnœa can be explained on the same lines. In the decerebrate cat with vagi cut the rate rarely changes by as much as 25 p.c. when the animal breathes into a closed space. With the vagi intact the rate may be more than doubled. Curves showing the frequency of the vagal impulses are given in Fig. 17, though, as before, the changes in lung volume might be substituted for them. Under the increased CO_2 there is (*a*) a steeper rise to a higher maximum frequency at inspiration, due to the more forcible movement, and (*b*) a more sudden fall to a lower minimum at expiration, due to the greater emptying of the lungs. If it had much after effect the greater vagal discharge at inspiration might tend to slow the rhythm by interfering with the recovery phase, but the cutting short of activity and the absence of any vagal discharge during recovery will both tend to quicken the rhythm. By exposing the thorax to reduced external pressure (Hammouda and Wilson's method) the greater collapse of the lungs can be prevented and the vagal discharge at expiration restored to its former value. This causes an immediate slowing of the rate, though as asphyxia supervenes the effect is less and less marked, owing, presumably, to the rapid building up of active material in the centre.

The stretch receptors and the expiratory muscles.

The emptying of the lungs may be an active as well as a passive process and the afferent discharge in the vagus may influence expiration as well as inspiration. It is a simple matter to record the action currents of the expiratory muscles with hypodermic needle electrodes, for these allow us to lead from the individual motor units in each muscle without dissection of the chest wall and without danger of interference from neighbouring muscles. By this method it can be seen that in cats and

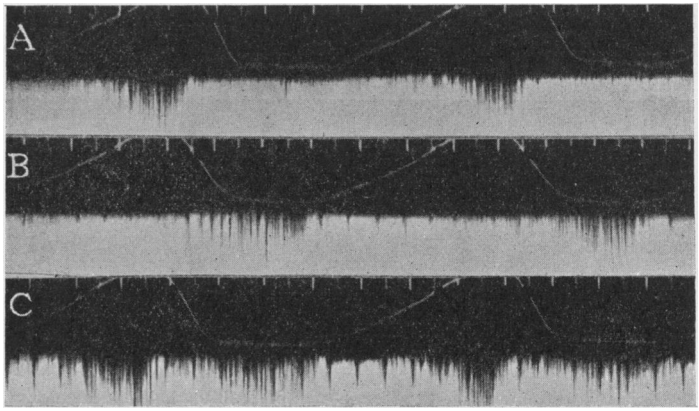

Fig. 18. Records from the external intercostal muscles (inspiratory) and the triangularis sterni (expiratory) made with hypodermic needle electrodes in a cat anæsthetized with chloralose. Signal moves upwards when lungs expand. A. External intercostal. B. Triangularis sterni. C. Both needles in parallel to show time relations of inspiratory and expiratory contraction. The regular excursions are due to the electrocardiogram.

rabbits under chloralose (and lying on the back or side) the triangularis sterni and the internal intercostals are regularly in action during the expiratory phase of the cycle. In decerebrate preparations and in animals under dial and urethane they are occasionally in action, in deep chloroform anæsthesia never. When they are not in action during quiet breathing they are not usually brought into action by moderate degree of dyspnœa.

Records from a cat under chloralose are given in Fig. 18. Two hypodermic electrodes were used, one in the external intercostal muscle and one with its point a few mm. deeper so that it led from the triangularis sterni. In record C both needles were connected in parallel with the

amplifier so as to show the time relations of the two discharges more clearly. The respiratory signal records the pressure change in a 20-litre bottle connected to the trachea tube. In these records the expiratory discharge fills up most of the gap between inspirations. If chloroform is given in addition to the chloralose the discharge becomes progressively shorter and is limited to the period when the deflation is at a maximum. Eventually it disappears, and in very deep anæsthesia the contraction of the external intercostals also ceases leaving only the diaphragm in action.

The periodic contraction of the expiratory muscles, when it occurs with the vagi intact, continues like that of the inspiratory muscles after the vagi are divided. The expiratory activity preserves its phase relationship to the inspiratory and both are unaffected by the state of expansion

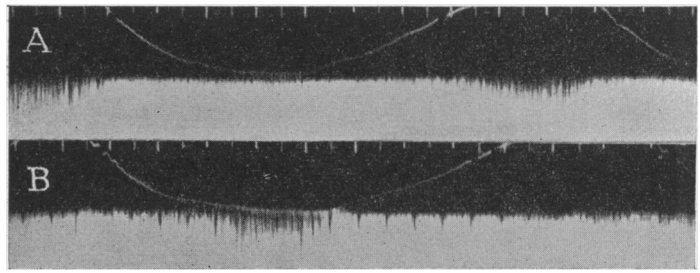

Fig. 19. Same preparation as Fig. 18 after section of both vagi. A. External intercostal. *B.* Triangularis sterni. Inflation or deflation of the lungs has now no effect on either discharge.

of the chest (Fig. 19). It is probable, therefore, that the expiratory discharge is as much a product of the automatic beating of the respiratory centre as the inspiratory. The nerve cells responsible for it are so linked to the nerve cells responsible for inspiration that the two groups cannot come into action simultaneously and normally the expiratory activity occurs as an after effect of the inspiratory. But it can also be made to occur independently by an afferent discharge from the stretch receptors. There is some variation in this respect between one preparation and another. In some an inflation of the lungs causes an immediate expiratory contraction even though it is timed so that the normal inspiratory contraction is completely suppressed. In others the expiratory contraction develops more slowly and an inflation of the lungs is a less potent stimulus than a period of inspiratory activity.

In his account of respiration in animals after various operations on the brain stem Lumsden [1923] states that electrical stimulation of the

vagus inhibits expiratory contractions. This may well be due to the effect of the nerve fibres coming from the endings which are excited by suction of air from the lungs. These cause an immediate reflex inspiration and an inhibition of the expiratory contraction, and on electrical stimulation of the vagus their effect may outweigh that of the fibres from the stretch receptors. The latter certainly favour expiratory as they inhibit inspiratory activity.

As far as the vagal control of breathing is concerned, the action of the expiratory muscles can be regarded merely as an additional factor tending to reverse the effect of inflation. In so far as it secures a smaller lung volume at expiration the contraction of these muscles will help to establish the type of vagal discharge which promotes rapid breathing. But in animals under chloralose there is often some tonic contraction of the diaphragm to oppose deflation. Thus the breathing may be no faster than it is in animals with no expiratory activity but more complete muscular relaxation.

Discussion.

As usual it is easier to reach definite conclusions about the sensory mechanism than about its action on the central nervous system. The main group of sense organs in the lung behaves no differently from the muscle spindles or stretch receptors in other parts of the body. They give the usual serial discharge of impulses when they are stretched, they become very slowly adapted to the stimulus, they are relatively unaffected by anæsthetics, lack of oxygen, etc. Their function is to signal the volume of the lungs at each moment and they continue to do this for half an hour or more after the heart has stopped beating. Since the volume of the lung changes relatively slowly, the endings must be of the slowly adapting or postural type. The only evidence of rapidly adapting endings supplied by the vagus is the occurrence of an initial brief discharge in some preparations when the lungs are collapsed by suction, but these have not yet been analysed in records made from a few nerve fibres.

The stretch receptors in the lung resemble those in muscle in their effect on the central nervous system. Both influence it to cut short the movement which has stimulated them, and by so doing prevent the inconvenience or damage which might come from unrestrained motor activity. But the lungs must be adequately ventilated, and if the range of movement is restricted the movements must succeed one another at shorter intervals. Without the vagal mechanism the respiratory centre (in the conditions of these experiments) slowly charges and discharges

itself with little variation of rhythm. The impulses from the stretch receptors quicken the rhythm by cutting short the discharge and so hastening the recharging process. They are inhibitory, but they seem to act mainly by raising the discharge threshold, not by preventing the accumulation of active material.

This view need not be further elaborated since it was stated with more detailed evidence in Head's paper. It postulates a type of inhibition which seems to agree in general with the results of Eccles and Sherrington on the limb reflexes. It is natural to compare the inhibition of the respiratory beat with that of the heart beat, and at first sight the results seem to differ radically, for the respiratory beat is quickened and the heart beat slowed. But the former is quickened by inhibition confined more or less to each period of activity; it is slowed if the inhibitory discharge fills up the whole cycle. When the heart is slowed by electrical stimulation of the vagus it is exposed to a steady inhibition comparable to that produced on the respiratory centre by holding the lungs inflated. The slow subsidence of the effect from single stimuli [Brown, Eccles and Hoff, 1932] makes it unlikely that the inhibition of the heart could be made to fluctuate rapidly enough in relation to the cycle to establish a fair parallel between the two cases.

Throughout the preceding discussion the term respiratory centre has been used as a name for that part of the central nervous system in which the rhythmic activity takes origin. Where this occurs is a matter for studies such as those of Lumsden [1923] and does not concern us here. Slow potential changes in phase with respiration can be detected in the brain stem of the rabbit and seem to resemble those found in the isolated brain stem of the goldfish by Adrian and Buytendijk [1930]. In the mammal, however, the brain stem cannot be isolated and it is a much more difficult matter to analyse the waves and to make sure that they are not artefacts due to movement of fluid, etc.

Summary.

The action of the vagus in respiration has been studied in the cat by recording the impulses in single afferent fibres.

1. Some of the discharges come from end organs which are not affected by lung movement, *e.g.* from end organs in relation to the heart and to the trachea.

2. Of the end organs which respond to lung movement and give measurable action currents, the only kind in action normally is that stimulated by expansion of the lung.

3. These end organs behave like the muscle spindles and stretch receptors in other parts of the body. They become very slowly adapted to the stimulus. In normal breathing the maximum frequency of the discharge in single fibres varies from 50 to 100 per sec., though rates as high as 300 per sec. are produced by extreme inflation. With moderate inflations the frequency varies directly with the lung volume.

4. Carbon dioxide in amounts higher than 10 p.c. produces a very slight diminution in the discharge to a test inflation, but the effect is not outside the range of error. Ventilation with nitrogen and failure of the circulation have no immediate effect. After 10–20 min. the discharge to a constant stimulus declines more rapidly, but there may still be some response an hour after the heart has stopped beating.

5. Chloroform vapour in amounts of 2·5 p.c. or less has no obvious effect on the response of the end organs. Higher proportions produce a rapid failure, but there is a rapid recovery as soon as the lungs are inflated with air.

6. Suction of air from the lungs stimulates a fresh set of end organs. These may come into action in pathological conditions, but they are not stimulated by the normal movement of the lung and there is no evidence of their activity in moderate dyspnœa. In the rabbit they are stimulated at expiration when the extra-thoracic pressure is increased.

7. The effect of the vagus on respiration must be due mainly to the impulses from the stretch receptors in the lung. These have an inhibitory effect on the respiratory centre, but the inhibition occurs mainly during the phase of activity. Periodic inhibitions may therefore quicken the rate of breathing, as Head suggested, by cutting short the motor discharge and so hastening recovery.

8. The expiratory muscles (triangularis sterni and internal intercostals) contract regularly in cats and rabbits anæsthetized with chloralose. They are sometimes in action in decerebrate cats but never in cats under deep chloroform anæsthesia. In chloralosed animals the expiratory muscles remain in action after section of both vagi.

9. The afferent control of the respiratory movements is discussed.

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