ON THE REGULATION OF RESPIRATION. BY HENRY HEAD, M.A. (Pl. I. to IX.).

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PART I. Experimental.

§ 1. The Method of Registering the Respiratory Movements.

The many methods now in use for studying the movements of respiration fall naturally into two main groups according to whether the movements of the air to and from the lungs or the contractions of the diaphragm are recorded. Those of the first class trace their origin from the "tambour enregistreur" of Marey. The original method of using this instrument for recording the respiratory movements was somewhat as follows. A T shaped cannula was inserted into the trachea and one of the limbs was connected with a tambour. The other limb was either left entirely open or was closed just sufficiently to allow the tambour to answer to the movements of the expired and inspired air. This method is so inefficient that it was soon modified as follows. A flask of considerable capacity was connected on the one hand with the tracheal cannula and on the other with the tambour. The animal now breathes out of and into the flask and the variations in the volume of the air of the flask are registered by the rise and fall of the lever of the tambour. But the tubing connecting the flask with the tracheal cannula must be extremely short if dyspnoea is to be avoided. I found that three inches of tubing attached to a cannula of at most an inch in length were quite sufficient to cause distinct dyspnoea. In order to obviate this error and to shorten the connexion between the flask and the trachea as much as possible Hering caused a flask to be constructed with the tracheal cannula let directly into one of its sides.

Gad has recently introduced a very accurate method depending on a modification of this principle. By means of his aeroplethysmograph


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he registers not only the amount of the air passing in and out of the lungs at each breath but also any change in their capacity which may take place in consequence of a tonic contraction of the inspiratory or expiratory muscles.

Knoll has registered the variations in the thoracic pressure by inserting a cannula into the pericardium, and Bernstein¹ has used the oesophagus for the same purpose.

Knoll² has also described a very useful piece of apparatus which has been in use in this laboratory for many years. It consists of a glass box in which the whole animal is enclosed. A cannula perforates one wall of this box and is connected with the trachea so that the animal breathes the air outside the box whilst the movements of the air inside the box are registered by means of a tambour.

However, all these methods, admirable as most of them are, failed in my experiments for the following reason. All “pneumatic” methods register simply the increase and decrease in the volume of the lungs, however caused. Now I purposed to continue the experiments of Hering and Breuer⁴, who used artificial alterations in the volume of the lungs as a means of stimulating the end organs of the vagi. But it is obvious that if, for instance, the lungs are inflated, the lever of the registering apparatus will be enormously affected and the whole curve will be altered by the very stimulus whose effect on the respiration we wish to study. Hering and Breuer in their experiments registered the respiratory movements with either a mercury or Fick manometer. A T shaped cannula was inserted into the trachea and was connected with a mercury manometer. The third limb was left open to the air. Through this third limb air was forced into the lungs, the mercury rose in the manometer and owing to the standstill in the respiration produced by the inflation remained for some considerable time steady at the same level. The writing point then began to rise slowly, but suddenly sank on the appearance of the first inspiration. The third limb of the T cannula was now opened, for the animal could not breathe in the confined space at its disposal. This experiment was sufficient to show that artificial


inflation of the lungs caused a standstill of the respiratory movements, and it is by no means difficult by watching the movements of the diaphragm to assure oneself that collapse of the lungs causes an inspiratory movement. But such a method although amply demonstrating the result of a single inflation is quite inadequate for the investigation of the complicated phenomena following the periodic repetition of such stimuli.

Some method depending on the registration of the movements of the diaphragm seemed to offer the best chance of success for work on these lines. But all the phrenographs in use labour under the same disadvantage, that any movement of the animal, whether passive or active, tends to cause such alterations in the curve that it is impossible to compare the curves obtained before and after such a disturbance. Suppose for instance that the lever of a Rosenthal phrenograph is inserted between the liver and the diaphragm and the point is marking regularly on the drum; on inflating the lungs the diaphragm and with it the lever is passively pushed downwards towards the abdomen; the pause caused by the inflation gives place to an active expiration and the lever is again passively pushed from its previous position—this time in an upward direction. These passive movements so obscured the phenomena following artificial variations in the volume of the lungs that a new method had to be found for registering the respiratory movements.

When the diaphragm of a rabbit is examined from the abdominal side the strong development of the two anterior limbs is very noticeable. They extend along the posterior surface of the xiphoid process and are comparatively sharply separated from the rest of the diaphragm. On dividing the skin and opening the abdomen in the middle line the xiphoid process comes into view, covered on each side by the lower part of the origin of the pectoralis major. On separating this part of the muscle by passing the scissors upwards on each side of the bony portion of the process the two slips of the diaphragm are seen each covered by a small band of muscle. This must be carefully removed and the two anterior limbs of the diaphragm are then laid bare, covered in the middle line by the bony portion of the xiphoid process. Each limb is supplied with blood from above by a small branch of the musculo-phrenic division of the internal mammary artery. This branch together with its accompanying vein runs alongside the bony part of the process, sending off a branch to supply the muscle of its side about midway between the ensiform cartilage and the base of the xiphoid process. By carefully inserting a fine pair of scissors between the muscles and the bone beginning in the
neighbourhood of the cartilage it is possible to separate the two limbs of the diaphragm without much injury to their tissue and without dividing the vessels which supply them. After the bone is thus prepared it is separated from the ensiform cartilage to which the muscles remain attached. The muscles are then separated as carefully as possible from the under surface of the bony process. We now have a muscular band slightly attached at the one end to the anterior wall of the thorax and in connection with the ensiform cartilage at the other end. The injury suffered by the muscles is confined to the small portion in the middle line where the two slips join one another and send a few fibres to be attached to the bony part of the xyphoid process. Neither the nerves nor the blood vessels supplying these muscles are affected if the operation has been properly carried out. But these limbs of the diaphragm no longer have a fixed origin for they arise from the ensiform cartilage. The ensiform cartilage was the fixed point from which by their contraction they pulled the diaphragm forwards and downwards. It thus becomes necessary to give them an artificial fixed point if we are to register their movements with accuracy. If they are fixed to the chest wall every inspiration will cause the cartilage to approach the sternum, owing to the contraction of the muscles, and the contraction curves will no longer be disturbed by the contraction of the remaining portions of the diaphragm. The muscles are best fixed to the chest walls as follows. A thread, carrying at the one end a small flat button, is passed from the abdominal side through the diaphragm and the walls of the thorax between the fifth and sixth ribs. As soon as the thread is drawn tight the button is pressed firmly against the muscle and thus fixes it to the anterior wall of the thorax. A similar operation is performed on the other side and the two threads are knotted together over the front of the sternum.

A thread is now attached to the ensiform cartilage and after passing over a pulley is attached to an ordinary writing lever such as is used to register the contractions of a frog's muscle. This marks on the smoked surface of the drum of a Hering kymograph.

Now as the fixed point of this system lies on the wall of the thorax anything that causes an alteration in the position of the chest wall will also affect the lever in connection with the muscle. It is therefore important to know how far the excursions of the lever are due to passive alterations in the position of the fixed point and how far they are due to active contractions of the muscles. An exactly similar lever is therefore attached to the knot formed by the union of the two threads and
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registers all movements of the chest wall whether passive or active. Now, when the chest wall moves, both levers will describe a similar curve, whereas a contraction of the diaphragm will only appear on the curve drawn by the lever in connection with the two separated slips of muscle. The action of, and necessity for, such a control is especially evident in the experiments on the effect of dividing the vagi.

To pass on to the disadvantages of this method, I must first of all mention that the muscles can never be prepared without some injury to their tissue. But the injury should only affect the inner (median) edge of each strip, and the vitality of the muscle seems but little affected by so small an injury. The real disadvantage caused by this injury lies in the formation of small blood-clots in the injured portion, which tend to obscure any contraction which lasts for an unusually long time. It is always advisable to gently touch the muscles with a small piece of sponge before beginning any series of experiments, and it is always well to so weight the lever that the muscles return to the same point after each normal inspiration. It is also a disadvantage that the curve is affected by the movements of the thorax, but in the rabbit such movements so rarely occur that they are of but little moment.

In spite of its apparent simplicity the preparation of the muscles at first presented considerable difficulty and it was some time before they could be prepared in a condition of unimpaired vitality. But even after considerable practice cases now and then occur, though rarely, where owing to degeneration in the muscles themselves or to some peculiarity in their nerve or blood supply the preparation entirely fails.

In every case the animals used were rabbits, and in every case they were more or less deeply narcotized. At first I injected chloral through a cannula tied into the internal jugular vein. A peculiar form of restlessness, which mostly took the form of periodic movements of swallowing, made its appearance so often that I gave up this method. In such cases I noticed that the urine became tinged with blood and an investigation of the kidney revealed clots of blood between the pyramids of startling size. I have since injected chloral under the skin and, since resorting to such hypodermic injections, this restlessness has entirely ceased to appear. The amount injected varied according to the experiment to be performed. Gad recommends 2 c.c. of a 1:2 solution per kilo, body weight. This produced a very deep narcosis, and is in my opinion too strong a dose for many experiments.
§ 2. Normal Respiration.

On examining the normal respiratory curve traced by the aeroplethysmograph or any other instrument which registers the movements of air to and from the lungs the following points will be noticed. The inspiration is sudden and sharp and its tracing is but slightly curved; the expiratory curve is at first very quick and sharp but rapidly becomes slower, so that the last part of the tracing is strongly curved; the expiration may then end by tracing a horizontal line.

However, this curve represents the movements of the air during respiration and not the actual movements of the respiratory muscles. We should therefore expect that such curves would differ slightly from those obtained by registering the actual movements of a portion of the inspiratory musculature. Curve x (Plate I) has been chosen as more or less typical of the normal movements of the muscular slips, used in my method, during the various phases of respiration. As the lever by which this curve was traced described an arc when the drum was at rest I have drawn lines at various points on the curve to show the curves which would have been produced by the lever had the drum not been in motion.

It will be seen that the contraction begins rapidly but soon becomes slower. The lever is still rising with considerable rapidity when the contraction suddenly ceases. The first portion of the descending curve is so rapid that it almost coincides with the line traced by the lever when the drum is at rest. The muscles continue to elongate but with decreased rapidity until they are completely relaxed. However it must not be forgotten when examining the fall of the lever that the downward curve will always appear steeper than is warranted by the actual rate of elongation in the muscles, in consequence of the weight attached to the lever. The writing point now traces a horizontal line representing the complete elongation of the muscular tissue.

I have already used the words inspiration and expiration in what may be considered a somewhat loose manner, and shall proceed to define what is understood in this paper by these terms. An inspiration is taken to mean a rhythmic contraction of the inspiratory muscles from its beginning to the moment when the muscles begin to relax again. An expiration on the other hand begins when the muscles begin to relax and ends with the birth of the next inspiration. Such an expiratory period may consist of three stages. Firstly, the time taken up in the relaxation of the muscles after the inspiratory contraction. Secondly,
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the pause—the stage during which the muscles remain completely relaxed. Lastly, under certain circumstances this pause may pass gradually into an active expiration, caused by the contraction of the abdominal muscles. I have refrained from dividing the respiratory period into inspiration, pause and expiration, for I think a closer analysis will show that, at any rate in the rabbit, the active expiration is but a stronger form of the same phenomenon which shows itself normally as a pause. The inspiration bursts through the pause and the inspiratory muscles contract with great rapidity at the beginning of the inspiratory phase. On the other hand if an active expiration appears it does not arise suddenly like the inspiratory contraction but the pause appears to give place to a slow but ever increasing contraction of the abdominal muscles. From the summit of this contraction arises the next inspiration by a sudden contraction of the inspiratory muscles following immediately on a sudden elongation of those of the abdomen. From the moment that the inspiratory curve ceases to rise to the birth of the next inspiration there is no violent change such as is seen at the close of the active expiration and beginning of the next inspiration.

I have just pointed out that of the three stages into which the expiratory period may be divided the last—active expiration—is often absent in the rabbit. Now we also find that under certain conditions the second stage—that occupied by the pause—also fails to make its appearance. The muscles begin to relax after the inspiratory contraction, but before they have elongated completely the next contraction begins (cf. Curve i, Plate I). Under such circumstances the muscles are never completely elongated, even at the most extreme point of the expiratory period, and remain in a permanent condition of tonic contraction. On this tonic contraction the rhythmic movements are superposed. Gad\(^1\) has already shown that under certain conditions the volume of the thorax is permanently enlarged by the tonic contraction of the muscles of the chest wall, and this tonic contraction of the diaphragm is the expression of the same phenomenon in the greatest of the inspiratory muscles.

It might be objected that the form assumed by the curves of elongation and contraction were not the expression of the activity of the respiratory centre but were in part due to some peculiarity in the activity of the two muscular slips. In order to examine this possible source of error I prepared and stimulated the phrenic nerve on one or on both sides with an interrupted current. If the drum was revolving

\(^1\) "Die Regulierung der normalen Atemung," du Bois Reymond's Archiv 1880.
at the ordinary pace the rise and fall of the lever, at the beginning and end of the stimulation, were so sudden as to be indistinguishable from an instantaneous rise and fall (Curve vii, Plate I). It was only when the drum was revolving at a pace enormously in excess of any used in my experiments that the line of the contraction curve appeared anything but instantaneous. The rapidity and promptness with which the muscles contract is beautifully shown by allowing the divided phrenic of the left side to lie on the heart, when every heart beat is followed by a contraction of the diaphragmatic muscles of the left side. On Curve vii, Plate I, the left phrenic nerve was stimulated electrically during the normal inspiratory contraction, and the difference in rate between the rise of the curve under the nervous influence of the inspiration and in consequence of the artificial stimulation is very distinctly shown. The second portion of this curve shows the result of stimulating the phrenic nerve during the expiratory pause. Again, in order to make sure that the contraction remainder which appeared on certain curves was really due to a tonic influence from the respiratory centre I divided the phrenics and the levers at once full to a position representing the complete elongation of the muscular slip.

§ 3. Division of the Vagi.

If we turn to the literature on the Physiology of Respiration we find that, next to artificial stimulation of the vagi, division of these nerves plays the largest part in the experiments of most observers. Yet there was scarcely any experiment which gave such contradictory results. If the vagi are cut or ligatured in the ordinary way it is quite impossible to prophesy the results. Sometimes the breathing becomes irregular and the animal restless, sometimes division is followed by long expiratory pauses, and sometimes the breathing at once assumed the type which in all cases ultimately followed division of the vagi. But when the vagi are divided in the ordinary way the experiment is complicated by the stimulation of the central end of the cut nerves; not only do we remove any influence which the vagi may normally exert on the breathing but we stimulate them at the same time. However Gad¹ has shown that we possess a method of dividing the vagi without stimulation. He states that if they are frozen all impulses from the periphery are at once cut off without the slightest stimulation to the nerves themselves and, as

¹ "Die Regulirung d. normalen Athmung."
far as my experience goes, I can entirely confirm his statement. For if one vagus is frozen a stimulus applied on the peripheral side of the frozen point is totally without effect on the breathing. If the frozen nerve is removed from the freezing apparatus it can be frozen again on the central side of the frozen point without causing any alteration in the respirations, although a mechanical or electrical stimulus is as active as ever.

But it would seem that the vagi are comparatively insensible to mechanical stimulation, and I think we must seek the cause of the extreme variability in the phenomena, which follow their division in the ordinary way, elsewhere than in the assumption of mechanical stimulation. Knoll\(^1\) has shown that it is extremely easy to stimulate the vagi by closing the current in the divided nerve itself. If the nerve be cut and allowed to fall into the wound in the neck or if it be moistened with "physiological" salt solution the nerve current is closed and all the phenomena of a slight expiratory stimulation make their appearance. If a small piece of dry gutta-percha or other non-conducting substance be laid under the prepared vagus, division whether by freezing or with a sharp pair of scissors always causes the same result. But if the gutta-percha is now moistened with salt solution or if the cut nerve is allowed to fall back into the moist wound the scene at once changes. Expiratory pauses, with or without irregularity in the breathing, at once make their appearance. Exactly the same changes appear when the nerve is taken from the freezing apparatus and allowed to fall back into the wound. In fact electrical stimulation of the divided nerves by their own current seems to be the most important factor in the production of the phenomena which are said by most observers to follow the division of these nerves. Now although it is possible to divide the vagi with a sharp pair of scissors without stimulating them, the precautions necessary to avoid stimulation are so many that I far prefer Gad's method.

The apparatus I have used for cooling the vagi below 0° C. differs slightly from that used by Gad. An ordinary glass filter of suitable size is divided just above the tube and the bottom closed with a flattened cone of copper into which two bent copper wires are soldered. The filter is filled with pounded ice and salt and in a few seconds the temperature of the wires has sunk below 0° C.

Another method for dividing the vagi which is sometimes of great

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value is as follows. It is well known that a nerve can be completely anaesthetized by subjecting it to the vapour of ether\(^1\). The vagus is placed in a tube of indiarubber so constructed that ether vapour can be passed over it without affecting the atmosphere which the animal is breathing. In a few seconds the nerve is completely anaesthetized and is incapable of conducting impulses from the periphery. Now, by blowing air through the tube, instead of ether vapour, the nerve completely recovers its conducting power and seems to be totally unaffected, even if the process be repeated several times, provided no fluid ether has entered the tube.

The results which follow division of one vagus are generally very transitory. As soon as the nerve is completely frozen the inspirations become stronger. The rate of contraction is the same, but the strength and duration of the inspirations are increased and the curves become somewhat rounded at the summit (Curve i, Plate I). The expirations may be somewhat longer but generally remain unaltered. The animal will continue to breathe in this manner for a considerable time if left undisturbed. But after the space of about half an hour or even less, the breathing has almost completely returned to the original form although the vagus is completely divided. However division of one vagus is not infrequently followed, not only by an increase in the strength of the rhythmic inspiratory contractions, but also by a shortening of the expiratory period and the appearance of a varying amount of tonic contraction. But if only one vagus has been divided this tonic contraction rapidly wears off and ultimately, if the animal be left long enough, the breathing almost completely returns to the form it assumed in the intact animal. Thus division of vagus may cause changes of two distinct kinds. The inspirations are invariably more or less increased, both in strength and duration, but the expirations may either remain unaltered or, at any rate in the first few moments, be considerably shortened.

Now if the second vagus be frozen we see exactly the same changes as followed division of one vagus although in a more pronounced form (Curve ii, Plate I). As soon as the second nerve is divided the muscles contract to an extent far exceeding that of any normal inspiration. The inspiration forms a broad flat crested curve closely resembling those seen on closing the trachea of the same animal during the expiratory phase.

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A sudden fall proclaims the advent of the first expiration. Here again we find that removal of the influence which the vagi normally exert on the breathing leads to an increase in the force and duration of the inspiratory contractions but leaves the rate of contraction unaltered. The muscles may elongate completely after each contraction, in which case the expiratory periods are generally a little longer than normally. But far more often the elongations are incomplete and the base line of the curve appears to be raised. Now Gad has shown that in the rabbit the thorax generally assumes a permanently inspiratory position after division of the vagi. It therefore seemed possible that this apparent rise of the base line of the curve might be purely passive and be caused by the position of the thorax. I therefore divided the vagi, and as usual the base line of the curves traced by both levers rose, though the rise of the lever in connection with the muscular slips was distinctly more pronounced. Both phrenic nerves were then cut as rapidly as possible and the muscles at once elongated, showing that they were previously in a condition of permanent tonic contraction (Plate I, Curves iii and iv).

After the removal of the vagi it is no longer possible for a change in the volume of the lungs to affect the respiratory centre. We might therefore suppose that the form which the breathing assumed after division of these nerves was the expression of the independent activity of the respiratory centre. But Markwald1 has pointed out that there is still another factor to be taken into account. If the brain be separated from the medulla just above the auditory striae a rabbit will continue breathing rhythmically for a very considerable time. The changes produced by this operation are very different in different cases. The breathing either becomes rapid and the inspiratory contractions are increased in strength or it may become laboured, both expiration and inspiration being increased in strength and duration. If the cut has passed a little too low the animal lies perfectly passive, and although it does not breathe spontaneously it is the most perfect reflex machine. The slightest diminution in the volume of the lungs evokes a well formed inspiration. However in every case division of the vagi causes the same marked change. Directly the second vagus is divided the muscles begin to contract and an inspiration of enormous duration is produced (Curve v, Plate I). In a normal animal an in-

spiratory contraction after division of the vagi lasts at most five seconds—and even this is very long. If the brain has been previously separated from the medulla the inspiration which follows division of the second vagus frequently lasts 40 sec. and according to Markwald may reach the enormous duration of one minute seventy-five seconds. But here again a close examination of the curve reveals the fact that the rate of contraction of the inspiratory muscles remains unaltered although the strength and duration of the contraction are enormously increased. This strong inspiration is put an end to by a quick elongation of the muscle. Both thorax and diaphragm ultimately return to a condition of complete rest and the abdominal muscles then begin to contract slowly. When this active expiration has reached a considerable height the abdominal muscles suddenly relax and the inspiratory muscles at once contract violently, producing a second strong and long inspiration. It is a noticeable fact that, when the brain has been separated from the medulla previously to the division of the vagi, each expiration produces a complete return to the state of rest of both thorax and diaphragm. I have never seen even traces of a tonic contraction of the inspiratory musculature.

The first inspiration after dividing both vagi deserves closer attention, especially as Gad scarcely notices it in his description. It mostly far exceeds in duration though not in height any inspiration which follows it. The expiratory elongation which follows it is mostly very incomplete, and if a tonic contraction appears after dividing the vagi it is always most marked between the first and second inspirations. The duration of this first inspiration is intimately connected with the appearance of an inspiratory tone. The same influences which affect the one also affect the other. If the animal is narcotized with morphia or is very deeply under the influence of chloral or if it has been in any way maltreated, we invariably find that the tonic contraction of the inspiratory muscles is absent and that the first inspiration which follows the division of the vagi differs little from those which come after it. If the vagi are divided whilst the animal is breathing an atmosphere of hydrogen or is in any way dyspnœic both phenomena are again absent. It is therefore no wonder that a tonic contraction is absent when the vagi are divided after the separation of the brain from the medulla, for after the enormous inspiration which follows this operation the centre must be in a condition of violent dyspnœa. In fact we find that under such conditions if the animal be left to itself it gradually dies of slow asphyxia. On the other hand the most favourable conditions for the
appearance of an inspiratory tone and a long primary inspiration are a
light narcosis and the least possible exhaustion. The fact that the
animal is breathing an atmosphere of pure oxygen when the vagi are
divided is not of the slightest influence on either the tone or the
duration of the first inspiration except in as far as it assures the
absence of dyspnoea. The remaining factors which tend to prolong the
inspiration which immediately follows division of both vagi I shall
discuss in a further section.

A peculiar phenomenon must now be described which sometimes
makes its appearance after the vagi have been frozen. If the vagi are
removed from the freezing apparatus ("Thermode") as soon as they
are frozen, by means of a paint-brush moistened in salt solution, they
will regain their conducting power after a time although they have
been completely frozen. If the nerves are allowed to lie in the wound
so that they become completely thawed and are tested at stated
intervals (say of a minute) by inflating the lungs, a stage appears in
which the inflation instead of inhibiting the inspirations actually shortens
the expiratory period (Curve vi, Plate I). The strength of the inspiratory
contractions is not increased but their duration is prolonged, and owing
to the incomplete expiratory elongation a tonic inspiratory contrac-
tion appears during the inflation. After about an hour and a half this
phenomenon gradually disappears and inflation of the lungs produces
the normal effect. Thus if the vagi are carefully removed from the
freezing apparatus as soon as they are frozen three stages appear.
Firstly, a considerable time (10 min.) during which inflation of the
lungs produces no effect at all—the vagi have lost their conducting
power. Secondly, a stage during which an inflation produces an in-
spiratory effect; and thirdly, one in which inflation of the lungs produces
the usual inhibition of inspiration. If however the vagi are allowed to
remain some time (10 sec.) on the thermodes this paradoxical effect
ceases to make its appearance when the nerves are removed from
the freezing apparatus. It entirely fails to appear during the recovery
of the vagi after they have been anaesthetized with ether vapour, and
I am totally at a loss to account for its appearance. That this pheno-
menon is due to the vagi and not to some other nerve is proved by its
immediate disappearance when the vagi are divided with the scissors.
That it is not due to the alteration in blood-pressure caused by the

1 Gad calls the two bent wires on which the nerves are frozen "Thermodes." "Die
Regulirung der normalen Athmung."
inflation is shown by its ceasing to appear after the vagi have been cut through below the frozen spot although inflation of the lungs is still followed by the same change in the blood-pressure.

To sum up the results of the experiments described in this section:

1. We must be careful in dividing the vagi to guard against the stimulating effect which follows closure of the nerve current in the central end of the cut nerve.

2. Freezing the vagi does not stimulate them, and the mechanism by which the freezing is effected has the additional advantage of preventing the closure of the nerve current.

3. Division of the vagi without stimulation invariably produces an overpowering inspiratory effect on the breathing. The vagi normally exert an influence on the breathing, the absence of which shows itself in increased inspiratory activity of the respiratory centre, both tonic and rhythmic. There is no increase in the rapidity with which the inspiratory muscles contract but only an increase in the strength and duration of the contraction.

4. The tonic inspiratory contraction wears off after a time and we notice that the blood in the left side of the heart is distinctly darker than normal. This seems to show that the respiratory movements which follow division of the vagi are unable to keep the blood up to the normal standard of aeration. The appearance of an inspiratory tone is very dependent on the condition of the centre. Deep narcosis, dyspnoea or exhaustion of any kind tend to prevent its appearance.

§ 4. The Effect produced by increasing the Duration of the Normal Action of the Vagi.

We have just seen that the vagi undoubtedly exert some influence on the respiratory centre even during normal respiration. Let us assume with Hering and Breuer and with Gad that this influence is due to the effect produced on the end organs of these nerves by the periodic alterations in volume which occur during normal breathing. Now we obviously have the power of artificially altering this normal influence in two directions. We can either allow the lungs to expand or collapse under the influence of the normal respiratory movements and then by closing the trachea keep them for a greater or less time in one or other condition. By this means we increase the duration of the influence normally exerted by the vagi during respiration. Or,
secondly, we can actually inflate the lungs above the normal volume and allow them to collapse completely by puncturing the thorax. Here we increase the strength of the influence normally excited by the vagi.

If the trachea is closed at the moment that a normal inspiration has reached its height the breathing remains for a short time unchanged (Curve ix, Plate I). The inspiratory contraction ceases and the muscles elongate in the same way and at the same rate as normally. Then follows the usual pause, and it is here that we first notice anything unusual. The pause is enormously prolonged and, in those cases where a tonic contraction was present during the expiratory period, the muscles continue to relax and finally reach a condition of complete elongation. After a varying interval the pause is broken by a strong inspiratory contraction, considerably stronger than the normal inspirations. The elongation which follows is again complete, and a second long pause follows, which is however shorter than the one which preceded it though longer than the normal pauses. If the tracheal cannula is now opened the respiratory movements become very rapid. The expiratory elongations are frequently incomplete and an inspiratory tone appears during the first few moments following the opening of the trachea.

If on the other hand the trachea is closed during the expiratory pause the breathing suffers the converse change (Curve viii, Plate I). The pause during which the trachea is closed lasts the usual time and is followed by an inspiratory contraction of the normal rapidity. But when the inspiration has reached the normal strength, instead of ceasing abruptly, it goes on increasing until the curve reaches a point far above the crests of the normal inspiratory contractions. As the contraction decreases in rapidity, the curve gradually bends over until the lever traces an almost horizontal line. Thus closure of the trachea in the expiratory phase of respiration causes an increase in the strength and duration of the inspiratory contractions. This strong inspiratory contraction is followed by a quick and complete elongation, which is succeeded by a pause equal to, or at any rate not more than twice, the duration of the normal pause. From this pause arises a second long and strong inspiration closely resembling its predecessor. If the trachea is now opened the breathing resumes the normal type and we never find even a trace of the peculiar shortening of the expiratory period which is so common when the trachea is opened after closure in the inspiratory phase of respiration.

These experiments show that, as Hering and Breuer pointed out,
the stimulus to the vagi is not simply caused by the expansion of the lungs but by their expanded condition. For in every case the expansion was that caused by a normal inspiration and yet the breathing was affected as long as the lungs were kept in the expanded position.

Though the effect produced by closing the trachea during the different phases of respiration depends on the condition of the lungs and not on the act of collapse or expansion, yet the breathing does not cease to be rhythmic. Closure in the inspiratory phase produces a long pause, but this pause is always ultimately broken by a strong inspiration. Similarly the strong inspiration which follows closure in the expiratory phase is always followed by an expiration. Thus although the lungs remain permanently in a condition of collapse or dilatation the centre still continues to send out rhythmical impulses although these impulses are much modified by the effect produced by the condition of the lungs.

To sum up the results of the experiments described in this section.

1. Closure of the trachea in the inspiratory phase of respiration causes a decrease in the inspiratory activity of the centre, whilst closure in the expiratory phase causes an increase both in the strength and duration of the inspiratory contractions.

2. This effect is produced by the volume assumed by the lungs and not by the act of expansion or collapse.

3. In spite of the fact that the lungs remain permanently dilated when the trachea is closed at the height of the inspiratory phase, the pause so produced is broken by an inspiration. Conversely in spite of the permanently diminished volume which the lungs assume when the trachea is closed in the expiratory phase the strong expiration so produced is cut short by an expiration. Thus although the lungs do not materially alter in volume the activity of the centre, though profoundly altered, still remains rhythmic.

§ 5. Increase and Diminution in the Volume of the Lungs.

A. The immediate effect of increasing and diminishing the volume of the lungs.

In the previous section we examined the effect of increasing the duration of the natural stimulus. We now pass on to the results which follow an increase in its strength.
The first result of a gentle inflation of the lungs is an immediate cessation of all inspiratory activity. If the inflation falls in the period represented on the curve by the pause this same pause is immensely prolonged (Curve xiii, Plate I). It can last 15—20 sec. or even longer, but is always sooner or later broken by an inspiratory contraction. If on the contrary the inflation takes place in the middle of an inspiratory contraction this contraction is at once inhibited and the prolonged pause begins. I have already mentioned that under certain circumstances the expiratory elongations are incomplete. If the lungs are inflated under such conditions, the rhythmic inspiratory contractions cease at once and the lever sinks to the point it occupied between any two previous inspirations (Curve xi, Plate I). But if the lungs are allowed to remain in a dilated condition the lever continues to sink steadily, so that if the pause last long enough the muscles finally elongate completely. Thus an inflation of the lungs inhibits, firstly, the rhythmic inspiratory contractions and, secondly, any tonic contraction of the inspiratory muscles that may be present.

I must here reiterate the warning of Hering and Breuer\(^1\) against violent inflation. The inflation must always be made with care; for if the air is violently blown into the lungs an inspiration always precedes the inhibitory pause. This is especially the case with animals that are but lightly narcotized. It is in all probability due to stimulation of some sensory nerve in the body-wall, for I have seen it in but lightly narcotized animals even after division of the vagi. Just such an inspiration appears when any sensory nerve is stimulated electrically\(^2\). But this is not the only evil effect resulting from violent inflation. Violent distension of the lungs easily leads to lesions in their structure which appear in a post-mortem examination as permanent emphysematous distension of the alveoli.

If the lungs are kept in a dilated condition sufficiently long the pause is ultimately broken by an inspiration. This "interrupting" inspiration appears on the curve as a quick contraction often double the strength of that of a normal inspiration. The contraction is quick but of short duration compared with its strength, and it therefore traces a curve with a very sharp apex. It closely resembles the inspirations which often appear when the trachea is closed in the inspiratory phase and

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is very different from the strong flat-topped inspirations which follow division of the vagi or closure of the trachea in expiration.

There are two methods by which the volume of the lungs may be diminished. Either the thorax may be perforated and the lungs allowed to collapse completely¹ or the volume of the lungs may be diminished by applying suction to the opening of the tracheal cannula.

Hering and Breuer² describe the results which are produced by complete collapse of the lungs as follows:—"Beim plötzlichen Lungencollaps durch Pneumothorax tritt ein mächtiger Inspirations-tetanus ein, der, bei Kaninchen bis zu 8 und 10 Secunden Dauer hat und auch im weiteren Verlauf nur durch kleine Oscillationen des Zwergfells um seine Inspirationsstellung unterbrochen wird, bis allmählig bei wachsender Dyspnoe grössere expiratorische Erschlaaffungen des Diaphragmas eintreten."

Although Hering and Breuer did not use a graphic method for recording these results the words I have just quoted are an exact description of the curves I have obtained on allowing both lungs to collapse suddenly. If but one side of the thorax is opened we obtain a similar curve except that the tetanus is very much shorter than when both sides of the thorax are opened (Curve xi, Plate II). But on the other hand the animal recovers quite easily after opening one side of the thorax and there is no necessity to have recourse to artificial respiration, an advantage which will be appreciated later. If but one lung is allowed to collapse the inspiratory tetanus which is produced expands the lung on the sound side of the thorax to a very considerable extent. This expansion undoubtedly produces a depressing effect on the inspiratory activity of the centre and probably accounts for the comparative shortness of the tetanus produced by the collapse of only one lung. I hit upon the following method for obviating the inhibition from the sound lung and at the same time keeping the animal alive without artificial respiration. The right vagus was divided and as soon as the breathing had almost completely returned to the normal type the left side of the thorax was opened. Now in many cases the vagus of the left side but slightly supplies the right lung. Thus under favourable conditions we have almost completely got rid of all possibility of inhibition from expansion of the right lung (Curve viii, Plate II). On perforating the

¹ I need scarcely say that the lungs do not become atelectatic. As soon as the thorax is opened the lungs recede from the body-wall and assume a volume considerably below that which they reach in even extreme expiration. They however still contain air.

² Page 5, Bd. LVII. 1868.
left side of the thorax after dividing the right vagus the muscles contracted quickly and remained for over 20 sec. in a condition of tetanic contraction. The first incomplete expiratory elongations then appeared, but it was many minutes before the respiratory movements in any way approached the normal type. Finally the breathing assumed a form differing from the normal in the strength of the inspirations and the presence of a certain amount of inspiratory tone. I may add that the tetanus following collapse of one lung under such conditions is seldom so long as on Curve viii, Plate II which has been chosen for its extremely marked characteristics. Obviously it is now in the power of the experimenter by inflating the lungs of such an animal and then allowing them to collapse to repeat to a certain extent the phenomena attending the original collapse (Curve v, Plate II). But on attempting to reproduce the phenomena of the original collapse by this means, we find that the result of collapse is not always the same. Normally the inflation causes a pause in the breathing which as soon as the lungs are allowed to collapse gives way to a strong tonic contraction; the rhythmic breathing is completely abolished for several seconds. But if the animal is made dyspnoeic this tonic contraction ceases to appear on collapse of the lungs. The more dyspnoeic the animal, the less is the tone which follows collapse, and sometimes the only effect of the return of the lungs after the inflation is to slightly increase the strength of the rhythmic inspiratory contractions. The appearance of the tonic contractions is intimately dependent on the due aeration of the respiratory centre.

I pointed out above that after collapse of one lung the breathing was characterized by a certain amount of tonic contraction of the inspiratory muscles. After a considerable time this tone wears off and the muscles elongate completely after each inspiration. If the lungs are now inflated and allowed to collapse, not only do we observe the phenomena that I have just described but we also find that the tonic contraction has returned. After the immediate effect of the collapse has passed, the muscles still fail to elongate completely after each inspiration.

So far we have considered the effect of what may be called permanent inflation and collapse of the lungs. It is of especial importance for the study of the phenomena produced by artificial respiration to determine the effect of what may, in comparison, be called momentary expansion and collapse.

A momentary inflation must not be caused by a violent burst of air but the lungs must be gently inflated and allowed to return at once to
their normal volume. If such an inflation falls in the inspiratory period the sudden shortening of the inspiratory contraction is often the only result produced (Curve i, Plate II). If on the other hand the lungs are inflated during the expiratory pause, that pause is mostly considerably lengthened (Curve x, Plate II). If an inspiratory tone is present, a momentary inflation applied during the expiratory phase causes a slight elongation of the muscles, whereas if it falls in the inspiratory period it simply shortens the rhythmic inspiratory contraction and leaves the tone unaffected.

A momentary diminution in the volume of the lungs can be produced by sucking a small quantity of air from the trachea and allowing the lungs to return at once to their normal volume. If such a momentary collapse falls in the period occupied by the pause, an inspiratory contraction at once appears resembling a normal inspiration enlarged in every direction (Curve ix, Plate II). If the suction is applied when a normal inspiration has just reached its height the already rounded curve gives place to a sudden further contraction of the inspiratory muscles, which in its turn describes a rounded curve and suddenly ceases. Thus a second inspiration is produced taking its rise from the crest of the normal contraction of the inspiratory muscles. If the suction is applied during the expiratory elongation before the muscles have completely elongated, a fresh inspiration is produced rising from the still contracted diaphragm.

B. The positive afteraction caused by increase and diminution in the volume of the lungs.

The effect of a momentary increase or diminution is not confined to the period during which the inflation or suction lasted. Even after the lungs have returned to their normal volume the breathing is considerably modified. If the lungs are momentarily inflated during the expiratory pause, not only is that pause prolonged but the next inspiratory contraction is also considerably smaller than usual. Each succeeding inspiration gains in strength, but it is not until the sixth inspiration after an inflation lasting at most 1¼ sec., that the inspiratory contractions reach the normal strength (Curve ii, Plate II). This partial suppression of the contractions is frequently accompanied by a lengthening of the expiratory pauses although this is not always the case. On Curve i, Plate II the only effect produced by a momentary inflation was a diminution in the strength of the inspirations.
Now it appeared possible that this diminution in inspiratory activity which followed a momentary inflation might be due to some amelioration in the condition of the air in the lungs. I therefore substituted hydrogen for air as the means of inflation, but exactly the same afteraction appeared after inflation with either gas. In fact it would be impossible to tell on most of the curves which gas had been used in the inflation. However a slight difference sometimes appears in the later stages of the afteraction. For the afteraction, if strong, renders the inspirations so ineffactual that the hydrogen in the lungs is not sufficiently replaced by air and a certain amount of dyspnoea results. Even when air is used some dyspnoea not infrequently appears owing to the smallness of the inspirations caused by the afteraction following the inflation. If oxygen is used instead of air the same phenomena follow the inflation but dyspnoea fails to appear in spite of the smallness of the inspirations, and the afteraction continues to make itself felt undisturbed by dyspnœsic changes. Under otherwise similar conditions the afteraction produced by a momentary inflation of the lungs with oxygen, air or hydrogen is the same in kind and degree though not in duration.

Thus a momentary inflation of the lungs produces a depressing effect on the inspiratory activity of the centre not only during the time during which the lungs remain distended, but even after they have returned to their normal volume. We now see how such stimuli succeeding one another at a definite rate could undergo summation.

Such afteraction is not confined to a momentary inflation but also appears after a momentary diminution in the volume of the lungs. On Curve ix, Plate II the strong inspiration caused by the momentary suction is followed by an elongation of the inspiratory muscles. But the elongation has scarcely reached the crests of the normal inspirations before it becomes slow. Long before the muscles are completely elongated a second inspiration appears. This inspiration is followed by an elongation which though stronger than its predecessor is not complete. Thus each succeeding inspiration starts from a lower base line but 4—5 sec. elapse before the breathing becomes normal. During the first few seconds after a momentary diminution in the volume of the lungs the expiratory elongations are incomplete, the pause is absent and there is a distinct inspiratory tone—all signs that the centre is still under the influence of the diminution in volume.

Thus both momentary increase and diminution in the volume of
the lungs affect the respiratory centre, not only during the duration of the mechanical change of volume, but even after the lungs have returned to their normal condition.

C. The negative afteraction following increase and diminution in the volume of the lungs.

If the lungs are inflated the expiratory pause produced by the inflation is finally broken by an inspiratory contraction although the lungs are still dilated. This contraction is strong, of comparatively short duration and traces a curve with an extremely sharp crest. But if the lungs are allowed to return to the normal volume just before this interrupting inspiration would normally have made its appearance, the breathing undergoes a very different modification (Curve vi, Plate II). At the moment of collapse the inspiratory muscles contract strongly but somewhat slowly and produce a strong flat-topped curve. This contraction is of about the same strength as the interrupting inspiration but exceeds it greatly in duration. Thus sudden return of the lungs to the normal volume after an inflation of considerable duration produces a strong and long inspiratory contraction.

It might be objected that both the interrupting inspiration and the strong inspiratory effect which follows collapse after an inflation were due to the dyspnoea which must necessarily result during such a long pause in the breathing. However I think that this explanation will scarcely suffice to explain either phenomenon. For, provided the inflations are of the same strength, the pause is broken at almost exactly the same moment whether oxygen, air or hydrogen be used to inflate the lungs. It is true that the strength of the interrupting contraction is generally greatest when the lungs have been inflated with hydrogen, but the time of its appearance is the same with all three gases under otherwise similar conditions. Again the fact that the animal is breathing oxygen during and after the inflation does not diminish the strength of the inspiratory contraction which is produced by the sudden return of the lungs to their normal volume after the inflation. Indeed it is rather favourable, than otherwise, to its appearance, for if the animal is dyspnoeic this inspiratory contraction is of much shorter duration and is much more difficult to produce than when the lungs have been inflated with air or with oxygen. Thus the continued action of an inhibitory stimulus would appear to be favourable to the appearance of a burst of inspiratory energy at the moment
negative afteraction for want of a better name.

When the inflation has not lasted very long, return of the lungs to the normal volume is often followed by a slow inspiratory contraction of great duration but of comparatively small strength (Curve iii, Plate II). Although the contraction may last 3 sec. the curve scarcely reaches the summits of the normal inspiratory curves. The elongation which follows is very incomplete, and a varying amount of tonic inspiratory contraction is present. The normal breathing is not regained until after several inspirations. It appears as if the return of the lungs to the normal volume after an inflation, which lasts some little time, tends to throw the centre into a condition particularly favourable to the appearance of inspiratory tone and favours the abolition of rhythmic breathing. From this condition of tonic activity, the centre is awakened by the inhibitory stimulus produced by the dilatation of the lungs.

As I pointed out above, collapse of the lungs to a volume below the normal is particularly active when it follows an inflation. On Curve v, Plate II complete collapse of one lung after an inflation abolished rhythmic breathing for 7 secs. Even if but a little air is allowed to enter one side of the thorax (Curve xi, Plate I), collapse of the lungs after an inflation causes an inspiratory contraction of very great duration. Now during the normal breathing of an animal with slight pneumothorax, the diaphragm is in a condition of slight tonic contraction. If we wait until the tone has disappeared, and then inflate the lungs, not only is rhythmic breathing abolished for the first few secs. after the collapse of the lungs, but even after the animal again breathes rhythmically, we notice that the tone has returned. It again disappears after a minute or more to be again recalled by another inflation.

Thus a prolonged inflation of the lungs tends, on its removal, to throw the centre into a condition favourable to the appearance of a tonic inspiratory contraction and to the abolition of rhythmic breathing.

We might expect that if a prolonged inflation of the lungs produced an inspiratory negative afteraction, a prolonged diminution in their volume might be followed by a negative afteraction, which appeared as a decrease in the inspiratory activity of the centre. Under certain conditions this is actually the case. If suction is applied and care be taken that the lungs do not dilate again to any considerable extent, a strong inspiratory contraction is produced which often lasts many seconds before the first elongation appears. If the trachea is suddenly opened before the appearance of this expiratory elongation, the lungs dilate and
under certain circumstances the inspiratory muscles elongate at once. The pause which now follows is longer than normal, and there appear to be at any rate traces of an expiratory afteraction. However this negative afteraction is by no means so satisfactory as that which follows a prolonged inflation. For it is not at all easy by means of suction to produce a prolonged inspiratory contraction in any way comparable to the prolonged pause following an inflation. When the suction has lasted 3 or 4 seconds the rhythmic breathing begins again, and all chance of a negative afteraction is past. It is true that collapse of the lungs to a volume below the normal produces a prolonged inspiratory tetanus comparable to the long pause produced by inflation, but unfortunately we are unable to bring them back to their normal volume without actually inflating them. If however a large dose of chloral has been administered, or if the brain has been separated from the medulla, the negative afteraction is often very well marked (Curve vii, Plate II); and if the animal has been experimented on for a considerable time, the strong inspiration which follows suction is frequently followed by a prolonged expiratory pause, when the lungs return to their normal volume.

To sum up the results of the experiments described in this section—

(1) Increase in the volume of the lungs causes a cessation of all inspiratory movements whether rhythmic or tonic. The expiratory pause thus produced is always finally broken by a strong inspiration provided the lungs remain long enough in a dilated condition.

Decrease in volume causes an increase in the inspiratory activity of the centre, which shows itself in the development of a strong tonic inspiratory contraction.

(2) An inflation of the lungs of short duration not only depresses the inspiratory activity of the centre during the time it lasts but also influences the breathing after the lungs have returned to their normal volume.

Momentary diminution in the volume of the lungs not only causes a strong inspiratory contraction during the time that it lasts, but also causes an inspiratory tone to appear between the rhythmic inspirations which follow the return of the lungs to their normal volume.

This has been called the positive afteraction.

(3) Provided the inhibitory pause has not been interrupted by an inspiration, return of the lungs to their normal volume after a prolonged inflation causes an outburst of inspiratory energy which tends to abolish the normal rhythm and substitute tonic inspiratory innervation.
REGULATION OF RESPIRATION.

Under certain circumstances the return of the lungs after a diminution in their volume tends to increase the expiratory phase of respiration. This has been called the negative afteraction.

(4) The essential factors of all these phenomena are independent of the gas with which the lungs may be filled. However, dyspnoea is distinctly unfavourable to the appearance of tonic innervation of the inspiratory muscles, and decidedly favourable to the maintenance of rhythmic respiration.

§ 6. On certain other Stimuli which affect the Activity of the Respiratory Centre.

Besides the so-called "natural" stimulation of the vagi it is of course possible to stimulate the trunks of one or both nerves electrically. Rosenthal¹ states that electrical stimulation of the divided vagi caused an increase in the inspiratory rhythm, and if strong enough might lead to an actual tetanus of the inspiratory muscles. Expiration could only follow stimulation of the vagi when the current escaped onto the superior laryngeal nerve. But if we divide one vagus and stimulate the central end with the weakest interrupted current that in any way affects the breathing, a distinct expiratory effect is produced. The pauses between the inspiratory contractions become longer than normal and the inspirations themselves are generally less powerful. As Knoll² has shown this is just the effect which is produced when the divided nerve is stimulated by closing its own current. If the central end of the divided vagus is dropped into the wound in the neck or onto any moist surface the inspirations are diminished in height and the pauses which separate them increased in length. The stimulus rapidly decreases in intensity but can be renewed by raising the vagus and allowing it again to fall back onto the moist surface.

With the ordinary du Bois induction apparatus, this primary expiratory effect is not always easy to see, for we rapidly pass into a region where the stimulation produces an inspiratory effect. A slight increase in the strength of the stimulus then produces the well-known "tetanus" of Rosenthal. This "tetanus" is however not produced so much by a quickening in the inspiratory rhythm as by a decrease in the completeness of the expiratory elongations (cf. Curve xiii, Plate II). The breathing is but slightly increased in rate, but with every increase in

1 Die Athembewegungen und ihre Beziehung zum Nervus Vagus, Berlin, 1862.
the strength of the stimulus the muscles elongate less completely until the diaphragm finally falls into a condition of tonic contraction. A further increase in the strength of the stimulus leads to the appearance of active expiratory contractions of the abdominal muscles (Curve xii, Plate II). This effect is possibly produced by the escape of the current onto the superior laryngeal nerve.

Now it is interesting to notice that the behaviour of the vagus during electrical stimulation of varying strength is very similar to that of an efferent nerve containing two kinds of fibres. Biedermann\(^1\) has shown that the nerve which supplies the claw of the crayfish is composed of two kinds of fibres different in structure and in their behaviour to reagents. The smallest effective stimulus to this nerve causes the claw to open, whilst a slight increase in the strength of the stimulus causes it to close promptly.

If one vagus is divided and the central end stimulated electrically it is possible to regulate the stimulus so that it just fails to produce a complete “tetanus.” The diaphragm remains to a certain extent permanently contracted but the rhythmic movements are not completely abolished. If the lungs are inflated during such a stimulation the diaphragm at once elongates (Curve iv, Plate II). But as soon as the lungs return to the normal volume the muscles contract violently to a considerably greater extent than before the inflation and rhythmic respiration is completely abolished for several secs. Thus an electrical stimulus, which was unable to produce a complete tetanus, is able to entirely abolish rhythmic breathing after an inflation, in consequence of the negative afteraction.

If both vagi are divided and the electrical stimulus is increased until it produces an active expiration, cessation of the stimulation is followed by a very long inspiratory contraction (Curve xii, Plate II), similar to that seen on dividing both vagi in a normal animal. Here we have an instance of negative afteraction produced by electrical stimulation when both vagi are divided. When only one vagus has been divided this same phenomenon appears but in a much less marked form owing to the restraining effect produced by the dilatation of the lung of that side on which the vagus is intact.

The changes in respiration which normally follow death from chloroform are generally said to be due to stimulation of the ends of the vagi in the lungs by the chloroform vapour\(^2\). But I think

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2 Cf. Knoll.
that the following experiment points to a rather different conclusion. If the lungs of a normal animal are inflated with either chloroform or ether vapour an expiratory pause is produced as usual. But this pause is rapidly broken by a strong and long inspiration resembling that seen when the vagi are divided. Although the lungs remain dilated the muscular strips of the diaphragm trace curves closely resembling those seen after dividing the vagi. As soon as the trachea is opened the breathing gradually reassumes the normal type. It would seem from this experiment that the chloroform or ether vapour tended rather to paralyse than to stimulate the ends of the vagi in the lungs. Again it is singularly difficult to produce the usual results which follow increase and diminution in the volume of the lungs if the animal is breathing ether or chloroform, and it would seem as if both chloroform and ether tended to anaesthetize the end organs of the vagi. However owing to the complicated action of both chloroform and ether it is very difficult to assure oneself of the truth of this theory.

The application of chloroform vapour to the nasal mucous membrane of a rabbit acts, as Kratchmer\(^1\) showed, as an expiratory stimulation. The expiratory pauses become very long, the inspirations are weak, and if the stimulus is strong, active expirations may make their appearance. It is interesting to notice that the duration of the effect produced depends very much on whether the vagi are intact or not. In a normal animal the passage of a slight amount of chloroform vapour up one nostril caused an expiratory pause lasting 5 secs. One vagus was then divided and as nearly as possible the same stimulus caused a pause lasting 8 secs. Lastly the second vagus was divided and the pause was found to be increased to 15 secs. This experiment illustrates the effect produced by the vagi during normal respiration.

Electrical or mechanical stimulation of any ordinary sensory nerve produces an inspiratory change in the breathing\(^2\). But if the stomach or any of the abdominal viscera be stimulated mechanically or electrically the general result is either an increase in the expiratory pauses or more often a strong active expiration. Such an active expiration does not of course show itself on my curves except indirectly, but it is perfectly easy to assure oneself of its presence by watching the movements of the abdominal muscles and of the contents of the abdomen.

To sum up the results obtained from the experiments in this section—

\(^1\) Ueber Reflexe v. d. Nasenschleimhaut auf Athmung und Kreislauf, 1870.
\(^2\) Knoll.
(1) Electrical stimulation of the divided vagus produces \textit{firstly} an increase in the expiratory pauses and a decrease in the strength of the inspiratory contractions; \textit{secondly} Rosenthal's "tetanus" which is due rather to incomplete expiratory elongation of the inspiratory muscles than to an increase in the rapidity of the inspirations. And \textit{thirdly}, probably owing to escape of current, active expirations accompanied by movements of swallowing.

(2) The application of chloroform vapour to the nasal mucous membrane causes expiratory pauses the length of which are very dependent on whether the vagi are intact or not.

(3) Stimulation of any sensory nerve in the body wall produces an inspiratory effect, whereas stimulation of the visceral sensory nerves tends to cause an active expiration.

§ 7. \textit{Ventilation} or "\textit{Artificial Respiration}".

We have examined the effect of a single diminution or increase in the volume of the lungs and now pass on to the phenomena which follow their periodic repetition. Most of the machines for "Artificial Respiration" or "Ventilation" simply inflate the lungs periodically and allow them to return to the normal volume after each stroke of the pump. With all such apparatus, it is only possible to watch the effect of periodically repeating short inflations. But in 1870 Prof. Hering designed a double pump by which both periodic increase and periodic decrease in the volume of the lungs could be produced. When the whole pump is in action the first stroke pumps a certain quantity of air or other gas into the lungs and the next stroke removes exactly the same quantity. The strength and rate of the inflations and suctions can be regulated with the greatest nicety. Now it is obvious that by connecting one half only of the pump with the trachea it is possible to produce periodic inflations, whilst by using only the other half the ventilation consists simply of periodic suctions. Under such circumstances each inflation or each suction as the case may be is separated from the next by a nicely regulated pause during which the lungs can return to their normal volume. I have found it convenient to speak of ventilation which consists only of periodic inflations as positive; that consisting of periodic suctions as negative; and that consisting of alternate suctions and inflations as compound.

If the first inflation of positive ventilation happens to fall in the inspiratory phase the inspiratory contraction is at once cut short.
REGULATION OF RESPIRATION.

As soon as the first stroke of the pump is over another inspiration begins and may reach its full height before the occurrence of the next inflation. Thus the normal rhythm quickly adapts itself to the periodic stimulation and each stroke of the pump corresponds to a pause in the breathing, each pause in ventilation to an inspiratory contraction. The breathing now "follows" the artificial respiration.

But when discussing the effect of a single short inflation I pointed out that every inflation exerted a depressing influence on the inspiratory activity of the centre even after the lungs had returned to their normal volume. Thus every stroke of the pump during positive ventilation not only produces an expiratory pause during the time that it lasts but also tends to decrease the size of the following inspiratory contraction. During positive ventilation every inspiration is smaller than that which preceded it. The inspiratory contractions get smaller with every stroke of the pump until they entirely disappear (Curve vii, Plate V). See also b. woodcut, p. 31. The muscles then remain quiescent even between the strokes of the pump. If ventilation is now stopped a pause follows which Rosenthal called Apnoea. But we must not forget that the cessation of all rhythmic respiration during the time that the ventilation lasts is the same phenomenon as the pause which appears on stopping the ventilation, whatever theory we may adopt to explain it. I therefore propose to call the former Apnoea of Ventilation and the latter the Apnoea pause.

If we use the opposite form of ventilation in which each stroke of the pump sucks a given quantity of air out of the lungs the breathing is modified in a very different way (Curve vi, Plate III). The first suction causes a strong inspiratory contraction. As soon as the suction is over the lungs dilate and the inspiratory muscles elongate rapidly. Then follows the second stroke of the pump accompanied by a second strong inspiratory contraction. Here again the breathing "follows" the artificial respiration although with exactly the converse movements to those produced during periodic inflations. Here each stroke of the pump is accompanied by an inspiratory contraction and followed during the pause by an expiratory elongation. But as I showed above, each momentary suction tends not only to produce an inspiration during the time it lasts but also to depress the expiratory activity of the centre even after the lungs have returned to their normal volume. Thus every elongation is less complete than the one which preceded it, and finally all rhythmic respiratory movements are completely abolished. But although rhythmic breathing has ceased the inspiratory muscles
are contracted to an extent far in excess of any normal inspiration. This is exactly the converse phenomenon to the expiratory pause which finally results during periodic inflations and I propose to call it the Apnoea of negative Ventilation. See c. woodcut, p. 31.

Some may object to the use of the word apnoea for such a condition as this and insist that it can only be applied to a condition in which all the respiratory muscles are at rest. But there is nothing in the meaning of the word which prevents its application to the cessation of all rhythmic respiration, whether the inspiratory muscles be tonically contracted or not. The one type is so exactly the complement of the other that one generic term is required for both, and I shall therefore speak of the phenomena following negative ventilation as “Inspiratory Apnoea” and that following positive ventilation as “Expiratory or Inhibitory Apnoea”. If stress is laid on the form of the ventilation independent of the form of apnoea it produces, the apnoea will be spoken of as that of positive or negative ventilation as the case may be.

As we might expect, compound ventilation produces an apnoea intermediate between the other two forms (Curve v, Plate IV). Supposing the first stroke of the pump produces an inflation the inspiratory contraction is promptly cut short. But this inflation is at once followed by a suction which calls forth a strong inspiration. Thus each complete cycle of the pump produced two distinct effects—firstly an expiratory effect and secondly an inspiratory contraction; and the breathing takes up the rhythm of the ventilation. Now each inflation tends to abolish the inspiratory rhythm of the centre even after the lungs have returned to their normal volume. Each suction tends to produce an exactly opposite afteraction. The resultant of these two opposite afteractions is very interesting and consists in the total abolition of rhythmic respiration and the substitution of a certain amount of tonic inspiratory contraction. The inspiratory contractions and the expiratory elongations become very small and finally disappear, the lever tracing a line of varying height according to the relative value of the two stimuli. For although the actual increase in the volume of the lungs under the influence of the one stroke may be exactly equal to their diminution at the next stroke, the stimuli so caused are not always of equal value. The conditions which cause one form of stimulus to be more effective than the other will be described later on.

If the curve produced by ventilation composed of alternate inflations
and suctions is carefully examined and compared with those produced by positive and negative ventilation, the clearest traces of double action can be seen. During positive ventilation each inspiratory curve is sharply pointed and is separated from the others by a considerable interval. During negative ventilation on the other hand the crests of the inspiratory curves are broad and elongated and the expiratory periods are very short. But during compound ventilation the crest of each inspiration is separated from that of the next inspiration by almost exactly the same interval that separates the trough of each elongation curve from the lowest point of the next elongation.

If one side of the thorax is opened so that the lung of that side collapses, periodic inflations produce an apnoea closely resembling that caused by compound ventilation (Curve v, Plate VI). Each inflation causes the usual decrease in inspiratory activity, but each return of the lungs to their abnormally diminished total volume produces a strong inspiratory effect. In fact the collapse of the lungs after each inflation may now produce quite as strong an inspiratory effect as if compound ventilation were applied to the lungs of an uninjured animal. Even if but a slight amount of air has been allowed to enter one side of the thorax, positive ventilation no longer produces a complete expiratory standstill
but leaves the diaphragm in a condition of slight tonic contraction after rhythmic breathing has been abolished.

But now and then even in a perfectly normal animal positive ventilation leaves the diaphragm slightly contracted after rhythmic breathing has been abolished. If the ventilation is continued for a considerable time after rhythmic respiration has ceased, the muscles gradually elongate and may finally elongate completely. But if the ventilation is weak and the animal very sensitive traces of inspiratory tone can be discovered even after the rhythmic breathing has ceased (Curves iv and viii, Plate V). Although not a normal occurrence this phenomenon is especially prone to appear in animals in which a single inflation was followed by a strong negative afteraction.

When we consider the form assumed by the apnoea in consequence of periodic suction, we must not forget that this form of ventilation is in reality only an extreme form of compound ventilation. For during the later stages of negative ventilation the lungs do not dilate to the normal volume after each suction but to a volume far above the normal. The diaphragm is strongly contracted even between the strokes of the pump and, as soon as each suction ceases, the lungs expand proportionately. It is indeed very doubtful whether during the later stages of negative ventilation the suction really reduce the volume of the lungs even to the normal. Yet in spite of this each suction undoubtedy still produces an inspiratory effect. Thus even negative ventilation is only an extreme variation of compound ventilation.

Now in certain animals expansion of the lungs appears to be a particularly active stimulus. The slightest dilatation of the lungs produces a marked effect on the breathing, whilst diminution in their volume produces comparatively little result. In such animals negative ventilation produces the usual abolition of rhythmic breathing, but the tonic contraction is scarcely stronger than that produced by compound ventilation in other animals (cf. Curves i and iii, Plate VI). Here the fact that the lungs return to a volume above the normal between the strokes of the pump seems to greatly decrease the strength of the inspiratory tone which is produced by this form of ventilation.

In one animal, out of the many used in these experiments, the inspiratory tone produced by negative ventilation was not nearly as great as that caused by compound ventilation in a normal animal. A slight inflation produced a pause of quite abnormal length, and on closing of the trachea in the inspiratory phase a pause appeared as long as that normally following an inflation.
To sum up the results of this section—

(1) Periodic inflations gradually abolish rhythmic breathing and produce a pause during which the inspiratory muscles generally remain completely elongated.

(2) Periodic suctions also abolish rhythmic respiration but the inspiratory muscles remain in a condition of permanent tonic contraction.

(3) Compound ventilation produces phenomena intermediate between those which are produced by the two other forms of ventilation.

(4) If one lung is allowed to collapse positive ventilation now produces an apnoea closely resembling that following compound ventilation, and under certain circumstances even in the normal animal the disappearance of rhythmic breathing in consequence of positive ventilation may be accompanied by the appearance of a slight inspiratory tone. Conversely, negative ventilation may sometimes produce an inspiratory tone but slightly stronger than that ordinarily caused by compound ventilation.

§ 8. The Apnoea Pause.

All forms of ventilation produce one phenomenon in common—the abolition of rhythmic respiration—although the condition of the inspiratory muscles varies very much according to the nature of the ventilation.

We have seen that positive ventilation leads to the production of an apnoea which is normally characterised by the complete elongation of the inspiratory muscles. When the ventilation ceases the muscles remain perfectly quiescent for a varying length of time (Curve vii, Plate V). The apnoea pause is finally broken by a small and shallow inspiratory contraction. Then follows a considerable pause, which is broken by a slightly stronger inspiration. The normal type of breathing is gradually regained by an increase in the strength of the inspiratory contractions and by a decrease in the pauses between them. Such an apnoea pause is the exact continuation of the apnoea which appeared during the positive ventilation. But the longer the pause lasts, the poorer must be the condition of the air in the lungs, until finally the pause is broken by an inspiration. But the centre is still dominated by the afteraction of the ventilation and a very slight dilatation of the lungs is sufficient to check the inspiratory contractions. As the influ-
ence of the afteraction gradually wears off the inspirations increase in size and the expiratory pauses decrease in duration. In fact the recovery of the centre after an apnoea pause is accompanied by the same phenomenon that appeared after a momentary inflation. The assumption that the pause was broken by an inspiration in consequence of the growing dyspnoea is supported by the fact that the only difference between the apnoea produced with oxygen or with air lies in the postponement of the first inspiration.

But this is not the only type of pause which follows the cessation of positive ventilation. If the ventilation is stopped as soon as the rhythmic breathing has ceased, the muscles frequently do not remain elongated (Curve iii, Plate III). They begin to contract slowly as soon as the ventilation ceases and trace a slow contraction curve which may finally reach the height of the crests of the normal inspirations. In this case the pause is replaced by a slow inspiratory contraction of great duration. This contraction is followed by an incomplete elongation of the inspiratory muscles, and the normal breathing is gradually regained by an increase in the expiratory elongations and by a slight simultaneous increase in the strength of the inspiratory contractions. I long thought that this phenomenon was due to dyspnoea but the substitution of hydrogen for air as the medium of ventilation led rather to the abolition of this gradual rise than to its increase.

If we count the number of inflations that are sufficient to produce this form of pause and then repeat the experiment, increasing the duration of the ventilation, the pause is modified. For the first few seconds after the ventilation has ceased the muscles remain relaxed and a true expiratory pause appears. But the muscles then begin to contract slowly and form the same long slow contraction curve that I have just described. If on the other hand we decrease the duration of the positive ventilation the breathing assumes a peculiar type when the ventilation ceases (Curve v, Plate III). The muscles contract quickly to about half the height of a normal inspiration and trace a long flat curve lasting about three seconds. Then follows the first elongation, which is cut short by the appearance of another flat inspiration. Each subsequent inspiration becomes stronger and each expiratory period longer until the normal type of breathing is regained. Thus if the duration of the ventilation is short and the animal sensitive a more or less tonic form of inspiratory energy seems particularly liable to invade the period which intervenes before the normal rhythm is reestablished.

I pointed out above that the apnoea which appears during negative
ventilation is the resultant of the action of two opposing forces, the diminution in volume caused by the suction and the return to a volume, considerably exceeding the normal, after each stroke of the pump. The rhythm is abolished and the muscles remain in a condition of tonic contraction of varying strength. Now this resultant afteraction lasts even after the ventilation has ceased just as was the case with the afteraction caused by positive ventilation. As soon as the ventilation stops, the muscles begin to elongate (Curves iv and vi, Plate III). But long before they have completely elongated they remain for a moment stationary and then contract again slightly. Then follows a more complete elongation and true rhythmic respiration begins again. But both the expiratory elongations and the inspiratory contractions are feeble and regular rhythmic breathing is not reestablished until several seconds have elapsed.

If this form of apnoea pause were the exact expression of the afteraction caused by the negative ventilation the muscles would remain contracted to exactly the same extent as during the ventilation. But we must not forget that the lungs are dilated to a quite abnormal extent. The strong tonic inspiratory contraction which is produced by the afteraction tends to cause its own destruction by enormously dilating the lungs. It is therefore no wonder that the muscles begin to elongate as soon as the ventilation ceases. The point to be noticed is that rhythmic breathing fails to appear for several seconds after the ventilation has ceased in spite of the great dilatation of the lungs. Even when the rhythmic breathing reappears, it is characterised by the incomplete expiratory elongations which we have so often taken as an indication that the centre is still under an inspiratory influence. The stronger the ventilation the more gradual is the elongation of the muscles and the longer the time that elapses before rhythmic breathing is reestablished (cf. Curves iv and vi, Plate III). The following experiment tends to show that, but for the dilatation of the lungs which it produces, the inspiratory afteraction would continue to cause exactly the same tonic contraction of the inspiratory muscles even after the ventilation ceased. The right vagus is divided and the left lung allowed to collapse by puncturing the thorax. As I pointed out above positive ventilation, in an animal so treated, causes a strong inspiratory apnoea. The rhythmic breathing is abolished, but the muscles remain strongly contracted just as during negative ventilation in a normal animal. If the ventilation is stopped the centre is under the influence of a strong inspiratory afteraction. But the left lung cannot expand
under its influence, and the expansion of the right lung does not, under favourable circumstances, influence the activity of the centre for the vagus which supplies it is divided. The inspiratory afteraction is therefore able to show itself unhindered by the changes in the capacity of the thorax which it produces. The inspiratory muscles remain permanently contracted until the advent of the first feeble expiratory elongation, and the lever traces a horizontal line without any trace of the fall which was so noticeable after negative ventilation in a normal animal. In fact the curve sometimes even rises during the apnoea, probably in consequence of some influence from the collapsed lung.

I shall describe fully later the effect of dividing both vagi without stimulation at the moment when the negative ventilation ceases. But what concerns us now is that, under such circumstances, the elongation of the inspiratory muscles entirely fails to make its appearance. If the vagi are successfully divided at the moment when the ventilation is stopped, the muscles remain contracted to the same extent as during the ventilation and the appearance of rhythmic respiration is considerably deferred. (Curve iv, Plate VI.)

Thus the form assumed by the apnoea pause which follows negative ventilation depends upon the interaction of two antagonistic stimuli on the respiratory centre. (1) The afteraction which has been formed during the ventilation as the resultant of the inspiratory effect of the suctions and the expiratory effect of the return of the lungs between the strokes of the pump. And (2) the expiratory stimulus caused by the increased volume of the lungs which this afteraction tends to produce.

The cessation of compound ventilation is followed by a pause of considerable length. The muscles elongate slowly to a slight extent with even decreasing rapidity. Finally they contract again slowly, and then a quick but incomplete elongation marks the return of rhythmic respiration (Curve iii, Plate VI). The amount to which the muscles elongate during the apnoea pause is inversely as the amount of tonic contraction produced by the ventilation. If the ventilation causes an apnoea more nearly approaching the inspiratory form the elongation is considerable; if on the other hand the tonic contraction produced by the compound ventilation is comparatively small the curve traced by the apnoea pause is an almost complete continuation of the curve of ventilation. But in every case the fall during the apnoea is less abrupt than during the apnoea caused by negative ventilation in the same
animal. This is probably due to the small extent to which the lungs are dilated by the afteraction of this form of ventilation compared with the dilation caused by the afteraction of negative ventilation. The inhibition from the lungs is therefore weaker and the muscles elongate more slowly.

The explanation I have given for the various forms assumed by the apnoea pause rests upon the assumption that the centre can be influenced by stimuli from the lungs even during apnoea. But Rosenthal\textsuperscript{1} states that stimulation (electrical) of the vagi is entirely without effect during apnoea. In their first communication Hering and Breuer\textsuperscript{2} make the same statement, but in their second paper they show that collapse of the lungs causes an inspiration even during apnoea, provided it be not too deep.

If the lungs are inflated during an inspiratory apnoea the inspiratory muscles elongate rapidly and remain completely quiescent during the duration of the inflation (Curve i, Plate IV). In fact this form of stimulation appears to be particularly active during an inspiratory apnoea, to judge by the length of time which elapses before the pause is broken by an “interrupting” inspiration. If this inflation is of short duration the muscles elongate as before but contract again strongly as soon as the inflation is over (Curve iv, Plate VII). This contraction is terminated by a slight elongation, which is quickly followed by another contraction, so that for many seconds the rhythmic respiratory movements oscillate about a raised base line. Thus the production of an inflation during an inspiratory apnoea tends to increase those phenomena which I described above under the term of negative afteraction.

It is obvious that an inflation can cause no additional elongation during a purely inhibitory apnoea, caused by positive ventilation. But after positive ventilation, the period, which intervenes before the rhythmic breathing is reestablished, is frequently occupied by a slow contraction of the inspiratory muscles (vide p. 34). In this case an inflation at once cuts short the contraction and the muscles remain in a condition of complete elongation until the pause is broken by a strong “interrupting” inspiration (Curve ii, Plate III) such as normally terminates the pause caused by an inflation. Thus we see that this gradual rise can be stopped by applying a stimulus of the same kind

\textsuperscript{1} Cap. 8. \textit{Die Athembewegungen u. ihre Beziehung z. Vagus.}
as the afteraction of the ventilation. A short inflation also causes an elongation, but as soon as it is over the muscles contract to a point considerably above the level they had reached when the inflation began. Thus whilst the actual inflation annihilates the slow contraction in this form of apnoea the negative afteraction of an inflation distinctly increases it.

If the lungs are diminished in volume during a complete expiratory apnoea following positive ventilation an enormous inspiratory contraction is produced. This inspiration is both stronger and of longer duration than any inspiration after the vagi have been divided. It is also noticeable that the inspiration produced by a suction applied during this form of apnoea is of much greater duration than when the suction is applied during normal breathing. Diminution in the volume of the lungs seems to act more effectively, to judge by the strength and duration of the contraction it produces, when the centre has been made apnoic by periodic inflations. If the muscles are slowly contracting during the apnoea, diminution in the volume of the lungs hastens and enormously increases the contraction (Curve i, Plate III). If the suction is of short duration ("momentary") the muscles contract rapidly but do not elongate completely after the suction is over (Curve iii, Plate VII). The cessation of the suction is followed by a slow elongation of the inspiratory muscles, and even when the rhythmic breathing begins again, an inspiratory tone is distinctly present. This effect is probably due to the positive afteraction of the momentary diminution in the volume of the lungs.

Thus we find that, whatever form the apnoea pause may assume after positive ventilation, it is greatly modified by a diminution in the volume of the lungs. It would appear as if the centre were particularly sensitive to this form of stimulation when under the influence of an apnoea caused by periodic inflations.

Diminution in the volume of the lungs, whether momentary or of considerable duration, also greatly modifies the form assumed by an inspiratory apnoea (Curve iv, Plate IV). If the muscles have begun to elongate when the suction is applied, they contract again and trace an even stronger curve than during the ventilation.

When treating of the form which the pause assumed after negative ventilation, I explained the fall in the curve as due to the inhibitions caused by the dilatation of the lungs. Here we have removed the influence of this dilatation by diminishing the volume
of the lungs and the curve therefore rises again. The inspiratory after-action has been strengthened by the removal of the inhibition from the dilated lungs which hampered its activity.

It is scarcely necessary to add that both increase and diminution in the volume of the lungs greatly alter the apnoea pause produced by compound ventilation. In fact this form of apnoea pause acts in every way like an apnoea produced by negative ventilation in which the tonic inspiratory contraction is feeble.

To sum up the results of the experiments just described—

(1) The apnoea pause which follows periodic inflations of the lungs may vary between two extreme types. It may either consist of a pause during which the inspiratory muscles are completely relaxed; or the period which elapses between the close of ventilation and the beginning of rhythmic breathing may be occupied by a slow contraction of the inspiratory muscles.

(2) The apnoea produced by negative ventilation consists of a slow elongation of the tonically contracted inspiratory muscles; but even when rhythmic breathing begins again a strong inspiratory tone is still present.

(3) Compound ventilation produces a similar apnoea pause which is of longer duration and is characterised by less tonic contraction than that produced by negative ventilation.

(4) Both increase and diminution in the volume of the lungs are active stimuli during all forms of apnoea, provided the ventilation has not lasted too long.

(5) The various forms assumed by the apnoea pause under different conditions are due to the modifying influence which the position of the lungs exerts on the afteraction produced by the various forms of ventilation.

Note. In all these experiments I have only applied Artificial Respiration (Ventilation) for a very short time. For the experiments I have so far described it was not necessary to continue it after rhythmic respiration had been abolished. But I must here add a warning against the evil effects produced by long-continued positive ventilation. Positive ventilation causes a considerable fall in the blood-pressure and also great loss of animal heat if continued for long. After about ten minutes of positive ventilation the centre no longer acts with the same promptness to various stimuli, and even half-an-hour after the ventilation has ceased it is apparently still enfeebled. (Cf. Knoll who states that long-continued ventilation may even cause anaemia of the brain.) In every case where it is necessary to apply artificial respiration for long, it should consist of alternating suctions and inflations.
§ 9. The Effect produced by the Gas used in Ventilation on the form
assumed by the Apnoea.

So far artificial respiration has been treated purely as the periodic
repetition of certain mechanical stimuli. We have watched the gradual
development of the apnoea under the influence of each stroke of the
pump and we noticed how the form assumed by the pause depended on
the character of the ventilation and on the particular volume assumed
by the lungs. It is thus extremely improbable that the increased aeration
of the blood is the cause of the phenomena of apnoea in the normal
animal. For the varying forms of apnoea are so exactly what we
should expect from the study of the results produced by a single inflation
or collapse of the lungs that we are compelled to explain them as the
result of summation of rhythmic stimulations. Yet on the other hand
the constitution of the air in the lungs does play a very important
part in the production of apnoea even when the vagi are intact.

If the lungs are inflated with hydrogen or with oxygen, the result
is in all cases the same. The only difference in the result produced by
a momentary inflation lay in the duration of the afteraction. Now the
two gases play exactly the same part when the stimulus is periodically
repeated. If the lungs are periodically inflated with pure hydrogen,
each stroke of the pump tends to decrease the inspiratory activity of
the centre. The inspirations get gradually smaller, and finally all
rhythmic movements disappear and a true apnoea of ventilation is
produced just as if the lungs had been periodically inflated with air.
If the ventilation is stopped a true apnoea pause is sometimes, though
rarely, seen. More frequently rhythmic breathing begins again as soon
as ventilation ceases although in a greatly modified form (Curve vi,
Plate V). The first inspiration is very small and is followed by a
considerable pause. The next is somewhat stronger and the contractions
increase in strength until they reach a height above that of the normal
inspirations. The breathing has become distinctly dyspnoeic for the
inspirations do not last longer than the normal and each is followed by a
complete pause. We have thus succeeded in producing the complete
abolition of the respiratory rhythm by periodically inflating the lungs
with hydrogen. On ceasing the ventilation the dyspnoea is so great
that the breathing frequently recommences although the inspiratory
activity is distinctly checked by the afteraction of the ventilation. As
this afteraction is gradually overcome the inspirations assume the
normal dyspnœic type—they are strong but of comparatively short duration and are not accompanied by the presence of an inspiratory tone. Now it is interesting to notice that the curve traced by the gradual development of the normal breathing after ventilation with hydrogen very closely resembles that produced by the gradual development of rhythmic breathing after an inhibitory apnoea pause (cf. Curves vi and vii, Plate V).

If ventilation with hydrogen is continued after the rhythmic breathing has ceased, the dyspnœa becomes so strong that the inspirations begin again during the ventilation. Rhythmic breathing reappears in exactly the reverse order to that in which it was abolished. The first inspiration is very small and is followed by a pause which corresponds to a stroke of the pump. As soon as this inflation is over a slightly stronger inspiration makes its appearance. On the curve which I have chosen to illustrate this phenomenon (Curve v, Plate V), the ventilation was stopped after the fourth inspiration, and the dyspnœa now appeared in full force unchecked by the ventilation. The inspiration which follows the cessation of ventilation is nearly five times as strong as its predecessor. The inspirations continue to increase in strength until the lungs have been freed from hydrogen. The expiratory pauses are however quite as long and sometimes longer than the normal and the inspiratory contractions are of comparatively short duration compared with their strength.

I had hoped to be able to show that negative ventilation could also produce an apnoea when the lungs were filled with hydrogen. But the technical difficulties were so great that we must be content with but an indirect proof. I pointed out above that negative ventilation was in reality only an extreme form of compound ventilation, and that the inspiratory apnoea produced by compound ventilation is only an inspiratory apnoea weakened by the inflations which alternate with the suctions. Now it is perfectly easy to use hydrogen as the medium for compound ventilation. The first stroke of the pump inflates the lungs with hydrogen and the second stroke removes the same amount of the mixed gases in the lungs. After the first few strokes the atmosphere in the lungs must consist, if not entirely at any rate to a very large extent, of hydrogen. Now not only does this form of ventilation abolish all rhythmic respiratory movements and produce the usual inspiratory apnoea but cessation of ventilation is generally ever followed by a considerable apnoea pause (Curve vi, Plate IV). In a normal animal 14 double strokes of the pump produced an apnoea
pause of 16 secs. when air was used (Curve v, Plate IV). The same number of strokes of the pump with hydrogen also produced a distinct pause lasting six secs. from which the normal breathing is regained as usual (Curve vi, Plate IV).

Thus the substitution of hydrogen for air as the medium of inflation does not materially alter the appearance of the inspiratory apnoea produced by compound ventilation. Now the tonic inspiratory contraction is produced by the periodic suction which alternate with the inflations, and as the former still produce the normal effect although the lungs are filled with hydrogen there is no reason for supposing that negative ventilation would not produce an apnoea under the same conditions provided we were able to apply it.

The substitution of oxygen for air as the medium of ventilation causes but slight changes. I showed in a previous section, when discussing short inflations, that oxygen postpones the advent of dyspnoea and so allows the afteraction of the inflation to show itself for a longer time than would otherwise have been possible. When ventilation is carried on with oxygen the rhythmic breathing is not abolished any more rapidly than normal; the same number of strokes of the pump are required to annihilate the inspirations with oxygen as with air (cf. Curves ii and iii, Plate IV). The pause which follows the cessation of ventilation is exactly of the same nature whichever gas has been used, though it tends to last longer when the lungs have been periodically inflated with oxygen (cf. Curves iv and viii, Plate V). But not only does the pause last longer but we also find that the breathing returns more slowly to the normal type than if air had been used. This would seem to show that even when the apnoea pause has been broken by a rhythmic respiratory movement, the afteraction of the ventilation is only weakened, not exhausted. Otherwise it is difficult to understand why the return to the normal type should be delayed, when dyspnoea is prevented by filling the lungs with oxygen.

In the same way oxygen does not alter the phenomena produced by compound ventilation. Rhythmic breathing disappears at the same rate and the tonic inspiratory contraction is of the same strength as if air had been used. The only difference lies in the slightly increased length of the apnoea pause.

I at one time thought that the long slow contraction of the inspiratory muscles which sometimes occupies the period of apnoea after positive ventilation might be due to a struggle between the afteraction and dyspnoea. However on substituting hydrogen for air I found that
the apnoea was shorter and that the rise was generally less than when air was used (cf. Curves i and ii, Plate V). Oxygen seemed neither to increase nor decrease this form of apnoea. The muscles began to contract as soon as the ventilation ceased and, as soon as the curve reached a certain height, the muscles elongated as usual and the normal breathing was regained in the usual manner. Thus this form of apnoea cannot be due to the struggle between dyspnoea and the afteraction of the ventilation but is probably produced by some condition of the centre perhaps analogous to the negative afteraction which sometimes follows a single inflation.

To sum up the experiments in this section—

(1) Periodic inflations with pure hydrogen abolish rhythmic breathing as usual. An actual apnoea pause of short duration may appear when the ventilation ceases but more often the rhythmic breathing begins again at once. In the latter case the first inspirations are small and the contractions gather strength until the breathing assumes a distinctly dyspnoeic type.

(2) Compound ventilation with hydrogen produces the normal results except that the pause is considerably shorter than if air is the medium of inflation.

(3) The substitution of oxygen for air in either positive or compound ventilation increases the length of the apnoea pause but in no way hastens the abolition of normal rhythmic breathing.

(4) The constitution of the atmosphere in the lungs does not determine the form assumed by the apnoea in a normal animal. This apnoea is due to the summation of the stimuli caused by the periodic alterations in the volume of the lungs. Dyspnoea tends to cut short the appearance of this afteraction by causing the reappearance of rhythmic breathing. Thus oxygen increases the length of the apnoea by averting dyspnoea and hydrogen shortens the pause owing to the dyspnoea which it causes.

§ 10. Apnoea after Division of the Vagi.

Rosenthal in his well-known work on the nervous mechanism of respiration stated that apnoea was due to an over oxydation of the blood which put the centre to rest by removing its normal stimulus. But of late years several physiologists have insisted on the part played by the vagi in the production of apnoea in the normal animal. Meischer-Rüsch\(^1\) distinguished an “apnoea vera and an apnoea vagi”; but to the

\(^1\) du Bois Reymond’s Archiv, Heft 5 and 6, 1885.
H. HEAD.

best of my knowledge he did not point out how they differed from one another. Knoll\(^1\) found that it was generally impossible to produce an apnoea after the vagi had been divided, and states that a true apnoea can only be produced when the vagi are intact. However he found that the breathing was in all cases weakened and flattened by ventilation after division of the vagi, and that he could on two occasions produce a real apnoea pause. But he dismisses these apparent exceptions with the remark that apnoea only occurs, after division of the vagi, when the irritability of the centre is diminished owing either to the narcotic or to the fact that the animal has been experimented on for a long time. But it is \textit{a priori} by no means improbable that the very fact that the vagi are divided tends either directly or indirectly to diminish the irritability of the respiratory centre.

There is however one fundamental difference between the behaviour of the centre before and after division of the vagi. As I pointed out in the previous section ventilation with hydrogen is able to abolish rhythmic respiration in the normal animal. Now if the vagi are divided the only effect of ventilation with hydrogen is the production of a violent dyspnoea. The inspirations get gradually stronger as ventilation continues, and finally the experiment is ended by violent movements of the whole animal. There is not a trace of the gradual abolition of rhythmic breathing which always follows the first few strokes of the pump in the normal animal.

But if air is used to periodically inflate the lungs both inspiratory contractions and expiratory elongations decrease in strength. The inspiratory tone which is generally present after the vagi have been divided grows stronger, owing to the decrease in the expiratory elongations, and the inspirations become shallow. But the breathing does not "follow" the strokes of the pump, as was the case before the vagi were divided; the respiratory movements remain entirely independent of the rhythm of ventilation although they gradually decrease in strength. After some 40 secs. of rapid ventilation this is frequently the only result produced. But under certain circumstances both inspirations and expirations decrease in strength until the rhythm disappears, leaving the diaphragm in a condition of greater or less tonic contraction (Curve i, Plate IX). After the close of ventilation the muscles remain quiescent for a varying time, producing an apnoea pause which is characterised by a varying amount of inspiratory tone. The rhythmic breathing may then

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\(^{1}\) Mittheilung III. \textit{Ueber Apnoe}.
be reestablished by a gradual increase in the strength of the inspirations and expirations. In fact the centre sometimes recovers from the apnoea by exactly the reverse stages to those by which it became apnoeic. There is scarcely room for doubt that the muscles are really strongly contracted during the apnoea pause after examining Curve i, Plate IX, but in order to be assured of the fact I divided the phrenic nerves during a similar though somewhat stronger apnoea pause. The point of the lever at once fell 4:5 c.m., showing that the tonic contraction was very considerable.

The longer the vagi have been divided the easier it becomes to produce an apnoea and the weaker is the tonic contraction that appears during the pause. We can watch the gradual decrease in the tone by resorting to apnoea every five minutes after dividing the vagi. The greatest number of strokes of the pump are required immediately after division, but the tone is then very strong. As time advances fewer strokes suffice, but the tone is much weaker. In fact we often find that, as time goes on, it gradually becomes possible to produce an apnoea even in those animals in which ventilation failed to completely abolish rhythmic breathing immediately after the vagi were divided. The normal breathing is now often regained in a somewhat different manner to that described above. After the pause has lasted a variable time the lever begins to rise slowly. This contraction of the inspiratory muscles is extremely gradual and may last as long as half a minute. When the curve has reached the height of an ordinary inspiration (after division of the vagi) the muscles elongate quickly. This elongation is often incomplete, and we frequently find that the tonic contraction which may have disappeared before the ventilation was begun has now reappeared. But even when the tone does not reappear it is noticeable that the inspiratory contractions which follow the apnoea last considerably longer, though they may not be stronger than those which preceded the ventilation.

The method by which rhythmic breathing is reestablished after an apnoea, when the vagi are divided, is very variable and may present many modifications of the two extreme types that I have described.

It is scarcely necessary to add that ventilation consisting of periodic suctions and inflations (compound) produces an apnoea in every case where it can be produced by periodic inflations. But it is interesting to notice that in those cases where an apnoea can be produced with ease negative ventilation is also sometimes able to abolish the rhythmic breathing. The apnoea is however in all cases the same whatever
the ventilation may be. The nature of the ventilation has no influence on the form assumed by the apnoea as was the case before the vagi were divided.

How are we to explain the occurrence of apnoea after division of the vagi? It is probably not due to the stimulation of other sensory nerves, for the respiratory movements which occur during the time ventilation is being carried on do not bear any relation to the strokes of the pump. Again, it is possible to produce an apnoea if the greater part of the wall of the thorax be removed and if the spinal cord has been divided between the sixth and seventh cervical vertebra. It appears to bear the most distinct relation to the condition of the air in the lungs, and yet after the recent researches of Gad and others we are scarcely justified in assuming that it is due to the over-oxydation of the blood. In order to show that the blood was not overloaded with oxygen during the apnoea Gad 1 devised the following simple experiment. He cut away part of the chest wall of a rabbit in the middle line and watched the colour of the heart during normal respiration. This can be easily done in a rabbit, for the anterior mediastinum is so large that a considerable opening can be made in the chest wall without causing the lungs to collapse. Ventilation was now begun and an apnoea produced. Now Gad noticed that even during complete apnoea the right side of the heart was darkly venous, showing that at any rate one half of the blood was not overloaded with oxygen. But as far as I can gather the vagi were still intact in the animal on which he made this observation and the apnoea he produced was therefore probably a vagus apnoea. I therefore repeated his experiment after dividing the vagi. If some time has elapsed since the vagi were divided the blood on the left side of the heart appears to be somewhat darker than in a normal animal. A few seconds after ventilation begins the left side of the heart gets distinctly redder, and just before the rhythmic breathing ceases the heart appears to have assumed its normal bright colour. The right side of the heart however remains dark coloured, even at the end of ventilation. If ventilation is now stopped the left side of the heart gets steadily darker during the apnoea pause. Just before the first rhythmic movement appears the blood on the left side of the heart appears to have reached a quite abnormal degree of venocity. The results of the experiment render it difficult to assume that the blood in the whole system is overcharged with oxygen during the apnoea, for

1 Apnoe, p. 3, Würzburg, 1880.
even at the height of ventilation the right side of the heart still remains venous. It would appear as if the blood on the left side of the heart was permanently below the normal degree of oxydation owing to the inefficient respiratory movements which follow division of the vagi. Now if we suppose that the respiratory centre gradually adapts itself to this dyspnoeic mixture it is easy to see how ventilation could produce an apnoea. Each stroke of the pump improves the constitution of the atmosphere in the lungs and thus enables the blood to take up an increased amount of oxygen until it even reaches its normal oxydation. But the centre is adapted to a mixture containing less oxygen and thus even normal blood will now appear hyperarterialised. If the ventilation is now stopped the atmosphere in the lungs is able to supply the blood with oxygen during several journeys round the system, for rhythmic breathing need not begin until the air in the lungs has become distinctly dyspnoeic. In addition to this we must bear in mind that division of the vagi possibly directly lowers the irritability of the respiratory centre. According to the view I have just put forward the blood is not overloaded with oxygen during apnoea following division of the vagi; but partly owing to direct diminution in the vitality of the centre and partly owing to the fact that it has become adapted to a dyspnoeic condition of the blood an increase in the oxygen of the blood even up to the normal amount produces an apnoea. The following comparative experiments help to illustrate the part which the amount of air in the lungs plays during the form of apnoea. After dividing the vagi, ventilation was applied and apnoea was produced; the lungs were allowed to return to their normal volume after the ventilation and 17 secs. elapsed before the appearance of the first rhythmic respiratory movement. Both sides of the thorax were then opened and the same number of strokes of the pump applied. But at the close of ventilation the lungs were allowed to collapse completely, and the pause was found to last but nine secs. After a short time an apnoea was again produced by the same number of strokes of the pump, but the lungs were inflated above their normal volume immediately on the cessation of ventilation. The pause in this case lasted 23 secs. This experiment was repeated many times with the same result, though of course the length of the apnoea pause varied in different animals. Thus when the lungs were completely collapsed the apnoea pause lasted nine secs. whilst the fact that the lungs were inflated at the end of the ventilation served to prolong the pause to 23 secs. Thus Gad’s statement that the air in the lungs under these circum-
stances is able to supply the blood with oxygen for more than one journey round the system would appear to be confirmed, and this phenomenon would seem to be one of the most important causes of the apnoea which is seen after division of the vagi.

It is interesting to notice that even during this form of apnoea the centre is sensitive to certain stimuli. If chloroform vapour is passed up one nostril during the apnoea pause consisting of a tonic inspiratory contraction, the muscles elongate at once. In fact I have found this an excellent method of estimating the amount of tone which really exists during the apnoea without having recourse to the extreme measure of dividing the phrenics. If the central end of the vagus is stimulated electrically with a stimulus just sufficient to cause an active expiration under normal conditions, exactly the same effect is produced even if the stimulus be applied during the apnoea. If the stimulus is of such a strength that it normally produces an inspiratory effect we can scarcely expect to see any change when it is applied during an apnoea pause consisting of a strong inspiratory tone. But if it is applied during the other form of apnoea, in which the muscles are almost completely elongated, a distinct rise in the curve is produced, showing that the muscles have contracted. Although the contraction does not reach the same height as if the stimulus were applied during rhythmic breathing it is sufficient to prove that the centre is still irritable, even during the form of apnoea pause, for we must not forget that this expiratory form of apnoea does not appear after division of the vagi until the vitality of the centre is probably considerably lowered.

Again, it is easy by stimulating the larynx mechanically or chemically to produce the usual movements of swallowing accompanied by elongation of the diaphragmatic muscles even though the centre is apnoeic.

To sum up the experiments detailed in this section—

(1) It is frequently possible to abolish rhythmic respiration and to produce an apnoea after the vagi are divided.

(2) The form assumed by the apnoea is in no way directly dependent on the form of the ventilation, and the rhythmic breathing during ventilation bears no relation to the rhythm of the pump.

(3) After division of the vagi ventilation with hydrogen only produces a violent dyspnoea.

(4) The forms assumed by the apnoea are very various, and the presence or absence of a tonic inspiratory contraction seems to depend on the greater or less vitality of the respiratory centre.
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(5) The respiratory centre is sensitive during the apnoeas to various stimuli, such as the application of chloroform vapour to the nasal mucous membrane, the mechanical or chemical stimulation of the larynx, and (to a variable extent) to electrical stimulation of the central end of the divided vagi.

(6) This apnoea is probably not caused by overarterialisation of the blood but rather by the interaction of the following factors,—

(a) The adaptation of the respiratory centre to a certain dyspnoeic condition of the blood in consequence of the inefficient respirations which follow division of the vagi. This would cause even normally arterialised blood to appear over oxygenated.

(β) The decrease in the vitality of the respiratory centre which possibly follows division of the vagi.

(γ) The fact that, after ventilation, when the vagi are divided, the atmosphere in the lungs is able to supply the blood with sufficient oxygen during a very considerable period.


We concluded above that when the vagi were intact apnoea, whether expiratory or inspiratory, was caused by the summation of certain stimuli. The question at once suggests itself where does this summation of stimuli take place? Gad1, who was the first to offer this explanation of apnoea, believed that the stimuli were summed in the peripheral end organs of the vagi. He produced apnoea by a known number of inflations and divided the vagi during the apnoea pause, and states that the pause was distinctly shortened by this operation. I have repeated this experiment many times with all forms of apnoea but am unfortunately unable to agree with Gad that the pause is shortened by dividing the vagi; indeed in certain cases it appears to be lengthened. But these experiments are interesting from another point of view. We saw how the afteraction of the ventilation was frequently greatly hampered by the alterations in the volume of the lungs which it tended to produce. Now if the summation takes place in the respiratory centre we shall be able to observe its unhindered activity, if the vagi are divided without stimulation at the close of ventilation. The vagi remain intact during the ventilation and the summation takes place as

usual, but the moment it is complete the vagi are divided and henceforth alterations in the volume of the lungs cannot affect the activity of the centre.

No form of apnoea is so hampered by the condition of the lungs which it tends to produce as that caused by negative ventilation. We therefore find that division of the vagi at the close of ventilation considerably modifies the form assumed by this apnoea. On Curve ii, Plate VI, 20 periodic suctions produced a very inefficient apnoea. The muscles elongated quickly when ventilation ceased and rhythmic breathing began again after but a few seconds. After a short interval ventilation was again applied and the second vagus was divided at the 21st stroke of the pump. Now instead of elongating the muscles began to contract still more, and the curve rose steadily during the space of 14 secs. (Curve iv, Plate VI). Then followed a short elongation of the inspiratory muscles, which was almost at once cut short by a fresh contraction. The animal now became extremely unquiet. Now this disturbance (of which not the slightest trace had previously appeared), recalls at once the restlessness produced when the animal has breathed an atmosphere of hydrogen for some considerable time and it is probably a sign of great dyspnoea. As soon as the animal became quiet again the negative ventilation was repeated but even after 41 strokes of the pump no apnoea could be produced. Thus by dividing the vagi at the close of ventilation we have been able to convert a feeble inspiratory apnoea lasting at the most two secs. into a steady contraction of the inspiratory muscles which lasted 14 secs.

When discussing the inspiratory apnoea produced by periodic inflations when one lung had been allowed to collapse completely, I pointed out that in this case the inspiratory afteraction was comparatively little hampered by alterations in the volume of the lungs. But here again we find that division of the vagi at the close of ventilation almost doubles the duration of the apnoea and converts an almost horizontal curve into a slowly increasing contraction of the inspiratory muscles (cf. Curves v and vi, Plate VI).

I pointed out above that the apnoea produced by positive ventilation varied between two types. Curve iv, Plate VIII, is a good instance of an apnoea pause accompanied by complete elongation of the inspiratory muscles. The left vagus was divided and ventilation consisting of 15 inflations sufficed to produce an apnoea pause lasting six seconds. This pause was finally broken by a minute inspiration and 10 seconds elapsed before rhythmic breathing was completely re-
established. After a short interval the drum was again set in motion and ventilation was begun. At the twelfth inflation the right vagus was divided. A pause followed which lasted 4½ secs. (Curve iii, Plate VIII). The inspiratory muscles then began to contract just as in the previous case. But both vagi are divided and expansion of the lungs no longer checked the inspiratory activity of the centre. The muscles therefore did not relax but continued to contract steadily for 14½ secs. This strong inspiratory contraction was followed by a complete elongation, and the breathing settled down into the type so often seen after division of the vagi. Ventilation was now begun again but after 25 strokes of the pump rhythmic breathing still continued, although in a diminished form. Now, in this case at any rate, the afteraction still affected the respiratory centre even after the vagi were divided. For considering that twice as many strokes of the pump failed to produce an apnoea pause after the vagi were divided it is very unlikely that the pause which followed the division of the vagi at the close of ventilation was due to the increased oxydation of the blood. As we have already seen division of the vagi in the normal animal produces a strong inspiratory contraction, and it is interesting to notice how the last remains of the afteraction of the ventilation modify this inspiration. Normally division of the vagi is followed by the appearance of a quick strong inspiration lasting four or five seconds. But when the vagi are divided at the close of positive ventilation, the contraction which follows the apnoea pause is slow and gradual and lasts 14 secs. Thus the fact that positive ventilation has preceded the division of the vagi appears to increase the duration of the first inspiration four or five times. The slowness of the contraction is probably due to the remains of the afteraction which still tends somewhat to depress the inspiratory activity of the centre; for the afteraction is probably still exerting some influence on the centre even though the apnoea pause is broken by an inspiratory contraction.

Exactly the same phenomenon appears with great clearness in those cases in which positive ventilation produces a slow contraction of the inspiratory muscles in place of a pause. Curve i, Plate VIII, is a good instance of this type of apnoea. As soon as the ventilation ceases the inspiratory muscles begin to contract slowly. Ten seconds after the close of ventilation the first expiratory elongation appears and rhythmic breathing is slowly regained by an increase in the strength, but decrease in the duration of the inspirations. After a pause, positive ventilation is again started and the left vagus is frozen at the 19th
stroke of the pump. Ventilation is stopped after 26 inflations and the right vagus is at once placed on the freezing apparatus (Curve ii, Plate VIII). The apnoea pause begins just as before though the muscles contract slightly less rapidly. However, 10 seconds after the cessation of ventilation they have apparently reached almost exactly the same amount of contraction as in the normal animal. But instead of elongating they continue to contract; for the change in volume of the lungs is no longer able to affect the centre. The curve therefore rises to a point far above the crests of the normal inspirations, and the first expiratory elongation does not appear until 25 seconds after the cessation of ventilation. We now see the effect that would be produced by the slow contraction of the inspiratory muscles which sometimes follows positive ventilation, provided it were not hampered by the expansion of the lungs. The first part of the curve is almost exactly the same in both cases, but whereas the contraction is checked in the normal animal after 10 secs., it continues to increase for more than twice this time if the vagi are divided. Here again the fact that periodic inflations of the lungs preceded division of the vagi seems to enormously increase the inspiratory activity of the centre.

It is sometimes possible to produce an apnoea pause after the vagi have been divided with the same number of strokes of the pump as were required to produce apnoea in the normal animal. But in such a case, apnoea before and after division of the vagi were very different in character. After division the apnoea pause was characterised by a moderately strong inspiratory tone which was considerably weaker than that produced by negative ventilation and was very different from the complete relaxation of the inspiratory muscles which followed positive ventilation. Now in such a case as this, if the periodic stimuli undergo summation in the end organs of the vagi, it is difficult to understand why the breathing does not assume the form of a blood apnoea immediately the vagi are divided. That is to say, we should expect that, when the vagi were divided during the apnoea, the inspiratory muscles would at once contract to the same extent as during the blood apnoea. But this is by no means the case, and in the experiment in question the muscles remained in a condition of complete elongation even longer than normal though the vagi had been divided at the close of ventilation.

When the vagi are divided at the close of compound ventilation the apnoea is very markedly prolonged. On Curve i, Plate VII, compound ventilation produced but an insignificant pause lasting but four secs. I
have purposely chosen this experiment for it very distinctly shows the way in which the expansion of the lungs tends to influence even the apnoea of compound ventilation. The same ventilation was now repeated and one vagus was divided at about the 14th stroke of the pump, the other at the close of ventilation. The muscles now remained in steady tonic contraction for 10 seconds (Curve ii, Plate VII). The rhythmic breathing was then regained by an increase in the strength both of the inspirations and expirations. Thus the division of the vagi at the close of ventilation, far from cutting short the apnoea, converted a short and feeble pause into a steady apnoea of twice the length. In this case again the same number of strokes of the pump were unable to cause apnoea after the vagi were divided.

The experiments in the section would seem to show

1. That whatever the form assumed by the ventilation the periodic stimuli undergo summation in the respiratory centre and not in the peripheral end organs of the vagi.

2. If the vagi are divided at the close of ventilation it is possible to watch the effect produced by the afteraction when unhampered by afferent impulses from the lungs.

§ 12. On Adaptation and the Phenomena which accompany it.

It is extremely important to know what effect is produced on the breathing when one or both lungs remain permanently at the same volume, whether above or below the normal. But when we were discussing the phenomena which follow inflation or collapse of the lungs, I pointed out that the results were always complicated by dyspnoea. If for instance the lungs are inflated the trachea must remain closed during the whole duration of the inflation and the air in the lungs must stagnate. Moreover the stimulation of the vagi caused by the inflation produces a cessation of rhythmic breathing lasting some 20 secs. This again helps to prevent the renewal of the air in the lungs. During all this time the blood is becoming increasingly dyspnoeic and it is less and less possible for the centre to react in a normal manner. Thus if we wish to examine the changes in the activity of the respiratory centre produced by allowing the lungs to remain permanently at a certain volume it is necessary to find some means of eliminating the dyspnoea.

I have succeeded in overcoming this difficulty in the following manner. A cannula was constructed on the principle of Marey's Cardiac sounds. A fine tube (see figure A) was so bent that it could be
passed with ease down the trachea into the right bronchus. To this tube was soldered a still finer, tube which was slightly shorter and opened freely just below the bend. A piece of thin indiarubber tubing was passed over the far end of both tubes and tied firmly at the bend and at the extreme end of the larger tube. The smaller tube, which is shorter than its fellow, now opens into a chamber formed by the indiarubber tubing, and fluid forced down the smaller tube will distend the walls of this chamber. The larger tube on the other hand passes right through the chamber and opens freely beyond it. If this cannula is passed down the trachea (see figure B) into the right bronchus distension of the indiarubber chamber will shut off the right lung entirely except for the opening afforded by the larger tube of the cannula. But advent of air to the left lung will not in any way be hindered, for it is easy to arrange the size of the cannula so that when it is in position at least half of the trachea remains perfectly free. A piece of brass tubing, with a wide bore, is attached to the cannula at such a height that when
the indiarubber bag lies in the right bronchus the divided trachea just slips over the end of the tube. A thread, passed round the trachea below the opening, is then tied firmly round the whole apparatus just as if an ordinary tracheal cannula had been inserted into the windpipe. By this means the trachea is kept open and the cannula remains in its proper position. It is now possible to apply ventilation to the left lung, without affecting the right lung, by connecting the mouth of this wide brass tube with the tubes from the pump. I have found it best to inflate the indiarubber chamber with glycerine by means of a stiff syringe, which is connected with the smallest tube of the cannula by means of a piece of nondistensible but elastic catheter tubing.

The right side of the thorax is opened and the lung allowed to collapse completely. The effect of the collapse gradually wears off and the animal breathes rhythmically though it is somewhat dyspnoeic. If the left vagus is now divided and each vagus only supplies the lung of its own side an alteration in the volume of the left lung will no longer directly affect the action of the respiratory centre. If the cannula is now inserted into the right bronchus and the indiarubber chamber be inflated, we are able to distend the right lung without affecting the volume of the left lung. Moreover the volume of the right lung remains unchanged no matter what respiratory movements the animal may make, for the right half of the thorax is freely open. But although the left lung is perfectly open to the air inflation of the right lung produces such a long standstill in the breathing that the animal of necessity becomes dyspnoeic. Ventilation is therefore kept up continuously on the left side all through the experiment whether the animal is breathing rhythmically or not. Thus one lung remains at a constant volume whilst the air in the other is kept of a constant composition. If the vagi do not cross this ventilation does not in any way directly affect the activity of the respiratory centre, for the left vagus (supplying the lung which is periodically inflated) has been divided before the experiment began. Now we might suppose that, even if the vagi did not cross, ventilation would still produce an apnoea such as is seen after division of the vagi. However, as far as my experience goes, this is never the case. It may be that ventilation of one lung only is not sufficient to produce an apnoea; or perhaps the fact that one vagus is still intact prevents the vitality of the centre sinking to a point sufficient for the production of a blood apnoea. Whatever the cause may be, the breathing remains steadily rhythmic during the whole duration of the ventilation of the left lung, provided the vagi do not cross at all. Now
it is extremely important for these experiments to know whether the vagi cross or not. Luckily we possess a very simple test, for if the vagi cross sufficiently to affect the breathing, closure of the trachea in the expiratory phase, after the cannula is in situ, must produce the usual strong inspiratory changes. The amount of the change will be dependent on the extent to which the vagus of the right side supplies the left lung. Again, if the vagi cross, even slightly, the breathing gradually takes up the rhythm of the strokes of the pump, and if the crossing is considerable an apnoea gradually appears. Any animal in which these phenomena appear is therefore useless for the experiments I shall now describe.

Now after we have assured ourselves that the vagi do not cross, compound ventilation is started on the left side of the thorax and the animal breathes rhythmically without any signs of dyspnoea although the right lung is collapsed. The right lung is now inflated through the cannula which has been passed into the right bronchus. All rhythmic breathing at once ceases as usual. But the ventilation now keeps the air in the left lung in exactly the same condition as if the animal was breathing rhythmically and the blood no longer becomes dyspnoic. The pause in the breathing may be broken after a certain interval by rhythmic inspirations, but I shall first describe a case where this did not occur not because it is the rule but because, when rhythmic movements appear, they are simply superposed on the phenomena now to be described. After the pause has lasted 10—15 secs. the lever begins to rise very slowly in consequence of a slow tonic contraction of the diaphragm (cf. Curve v, Plate VII). The contraction increases very gradually, and it finally remains stationary, the lever tracing a horizontal line at a variable height above the base line. If the right lung still remains at the same volume extremely small oscillations appear on the curve, which gradually increase in strength (Curve v, Plate VIII). This is the beginning of rhythmic respiration. The muscles elongate and contract with ever increasing strength until regular rhythmic breathing is reestablished in spite of the fact that the right lung is still considerably above the normal volume.

The results which follow the inflation of the collapsed lung generally differ somewhat from this type; for the pause is mostly broken sooner or later by an inspiration (cf. Curve vi, Plate IX). This inspiratory contraction is strong and quick and traces a sharp crested curve. It is followed by a second pause, which is broken by a second inspiration. But it is a curious fact that this inspiration is smaller than its
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predecessor. Each pause is now shorter and each inspiration smaller than the one which preceded it. But the diaphragm has now begun to fall into the condition of slow tonic contraction which I have just described. The ever decreasing rhythmic inspirations are therefore superposed on a steadily increasing tonic contraction of the inspiratory muscles. Rhythmic breathing then disappears entirely and the rest of the curve, including the reestablishment of the rhythmic breathing, is exactly similar to the type I described above in which the pause was not interrupted at all by rhythmic inspirations.

Thus it appears that if the right lung is kept permanently above the normal volume, the centre gradually adapts itself to the altered volume in a very peculiar manner and rhythmic breathing begins again.

If we wait until the animal breathes regularly in spite of the distension of the right lung and then allow the lung to return to the volume which it normally occupied or to collapse completely, a strong inspiratory contraction appears. The muscles contract quickly and the rhythmic breathing disappears or becomes very small. After a few seconds the rhythmic breathing becomes stronger but a considerable amount of tonic contraction still remains. Finally, after a certain length of time all tone has disappeared and the breathing presents all the characteristics of normal rhythmic respiration although the right lung is now either collapsed or much diminished in volume.

If the right lung is allowed to collapse completely when the tonic contraction which appears during the inflation is at its height, this tonic contraction is still further increased (Curve vi, Plate IX). The curve rises still further, and after a considerable interval the small oscillations make their appearance, marking the advent of rhythmic respiration. We might have expected that collapse of the lungs at the height of the tonic contraction which appears during the inflation would have caused rhythmic breathing to begin at once. But as a matter of fact the collapse rather retards than hastens the appearance of rhythmic respiration.

If on the other hand the lung is allowed to collapse very slowly, at the same point in the experiment, the tonic contraction does not increase but the lever continues to trace a horizontal line (Curve v, Plate VII). The muscles remain contracted to the same extent for about 10 secs. after the right lung had completely collapsed and rhythmic breathing then began in the usual manner. Thus here again we see the difference between a sudden collapse of the lungs and a very gradual return to the
normal volume. The former produces a strong inspiratory effect, whilst the latter produces scarcely any change in the respiratory curve.

These experiments are obviously open to many sources of error. After all the technical preparations for the experiment have been successfully made we still have to assure ourselves that the right vagus does not supply the left lung. If the breathing shows a tendency to take up the rhythm of the ventilation or if closure of the trachea in the expiratory phase produces the slightest effect on the breathing after the cannula is in situ, the animal must be rejected as unfit for these experiments. It is therefore impossible to repeat such experiments as these with the ease and certainty with which we can produce the other phenomena described in this paper.

Even when everything has succeeded we have to make quite sure that the lung has not collapsed slowly during the long inflation. The opening in the right side of the thorax should therefore be made large enough to leave the expanded lung room and to allow the experimenter to see at a glance if it still remains at the original volume. But this control is very rough. However, do not I think it likely that this error can have crept into the experiments I have just cited for the following reason. In all cases a strong inspiratory effect was produced by opening the tube in connection with the inflated right lung. Now if the lung had gradually collapsed during the duration of the inflation, it is difficult to see how opening a free passage to the lung could produce any effect.

Again, the ventilation must not be too strong. For if the periodic alterations in the volume of the left lung are too great or if the opening on the right side of the thorax be too small, every inflation of the left lung causes it to press on the inflated right lung. Thus at every stroke of the pump the right lung is diminished in volume owing to the pressure of the expanded left lung, and the breathing gradually becomes synchronous with the ventilation. This source of error may be avoided by making a wide opening on the right side of the thorax, by carefully regulating the ventilation and by not inflating the right lung too violently.

These experiments would seem to show—

(1) That if the animal is breathing rhythmically the first effect of a permanent increase or decrease in the volume of the lungs is to cause the abolition of rhythmic breathing. If the lungs are inflated the inspiratory muscles remain in a condition of complete elongation; if on the other hand they are diminished in volume the inspiratory muscles fall into a condition of tonic contraction.
(2) But in either case, provided the advent of dyspnoea is averted, the centre ultimately adapts itself to the permanently increased or diminished volume of the lungs and the breathing again becomes rhythmic. In the case of a permanent inflation this redevelopment of rhythmic breathing is preceded by a peculiar slow tonic contraction of the diaphragm.

(3) As soon as this adaptation has taken place the "normal" volume or zero is found to be altered. For instance, let us assume that the centre has become adapted to a certain volume $A$. The lung is then inflated to a volume $B$. We now find that as soon as the centre has become adapted to the volume $B$ collapse to the volume $A$ which previously produced no effect upon the centre acts as a strong inspiratory stimulus.

EXPLANATION OF THE PLATES.

PLATE I.

Curve I. The uppermost line of the curve is traced by a control lever attached to the chest wall of the rabbit as described on p. 4.

The middle curve is traced by the lever of a Marey's tambour. This tambour is in connection with a large flask into the sides of which a cannula is fixed, which is tied directly into the trachea of the rabbit.

The lowest curve is traced by the moments of the anterior slips of the diaphragm separated and prepared according to the description on p. 4.

At the point marked with a cross the left vagus was placed upon the freezing apparatus. This curve illustrates the effect produced by dividing one vagus in a narcotised but otherwise normal animal.

Curve II. Follows on Curve I after the interval of 30 sec.

It shows the effect produced by freezing the second vagus in the same animal. During the first few respirations after division of both nerves the expiratory elongations are incomplete.

Curve III. Follows on Curve II after an interval of one minute.

The left phrenic nerve was divided in the neck at the point marked on the curve by a cross. The left side of the diaphragm and with it the left muscular slip is immediately paralysed and the whole level of the curve sinks. The curve traced by the level attached to the chest wall remains unaltered.

Curve IV. Follows on Curve III after the interval of 30 secs.

At the point on the curve marked with a cross the right phrenic nerve
was divided in the neck and the lowest curve traced by the lever in connection with the anterior slips of the diaphragm becomes practically a straight line. It now corresponds exactly with the curve traced by the control lever attached to the chest wall.

Curve V. Taken from a rabbit, weight 1550 grm. narcotised with $\frac{1}{4}$ grm. Chloral Hydrate (Hypodermic Injection).

The medulla oblongata was separated from the brain above the striae acousticae and the left vagus had been divided. At the point on the curve marked with a cross the right vagus was frozen. The curve shows the immense inspiratory contractions thus produced.

Curve VI. From a rabbit weight 2000 grm. narcotised with $1\frac{1}{2}$ grm. of Chloral Hydrate (Hypodermic Injection).

The middle curve is traced by the writing point of a mercury manometer in connection with the carotid.

Both vagi were frozen and at once removed from the freezing apparatus. An inflation of the lungs was now found to produce no change in the breathing owing to complete interruption of conducting power in the vagi.

After an interval of 10 min. an inflation was found to produce the peculiar inspiratory effect seen on this curve.

Curve VII. The right phrenic nerve was dissected out in the neck and stimulated electrically.

The first stimulation began at the height of an inspiratory contraction and ended just before a normal inspiration had reached its full strength. The difference between the rate of contraction and elongation of the muscles during a normal respiratory movement and during a contraction induced by stimulation of the phrenic nerve is very evident.

The second stimulation of the phrenic began and ended in the expiratory period.

Two lines are drawn upon the curve to represent the curve traced by the up and down movements of the lever when the drum is at rest.

Curve VIII. Shows the effect produced by closing the trachea during the expiratory pause.

The trachea was suddenly closed at the point marked with a cross (+) and was opened again at the point marked with a circle (○).

Curve IX. Shows the effect produced by closing the trachea at the height of the inspiratory period.

The trachea was suddenly closed at the point marked with a cross (+) and was opened again at the point marked with a circle (○).

Curve X. Is selected to show the typical activity of the inspiratory muscular slips during respiration.
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The slightly curved lines superposed upon the curve represent the curves traced by the lever when the drum is at rest.

Curve XI. The uppermost of the three curves is traced by the control lever attached to the chest wall.

The dotted middle curve shows the movements of a mercury manometer connected with the trachea. When the lungs are inflated the manometer registers the rise of pressure and serves as a time marker and also as a useful guard against too violent inflation.

The lowest curve, traced by the movements of the muscular slips, shows the effect produced by an inflation of the lungs when the expiratory period is incomplete and a certain amount of tonic inspiratory contraction is present even during rhythmic respirations. This condition was produced by admitting a small amount of air into the right side of the thorax (slight pneumothorax).

During the first three respirations on this curve the expiratory pause is absent and each inspiration begins before the inspiratory muscles have completely relaxed. The gentle inflation (at the point marked with a cross) first causes the cessation of rhythmic inspiration and then the gradual abolition of the permanent inspiratory tone, as shown by the slow fall of the lever. As soon as the lungs were allowed to collapse a strong tonic inspiration is produced lasting nearly two seconds. Even when rhythmic breathing begins again the expiratory elongations are very incomplete.

Curve XII. This curve was traced by a lever which described a vertical line when the drum was at rest.

The right vagus has been divided and the left side of the thorax opened. In those cases where each vagus is distributed only to the lung of its own side no effect is produced by closing the trachea in the various phases of respiration. The present curve was however taken from an animal where these conditions were not fulfilled and shows the peculiar result produced by closing the trachea in the expiratory phase. Not only are the rhythmic inspirations increased in strength as on Curve VIII but a certain amount of inspiratory tone appears between the inspiratory contractions.

Curve XIII. Shows the effect produced by a long-continued inflation of the lungs. The inflation began at the point marked with a cross (+) and the lungs returned to their normal volume at the point marked with a circle (O).

PLATE II.

The dotted tracings on all the curves of this and subsequent plates represent the movements of a mercury manometer connected with the trachea. Thus any rise on the curve represents a rise of pressure in the lungs after closure of the trachea; on the other hand a fall in the curve shows that
suction has been applied to the orifice of the trachea in order to diminish the volume of the lungs.

Curve I. From a rabbit weighing 1350 grm. Chloral $\frac{3}{4}$ grm. At the point where the manometer curve rises (dotted curve) the lungs were inflated with pure oxygen. The animal was allowed to breathe pure oxygen for four or five inspirations preceding the inflation to insure inflation with the pure gas.

Curve II. Taken from the same animal.

The lungs were inflated with air at the point marked by the rise in the manometer curve.

Curve III. The lungs were inflated and allowed to return to their normal volume just before the time when the strong interrupting inspiration was expected to appear according to previous inflations of the same strength in the same animal.

Return to the normal volume was in this case accompanied by a great outburst of inspiratory energy. The slight fall in the level of the muscular curve is purely passive, as is shown by the coincident fall of the lever attached to the chest wall (the uppermost curve).

Curve IV. The left vagus was stimulated electrically with an interrupted current during the period marked by the rise on the excitation marker curve (the curve just above that traced by seconds pendulum). The stimulus chosen was of such a strength as, from previous experiments, was found to just fail in producing Rosenthal's "Tetanus" of the diaphragm (vide Curve XIII, which shows the effect produced by a stimulus of this strength in the same animal). During the stimulation both lungs were inflated for a period marked by the rise of the manometer curve (dotted). This inflation caused instant elongation of the inspiratory muscles. But as soon as the lungs were allowed to return to the normal volume the muscles again contracted under the influence of the electrical stimulation of the vagus and fell into a condition of complete tonic contraction. Thus an electrical stimulus which was unable to completely abolish rhythmic breathing was enabled to do so when aided by the inspiratory after effect of an inflation.

Curve V. The right vagus was divided and the left half of the thorax completely opened by excising portions of one or more ribs.

Inflation of the lungs produced the usual arrest of inspiration, but the return of the lungs after the inflation now produced an enormous tonic inspiration which only gradually gave way to rhythmic breathing.

Curve VI. From a rabbit weighing 1500 grm. Chloral $1\frac{1}{4}$ grm.

The lungs were inflated during normal respiration and allowed to return
REGULATION OF RESPIRATION.

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to the normal volume before the pause so produced had been broken by an "interrupting" inspiration.

Curve VII. The medulla oblongata in this animal had been separated from the rest of the brain by an incision passing just above the striae acusticae. The animal continued to breathe rhythmically after the operation.

At the point marked with a cross (+) the lungs were slightly diminished in volume by suction and allowed to return to their normal volume at the point marked with a circle. In the case the negative afteraction (expiratory) following the inspiratory effect produced by the diminution in volume of the lungs is extremely well marked.

Curve VIII. From a rabbit weighing 1600 grm. Chloral 1 grm.
The right vagus has been divided and the curve shows the effect produced by complete collapse of the left lung caused by perforating the left half of the thoracic wall.
The left lung collapsed at the point on the curve marked with a cross, and a very strong tonic inspiratory contraction was produced which lasted nearly 25 sec.

Curve IX. From a rabbit weighing 1850 grm. Chloral 1 ½ grm.
This curve shows the inspiratory effect produced by a "momentary" diminution in the volume of the lungs (suction) during normal respiration.
The manometer curve serves to register the duration of the suction.

Curve X. Is taken from the same animal as Curves I and II, with which it should be compared, and illustrates the effect produced by a "momentary" inflation by the lungs with pure hydrogen.

Curve XI. Shows the effect on normal respiration of sudden collapse of the right lung following perforation of the right half of the chest wall.

Curve XII. Both vagi have been divided. The central end of the right vagus was placed upon the electrodes and stimulated with an interrupted current of sufficient strength to produce active expirations. These active expirations appeared upon the muscle curve as small irregular passive movements, and affected both the muscle curve and the control curve (from chest wall) in the same direction and to the same amount.

This curve illustrates the strong inspiratory after effect which follows the cessation of an expiratory stimulation when both vagi are divided and the centre can act unhampered by afferent impulses from the lungs.

Curve XIII. Is taken from the same animal as Curve IV, with which it should be compared.
The right vagus was stimulated with an interrupted current just too weak to produce Rosenthal's "Tetanus."
This curve shows that the so-called "Tetanus" is in reality produced far more by decrease in the completeness of the expiratory elongation than by an increase in rate of the respiratory rhythm.

PLATE III.

On this Plate the dotted curves are traced by a mercury manometer connected with the trachea. During the periodic inflations or suctions of ventilation the mercury makes corresponding oscillations, thus registering and controlling the strokes of the pump.

Positive ventilation is taken to mean periodic inflations, negative ventilation periodic suctions, and compound ventilation the periodic alternation of inflation and suction.

Curve I. From a rabbit weighing 1500 grm. Chloral 1\1/2 grm.  
This curve shows the gradual abolition of rhythmic respiration under the influence of positive ventilation. An apnoea pause is produced which would have traced a curve resembling Curve III, had not the volume of the lungs been diminished (by suction) at the point marked by the fall in the dotted curve.

Curve II. From a rabbit weighing 1850 grm. Chloral 1\1/2 grm.  
Positive ventilation caused an apnoea pause consisting of a slow contraction of the muscles of the diaphragm (as in Curve III). This rise was cut short and replaced by an expiratory pause by inflating the lungs during the apnoea.

Curve III. From the same animal as Curve I.  
This curve illustrates the gradual abolition of rhythmic breathing under the influence of positive ventilation (periodic inflations). As soon as the ventilation ceased the muscular slips began slowly to contract and produced a contraction curve lasting 12 sec. A similar slow contraction was increased by a diminution in the volume of the lungs on Curve I, and cut short by an inflation on Curve II.

Curve IV. From a rabbit weighing 1650 grm. Chloral 1 grm.  
This curve shows the effect by negative ventilation (periodic suctions) during normal respiration. The greater number of small oscillations on the muscular curve during the ventilation are passive. This is shown by the synchronous and similar movements on the uppermost (control) curve traced by a lever attached to the chest wall.

Curve V. From the same animal as Curves I and III.  
This curve shows the peculiar alteration in the respiratory rhythm which follows the cessation of positive ventilation (of short duration, 8 strokes only) in an animal in which the apnoea pause is represented by a slow inspiratory contraction (vide Curve III).
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Curve VI. From the same animal as Curve IV.
Shows the effect of 7 suctions (negative ventilation) on the normal breathing.

**PLATE IV.**

Curve I. From a rabbit weighing 1850 grm. Chloral 1½ grm.
Shows the effect produced by inflating the lungs during the apnoea caused by negative ventilation. The duration of the inflation is shown by the rise on the dotted curve.

Curve II. From a rabbit weighing 1350 grm. Chloral ¾ grm.
Positive ventilation (16 strokes of the pump) is sufficient to abolish rhythmic breathing but insufficient to produce a pause after the ventilation ceases.

Air is the medium of inflation.

Curve III. From the same animal. To be compared with Curve II. 16 strokes of the pump are unable to produce an apnoea pause after the ventilation ceases even though pure oxygen is used as the medium of inflation. This shows that the abolition of rhythmic respiration by positive ventilation and the production of an apnoea pause is not due to the over oxydation of the blood provided the vagi are intact.

Curve IV. From the same animal as Curve I.
During the apnoea produced by negative ventilation the volume of the lungs was diminished (by suction), thus causing a considerable increase in the inspiratory contraction which characterises this form of apnoea.

Curve V. From a rabbit weighing 2450 grm. Chloral 1½ grm.
Shows the effect produced on the normal breathing by compound ventilation (alternate inflations and suctions).

Curve VI. From the same animal as Curve V., with which it is to be compared.
Shows the alteration in the effect of compound ventilation by the substitution of pure hydrogen for air as the medium of inflation.

**PLATE V.**

Curve I. From a rabbit weighing 1500 grm. Chloral 1 grm.
Shows the complete abolition of the respiratory rhythm produced by positive ventilation with pure hydrogen.

Curve II. From the same animal. To be compared with Curve I.
Shows the effect of the same number of strokes of the pump when air is the medium of inflation.

**PH. X.**
A comparison of the two curves shows that the only difference between the two curves lies in the shortness of the apnoea pause which follows ventilation with hydrogen in comparison with that produced when air is used. In both cases rhythmic breathing is completely abolished.

Curve III. From a rabbit weighing 2450 grm. Chloral 1½ grm.
To be compared with Curve V.
The left vagus was already divided and the curve shows the effect produced by freezing the right vagus during positive ventilation with hydrogen. The nerve is frozen at the point marked with a cross (+).

Curve IV. From a rabbit weighing 1600 grm. Chloral 1 grm.
This curve shows the peculiar form sometimes assumed by the apnoea caused by positive ventilation.
Rhythmic breathing is abolished but the inspiratory muscles do not elongate completely but remain slightly contracted. The contraction is so slight that it might fall within the errors incident to the method if its presence were not confirmed by the sudden fall which follows stimulation of the nasal mucous membrane with chloroform vapour during this form of apnoea.

Curve V. From the same animal as Curve III.
Shows the effect produced by continuing positive ventilation with hydrogen after rhythmic breathing has been abolished. The inspirations begin again during the ventilation owing to the increasing dyspnoea.

Curve VI. From a rabbit weighing 1750 grm. Chloral 1 grm.
Shows the effects of positive ventilation (5 inflations) with pure hydrogen.

Curve VII. From the same animal as Curve VI and to be compared with it, to show the effect produced by positive ventilation (6 strokes) when air is the medium of inflation. The difference between the two curves lies, not in the ease with which rhythmic breathing is abolished, but in the length of the apnoea pause. When air is used (Curve VII) a pause results lasting 9 sec., which is broken by gradually increasing inspiratory contractions. Where hydrogen is used (Curve VI) these small contractions begin directly the ventilation ceases in consequence of the dyspnoea.

Curve VIII. From the same animal as Curve IV, to show the effect produced by positive ventilation with pure oxygen.
A comparison of Curves IV and VIII shows that the only difference between the effect produced by positive ventilation with air or with oxygen lies in the length of the apnoea pause and not in its character or in the ease with which rhythmic respiration is abolished.
REGULATION OF RESPIRATION.

Curve I. From an animal weighing 1850 grm. Chloral 1½ grm.
Shows the apnoea produced by negative ventilation.

Curve II. From a rabbit weighing 1250 grm. Chloral ½ grm.
The left vagus has been divided and the curve shows the effect produced under these conditions by negative ventilation (20 suctions). To be compared with Curve IV from the same animal.

Curve III. From a rabbit weighing 1500 grm. Chloral 1½ grm.
Shows the effect produced by compound ventilation.

Curve IV. From the same animal as Curve II, on which it follows after an interval of about two minutes.
Negative ventilation was begun and at the 22nd stroke of the pump the right vagus was frozen.

On Curve II rhythmic breathing began almost immediately upon the cessation of ventilation, whereas on this curve the muscles begin to contract slowly to form a tonic inspiratory contraction of great duration (nearly 15 sec.) as soon as the remaining vagus is divided. Then follows a period of great irregularity in which the whole animal moved violently just as in those cases where great dyspnoea was known to exist (after breathing pure hydrogen).

Curve V. From a rabbit weighing 1500 grm. Chloral 3 grm. Slight pneumothorax existed on the right side of the thorax.
Positive ventilation lasting half a minute caused an apnoea closely resembling that usually produced by negative ventilation, for the return of the lungs after each inflation now became of more value than the effect of the inflation owing to the collapse of the right lung. The difference between this form of apnoea and that caused by negative ventilation in a normal animal lies in the form assumed by the apnoea pause, for instead of consisting of a steady relaxation of the inspiratory muscles the apnoea is here a direct continuation of the apnoea of ventilation.

Curve VI follows almost immediately on Curve V.
Positive ventilation was again begun and the left vagus was frozen after it had lasted 18 sec. When it had lasted 31 sec. the right vagus was also frozen and a lung tonic inspiration lasting over 9 sec. was produced.
The slight difference between the forms assumed by the apnoea on Curves V and VI compared with the great difference on Curves II and IV is noteworthy as showing how much the apnoea produced by negative ventilation is hampered by the dilatation of the lungs which it causes.
H. HEAD.

PLATE VII.

Curve I. From a rabbit weighing 1800 grm. Chloral 1½ grm.
Shows the effect produced by 22 strokes of compound ventilation.
Curve II follows closely on Curve I.
During the duration of compound ventilation the left vagus was frozen.
At the 22nd stroke of the pump the right vagus was frozen. On Curve I, 22 strokes of the pump only produced an apnoea pause lasting about 4 sec., whereas on the curve the pause lasts over 10 sec. owing to the division of the vagi at the close of ventilation. Thus we see that, firstly, the stimuli to the end organs of the vagi undergo summation in the centre and not in the peripheral end organs of these nerves, and, secondly, that this form of apnoea is considerably hampered in the normal animal by the dilatation of the lungs which it produces.

Curve III. From a rabbit weighing 1500 grm. Chloral 1½ grm.
Shows the effect of diminishing the volume of the lungs during the apnoea pause caused by positive ventilation. The diminution in volume of the lungs (suction) appears on the manometer curve (dotted) as a fall two seconds after the cessation of the ventilation.

Curve IV. From a rabbit weighing 1850 grm. Chloral 1½ grm. This curve is the converse of Curve III, for it shows the effect produced by a short inflation of the lungs during the apnoea caused by negative ventilation.

Curve V. Compound ventilation was continued during the whole duration of this curve on the right side.
For a full description vide p. 57.
The right lung collapsed slowly during the period between the two circles.

PLATE VIII.

Curve I. From a rabbit weighing 1500 grm. Chloral 1½ grm.
Shows the effect produced by 21 inflations (positive ventilation).

Curve II follows closely on Curve I, with which it is to be compared. Positive ventilation is repeated in the same animal after a short interval, and the left vagus is frozen during the ventilation. After 26 strokes of the pump the ventilation is stopped and the right vagus is frozen as quickly as possible. Nevertheless the apnoea pause takes an almost absolutely identical form to that seen in the normal animal (Curve I) except that it gradually passes over into a strong tonic inspiratory contraction. Whereas in the normal animal rhythmic breathing was ushered in by an expiratory elongation after the pause had lasted 10 seconds, the first expiration does not appear for 25 seconds when the vagi were divided at the close of ventilation, showing that this
operation far from cutting short a vagus apnoea rather tends to prolong its duration.

Curves III and IV are both taken from an animal weighing 2000 grm. Chloral 1 grm.

The left vagus was divided before the experiment began.

On Curve IV an apnoea was produced by 15 inflations. After a short pause positive ventilation was begun again and the right vagus was frozen at the twelfth inflation. Yet in spite of the fact that both vagi were divided a complete inhibitory apnoea pause was produced which gradually gave place to a slow tonic contraction of the inspiratory muscles. Now it is interesting to note that on Curve IV rhythmic respiration began again after the apnoea pause by a small inspiratory contraction, which was cut short after reaching but a very small height, whereas on Curve III the pause is broken by a long slow steady rise owing to the fact that dilatation of the lungs can no longer reflexly inhibit the inspiratory activity of the respiratory centre. Thus here again we see the controlling effect produced by the stimulation of the vagi produced by a change in the volume of the lungs.

Curve V. Compound ventilation was kept upon the left side of the thorax during the whole duration of this curve.

For a full description of this curve vide p. 56.

Plate IX.

Curve I. From a rabbit weighing 1300 grm. Chloral 1 grm.
Both vagi have been divided just previously to this curve.
Shows the tonic inspiratory type of blood apnoea which follows positive ventilation after the division of both vagi.

Curve II. From a rabbit weighing 1800 grm. Chloral 1½ grm.
Both vagi have been divided some time before this curve was taken.
Shows the expiratory type of blood apnoea which follows positive ventilation, especially when the animal is in any way exhausted or if the vagi have been divided some time before ventilation is resorted to.

Curve III shows the effect of inflating the lungs of a normal animal with chloroform vapour.
The inflation is marked by the rise on the manometer curve (dotted).
During the first few seconds following the inflation distinct traces of the normal inhibiting effect of an inflation are seen, but the breathing rapidly assumes the type seen on dividing both vagi. This tends to show that chloroform or ether vapour rather tends to paralyze than to stimulate the end organs of the vagi in the lungs.
Curves IV and V are taken from the same animal at intervals of a few minutes.

Curve IV shows the normal effect produced by inflating the lungs with air after division of the right vagus.

On Curve V the lungs were inflated in exactly the same way and apparently as nearly as possible to the same extent (to judge by the rise of the mercury manometer). But during the inflation the left vagus was frozen and we here find that the interrupting inspiration is replaced by a very strong inspiratory contraction of quite abnormal duration.

Curve VI. Compound ventilation was continued during the whole duration of this curve on the left side of the thorax.

The right lung collapsed suddenly at the point marked with a circle.

For a full description of this curve vide p. 57.

Part II. THEORETICAL, follows in a succeeding Number.
Curves I, II, and III illustrate the effects of freezing the left vagus nerve (L. Vagus frozen) and placing the right vagus nerve (R. Vagus) on a freezing apparatus. Additionally, the left phrenic nerve (L. Phrenie divided) is also shown.
Stim. of Phrenie

+ R. Phrenie divide.

Curve IV.
Positive Ventilation.
Positive Ventilation

Positive Ventilation

Positive Ventilation
Curve I.

Curve II.

R. Vagus frozen.

Respiratory Ventilation.
Positive Ventilation.
Ventilation

Curve V.

Five Ventilation.

Curve VI.

Ventilation.

Curve VII.
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Negative Ventilation.

Curve I.

Negative Ventilation.

Curve I

Compound Ventilation.

Curve III.
Negative Ventilation.

Positive Ventilation

L. Vagus frozen.
R Vagus frozen.

Curve IV.

R Vagus frozen

Curve V.

R Vagus frozen

Curve VI.
Compound Ventilation

L. Vagus f

+ Inflation of the right lung.
Right lung collapses completely.

Curve V.
Ventilation.

Curve III.

Negative Ventilation.

Curve IV.
Positive Ventilation.

Positive Ventilation.

L. V₂

+ Inflation of the right lung
Curve I

R. Vagus frozen

Curve II

gus frozen
Positive Ventilation.

Curve V.
R. Vagus frozen.

Curve III.

Positive Ventilation.

Curve IV.
the right lung still remains dilated
Positive Ventilation.

+ Inflation of the right lung.
Complete Collapse of the

Curve V
Curve III.

L. Vagus frozen.

right lung.
ON THE REGULATION OF RESPIRATION.
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PART II. Theoretical.

If we attempt to take a general survey of the nervous mechanism of respiration we must begin by confessing that we are entirely ignorant of the cause of the rhythmic activity of the respiratory centre. Although the vagi play an important part in regulating the breathing they certainly are not the ultimate cause of rhythmic respiration; for rhythmic breathing still continues, although in an altered form, even after the vagi have been divided. Moreover the centre still sends out rhythmic impulses even when the medulla oblongata is separated from the rest of the brain, the spinal cord severed below the seventh cervical vertebra and the vagi, superior laryngeal and glossopharyngeal nerves divided. Now whatever may be the stimulus which keeps up the activity of the respiratory centre it is certainly not of a rhythmic nature, and we are brought face to face with the difficulty that a continuous stimulus produces discontinuous activity in the organ upon which it acts. So far we are unable satisfactorily to explain why this should be, but it is one of the earliest phenomena which meet us in the study of vital activity. Postulating however a primitive rhythmic activity in the respiratory centre, it is possible to examine the various modifications which it undergoes under the influence of stimuli produced by alterations in the volume of the lungs.

As soon as the lungs are inflated all inspiratory activity ceases and a prolonged pause follows, during which the rhythm of the centre is in abeyance and the inspiratory muscles in a condition of complete relaxation. In the same way complete collapse of the lungs also abolishes rhythmic breathing but the inspiratory muscles are now in a condition of strong tonic contraction. In both cases rhythmic breathing is sup-

1 Part I, see p. 1.
pressed for a very considerable period in consequence of the sudden and permanent alteration in the volume of the lungs but under ordinary conditions it ultimately regains its rhythmic character in consequence of the growing dyspnoea. But even when precautions are taken to prevent dyspnoea, as in the experiments described in the previous section, the respiratory rhythm finally reappears even though the volume of the lungs remains unaltered. We must therefore conclude that the nervous mechanism of respiration possesses the power of adapting itself in some way or other to any volume which the lungs may permanently assume.

Now this adaptation might take place in one of two ways. Either the peripheral end organs of the vagus or the trunk of the nerve itself might become exhausted and so gradually cease to transmit the stimulus to the centre; or, the actual stimulus transmitted to the centre might remain practically constant and yet the gradual development of some antagonistic activity in the centre might lead to adaptation. Now there is little doubt that a stimulus passing up the vagi for a sufficient length of time would ultimately lead to the exhaustion of these nerves; but I think that a critical examination of the experiments, described in this paper, tends to show that this factor has little or nothing to do with the phenomena of adaptation under the conditions in which I have met with it.

Inflation of the lungs, under conditions which preclude any disturbance from dyspnoea, produces a long inhibitory pause in the breathing which is ultimately broken by an inspiratory contraction. Now if the end organs of the vagi or these nerves themselves gradually became exhausted we should expect that this inspiratory contraction would be very weak and would be followed after a long interval by a second contraction of somewhat greater strength. Thus, as exhaustion of the vagi proceeded, each inspiration would be stronger than that which came before it, and the pauses between these inspirations would gradually diminish. But as we saw in Part I. adaptation to a continuous inhibitory stimulus takes place in a very different manner. The pause, it is true, is ultimately broken by an inspiratory contraction, but far from being of diminutive size this contraction is actually stronger than that of any subsequent inspiration. Moreover the inspirations gradually decrease in strength and give place to a peculiar slow tonic contraction of the muscles of the diaphragm. The lever rises slowly, and finally remains for a short time steady at a certain height. Then small oscillations make their appearance and rhythmic breathing has
begun again although the lung remains in the same dilated condition as at the beginning of the experiment. Thus the actual modification which the breathing undergoes, during the time when the centre is becoming adapted to the dilated volume of the lungs, differs so greatly from that which we should expect if adaptation were due to a process of exhaustion in the nerve trunk, that I think we must assume that it is due to some change in the centre itself rather than to exhaustion of the peripheral mechanism.

Now if the centre possesses the power of adapting itself to any permanent volume of the lungs it is obvious that the sudden assumption of a certain medium volume will produce a different effect, according to whether the centre was previously adapted to a volume in excess of, or smaller than this medium volume. If the lungs have remained collapsed sufficiently long for adaptation to have taken place, a slight inflation up to a certain medium volume will produce an inhibitory stimulus and cause the cessation of all rhythmic inspiratory activity. If on the other hand the centre is adapted to a dilated condition of the lungs the sudden assumption of the same medium volume will produce a strong inspiratory effect. Thus the nature and extent of the influence produced by a certain volume of the lungs depends not only on the actual volume but also on its relation to the total volume to which the centre has become adapted.

Some physiologists are accustomed to regard inhibition, whether central or peripheral, as a decrease in the vitality of the organ whose external activity has been checked. The clearest expression of this idea is found in the statement that stimulation of the vagus causes stoppage of the heart by lowering its vitality. It is further assumed that this is the only effect produced by an inhibition, and the heart is said to be thrown into a condition of complete rest. But of late years many observers have called this view of peripheral inhibition in question, and I think that an examination of the experiments in this paper tends to show that it is insufficient to account for the phenomena of inhibition in the respiratory centre.

If the lungs are inflated and allowed after a few seconds to return to their normal volume, I pointed out that the pause so produced was frequently followed by the clearest traces of increased inspiratory activity. The diaphragm was more or less under the influence of a tonic inspi-

1 Especially Hering, Gaskell and Biedermann.
ratory innervation of which all traces had been previously absent. If we assume that the pause in the breathing produced by the inflation was caused simply by a diminution in the vitality of the respiratory centre we should expect that the breathing would return to the normal type as soon as the lungs returned to their normal volume. If we attempt to explain the increased inspiratory activity, which appears when the inflation is over, by the assumption that the centre has become dyspnœic during the inhibitory pause, it is difficult to see why the respiratory rhythm should be so profoundly altered. For, provided the vagi are intact, dyspnœa is characterised by strong inspiratory contractions noticeable for their comparatively short duration and for the completeness of the expiratory elongations by which they are followed. On the other hand the increased inspiratory activity, which follows the close of an inflation, is characterised by the prolonged duration of the inspiratory contractions and the incompleteness of the expiratory elongations. The expiratory period may be so shortened that, although the rhythmic contraction of the inspiratory muscles scarcely reaches the height of a normal inspiration, it is followed by the most distinct traces of a tonic contraction of the inspiratory muscles. Moreover these phenomena are seen to follow the close of an inflation with hydrogen almost as readily as when the oxygen has been the medium of inflation. Thus the expression of the increased inspiratory activity which follows the return of the lungs to their normal volume after an inflation is in every way different from the inspiratory changes in the breathing caused by dyspnœa; for the experiments described in this paper have repeatedly shown that dyspnœa caused by deficient oxydation is especially inimical to the development of an inspiratory tone.

We also saw that an inspiratory stimulus of known intensity gained additional activity if preceded by an inflation. Thus electrical stimulation of the central end of one vagus, which was not sufficiently strong to completely abolish the respiratory rhythm and produce Rosenthal’s “tetanus,” was enabled to cause this characteristic inspiratory contraction if preceded by an inflation.

Again under certain conditions negative ventilation is no longer able to completely annihilate rhythmic breathing, much less to produce an apnoea pause after the ventilation has ceased. If under such conditions the lungs are inflated for a few seconds during the negative ventilation, rhythmic breathing ceases under the influence of the next few strokes of the pump and cessation of ventilation is followed by the
usual apnoea pause so characteristic of negative ventilation. Thus a
rhythmic inspiratory stimulus which was unable to overcome the
rhythmic activity of the respiratory centre sufficiently to produce a
tonic inspiratory apnoea regains its full power when preceded by an
inflation.

All these experiments tend to show that an inhibitory stimulus
from the lungs not only diminishes the inspiratory energy expended by
the centre but also in some way increases its potential inspiratory
energy. Now Gad\(^1\) has already pointed out in his very suggestive
paper that there is no reason on analogy to suppose that a tissue can be
brought to a condition of complete rest by a stimulus but that on the
other hand we know of a number of phenomena in cell life which show
that the form assumed by the activity of the cell can be altered. He
applies this idea in detail to the respiratory centre and points out that,
whereas the one stimulus might increase the expenditure, the opposite
stimulus might turn the energy of the centre in the direction of
nutrition or of some other activity during which no stimulus passes from
the ganglion cells to the fibres of the motor nerves. He suggests that
whereas inspiratory stimuli tend especially to increase the destructive
activity of the respiratory centre, inhibitory stimuli may possibly in-
crease its constructive or anabolic activity.

Now assuming for the moment that an inhibitory stimulus produces
a preponderating constructive activity in the respiratory centre, it is
obvious that the longer it acts the greater will be the amount of
material stored up in the centre which, on breaking down, would give
rise to inspiratory energy. But the greater the amount of such material
stored up in the centre the less becomes the irritability of that centre
for the inhibitory stimulus; for the irritability of a centre for any
particular stimulus is inversely proportional to the amount of change
that stimulus has already produced. In other words, the greater the
amount of material collected in the centre the harder it becomes to add
permanently to that amount. Finally a stage must be reached in
which the amount of constructive activity due to the inhibitory stimulus
during any given period, exactly equals the expenditure of inspiratory
energy in the same time and adaptation is complete. But although
the constructive and destructive activity of the respiratory centre are
now equal as at the beginning of the experiment, the condition of

\(^1\) "Ueber die in der Lehre von der Regulirung der Athemthätigkeit angewandte
Terminologie." Würzburg, 1880.
the centre is in reality very different after adaptation has taken place from that which existed before it came under the influence of the continuous inhibitory stimulus. What might be called the "vitality" of the centre has been greatly increased, for it is now in a condition to respond with far greater vehemence to an inspiratory stimulus; moreover the slightest diminution in the inhibitory stimulus would at once lead to the liberation of inspiratory energy, apart from any inspiratory stimulus—in fact the whole level of activity has been shifted upwards. For, whereas before the centre came under the influence of the inhibitory stimulus it expended at any moment the same amount of energy as it accumulated and this had no balance upon which to fall back, it now has a store sufficient to meet considerable calls, in consequence of the accumulation which took place during the time when its constructive exceeded its destructive activity.

When Hering and Breuer proved that collapse of the lungs caused an inspiratory effect they assumed that diminution in the volume of the lungs produced an actual inspiratory stimulus analogous to the inhibitory stimulus caused by an inflation. Gad, on the other hand, explains the undoubted inspiratory effect produced by collapse as due rather to the complete removal of the inhibitory stimuli which normally ascend the vagi to act on the mainly inspiratory centre. It is extremely difficult to decide between these two views; for, as I pointed out above, the removal of a permanent inhibitory stimulus causes a great outburst of inspiratory energy, apart from the presence of any actual inspiratory stimulus. Then again, though the respiratory centre is not originally mainly inspiratory, as assumed by Gad, yet it undoubtedly becomes so under the continuous action of an inhibitory stimulus. We must therefore keep clearly in view the possibility that collapse of the lungs may produce two distinct effects both tending to modify the breathing in the same manner. Thus diminution in the volume of the lungs may evoke, firstly, the strongly inspiratory negative afteraction due to the removal of an inhibitory stimulus, and, secondly, an actual inspiratory stimulus analogous to the inhibitory stimulus produced by a dilatation of the lungs. Now as far as my experiments go towards solving this very difficult problem, the following reasons incline me rather to the original view of Hering and Breuer that diminution of the lungs below their normal volume is an actual inspiratory stimulus to the respiratory centre.
If both lungs are allowed to collapse suddenly by puncturing the thorax a much stronger inspiratory effect is produced than if both vagi were divided and yet, according to Gad's hypothesis, both operations equally remove the inhibitory stimuli normally passing up the vagi from the lungs. Again, a momentary suction will often produce a stronger inspiratory contraction than any which appears after the vagi are divided, even at the moment of division when the vitality of the centre cannot have materially fallen. Then too the very fact that a single momentary diminution in the volume of the lungs causes an effect which lasts after the actual diminution is past and which, when periodically repeated (negative ventilation), can undergo summation speaks in favour of an actual inspiratory stimulus.

I think it is difficult to explain these differences unless we assume that collapse of the lungs below the normal volume produces an actual inspiratory stimulus. On the other hand it would appear as if the normally diminished volume which the lungs assume when the chest is at rest, produces no stimulus to the end organs of the vagi although the sudden assumption of this same volume may produce an inspiratory or expiratory modification in the breathing if the centre was previously adapted to a permanently increased or decreased volume of the lungs. This hypothesis is borne out by the phenomena which follow closure of the trachea in the expiratory phase of breathing under certain special circumstances. For as we have already seen closure of the trachea in the expiratory phase in a normal animal greatly modifies the inspiratory portion of the breathing but leaves the expiratory phase almost unaltered; the inspirations are increased both in strength and duration and assume an appearance closely resembling that seen after division of the vagi. But if one side of the thorax has been opened and the vagus of the opposite side divided, closure of the trachea produces no alteration in the breathing provided each vagus only supplies the lung on its own side of the thorax, and in those cases where an alteration occurs we can be certain that there is some crossed innervation. Now if closure of the trachea in the expiratory phase does produce an alteration in the breathing under such conditions, not only are the inspiratory contractions increased in strength as was the case in the normal animal but the expirations are also shortened by the appearance of an inspiratory tone (Curve xii. Plate 1). This new factor cannot be explained on the hypothesis that inhibition is now more completely removed than was the case in the normal animal, for subsequent division of the intact vagus does not cause the appearance of a tonic.
inspiratory contraction under these conditions. Now if this tonic inspiratory contraction were due to contrast evoked by the sudden removal of all inhibition it ought equally to appear when all possibility of inhibition is suddenly removed by freezing the remaining vagus. So far I think the difference in the results obtained in the two cases can only be explained by supposing that the abnormally collapsed lung causes an actual inspiratory stimulation to the vagi which is set free to act as soon as the trachea is closed in the expiratory phase and which is removed, together with the inhibition, by the division of these nerves.

What is the nature of this inspiratory stimulus? We have already seen ground for supposing that an inhibitory stimulus caused by dilatation of the lungs increases the constructive activity of the centre, and on analogy we should be inclined to assign an opposite function to the inspiratory stimulus caused by abnormal collapse of the lungs. The following experiment, though not in any way conclusive, seems to throw some light on this question. If the brain has been separated from the medulla oblongata and both lungs are allowed to collapse a strong inspiratory tone is produced which gives place, as dyspnoea advances, to strong rhythmic inspirations accompanied by an ever decreasing tonic contraction of the inspiratory muscles. In the course of a few minutes the animal dies of dyspnoea if artificial respiration is not resorted to. But if both vagi are frozen through soon after the collapse of both lungs all inspiratory breathing ceases at once and a gigantic active expiration is developed, which slowly diminishes in strength to end in the death of the animal. Now as we have already seen division of both vagi after the medulla oblongata has been separated from the rest of the brain normally produces a very strong inspiration, which lasts as much as 40 sec. Thus the fact that division of the vagi was preceded by collapse of both lungs has fundamentally altered the result produced by division of these nerves; for, instead of a long inspiration, division is now followed by a strong active expiration. This strong expiration is not due to the dyspnoea necessarily caused by the collapse of the lungs, for the animal can be kept alive during the expiration by artificial ventilation and then allowed to die of pure dyspnoea by stopping the ventilation; death under these conditions is not characterised by any such violent expiration. These anomalous results can however be explained by assuming that before division of the vagi a powerful inspiratory stimulus from the collapsed lung was driving the centre to the utmost of its power, and that the
exhausted centre flew to the opposite extreme as soon as the inspiratory stimulus was removed, just as in a normal animal an outburst of inspiratory energy follows the removal of the inhibitory stimulus from the periodically dilated lungs.

Thus the inspiratory stimulus caused by diminution in the volume of the lungs would appear to be the true complement of the inhibitory stimulus caused by their dilatation. The inhibitory stimulus checks the inspiratory expenditure of the centre and at the same time stimulates it to greater constructive activity, thus tending to raise the level of its vitality. On the other hand the inspiratory stimulus would greatly increase the inspiratory expenditure and, by decreasing the constructive activity, tend to lower the level of vitality in the respiratory centre. Both stimuli tend indirectly to increase the irritability of the centre for the antagonistic stimulus and thus, provided sufficient time be allowed to elapse, adaptation to either form of stimulus must ultimately take place. When adaptation is complete rhythmic respiration will begin again, but the continuance of the stimulus is necessary to maintain the equilibrium of the centre; for its sudden removal at once throws the centre into the opposite form of activity (negative afteraction) without the intervention of any antagonistic stimulus.

When the vagi are divided the breathing finally settles down into a type characterised by long powerful inspiration; each inspiratory curve is broad and flat topped, and is terminated by a rapid fall of the lever, which may reach the base line of complete elongation. Here we have a form of rhythmic respiration entirely independent of any reflex regulation from the lungs, and it is interesting to consider the effect which would be produced by suddenly reinstating the vagi. The centre would send out a certain amount of inspiratory energy to produce one of the characteristic strong inspirations and the lungs would begin to dilate. But before the inspiration was half exhausted the dilatation of the lungs would cause an inhibitory stimulus and would check the inspiratory activity of the centre, the inspiratory muscles would elongate and a pause would be produced; for we saw that a momentary dilatation of the lungs not only checked the inspiration upon which it was superposed but also tended to hinder the production of the next inspiration. As soon as this positive afteraction was sufficiently diminished a second inspiration would appear, which would also be checked before it had reached its full height and would again cause an inhibitory afteraction.
Thus each inspiration is cut short by the dilatation of the lungs which it produces, and helps to add to the inhibitory condition of the respiratory centre. In addition each such inhibitory stimulus adds to the potential inspiratory energy of the centre and thus raises the vitality. Now as the store of inspiratory energy increases, the respiratory centre gradually becomes less irritable for the inhibitory stimuli, for the irritability of the centre for any particular stimulus is inversely as the change which that stimulus has produced. Finally a mean would be struck between the increased inspiratory energy of the centre and the periodic inhibitions from the periphery. The breathing would remain rhythmic but the inspiratory contractions would be smaller and more frequent than when the vagi are divided. Moreover the centre would be in a condition of increased vitality and would respond with much greater promptitude to an inspiratory stimulus or to a diminution in the inhibition, such as would be produced by dividing the vagi. Thus when the vagi are intact the centre has a constant tendency to exhibit inspiratory activity, whilst at the same time this inspiratory activity is checked and regulated by the dilatation of the lungs which it must necessarily produce. In fact we might now speak of the centre as being in a condition of "high level vitality." On the other hand when the vagi are divided the inspirations are no longer checked by the dilatation of the lungs, and are therefore of great strength and abnormal duration. If the centre is in a condition of high vitality at the time the vagi are divided the breathing at once becomes principally inspiratory, and the strong inspirations are accompanied by a permanent tonic inspiratory contraction during the expiratory phase. But later on the expirations gradually lengthen and the tonic inspiratory contraction disappears; this may occur immediately the vagi are divided if the vitality of the centre has been lowered by an excessive dose of chloral or some other maltreatment. Ultimately the centre settles down to a condition of spendthrift activity, regulated only by the impulses from the centres in the higher parts of the brain. Lastly, if the influence of these higher centres be removed by dividing the medulla oblongata just above the striae acusticae, all regulation disappears and enormous inspiratory contractions, which gradually decrease in duration, accompanied by ever increasing expiratory pauses quickly lead to the death of the respiratory centre from inanition.

During normal breathing the activity of the vagi produces two results—firstly, the inspiratory activity of the centre is regulated by
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the constant inhibitions produced by the dilatation of the lungs, and secondly, the potential inspiratory energy of the centre is raised. Thus division of the vagi will also produce a twofold effect upon the breathing. In the first place the inspiratory activity of the centre is no longer checked by the dilatation of the lungs, and the inspirations therefore increase both in strength and duration. Now if this was the only effect produced by dividing the vagi the breathing would at once assume a regular form, characterised by strong inspirations of considerable duration, followed by complete expiratory pauses. If the vitality of the centre is lowered by an excessive dose of chloral this is actually the case, but, if the centre is in a presumably normal condition, the inspiratory contractions which immediately follow division of the vagi differ greatly from those which appear subsequently. The first inspiration which follows division normally greatly exceeds its fellow in duration, and the tonic contraction of the diaphragm is always most marked between the first and second inspirations. The excessive duration of the first inspiration and the presence of inspiratory tone are ultimately connected with one another, for they are both abolished by a large dose of chloral, by dyspnoea or by anything which tends to lower the vitality of the respiratory centre. They are not primarily due to the condition of the air in the lungs, for they may be entirely absent although the animal is breathing an atmosphere of pure oxygen, provided the vitality of the centre has been depressed by an excessive dose of chloral. During dyspnoea both phenomena are absent although division of the vagi causes a great increase in the strength of the rhythmic inspiratory contractions. On the other hand the difference between the duration of the first and second inspirations can be increased by dividing the vagi during an inflation, even if the lungs have been inflated with hydrogen. Now in this case the inhibition which was removed on dividing the vagi has been increased, and, as a consequence of this increase, the difference between the duration of the first and subsequent inspiration is more marked than usual. In the same way we have already seen that, when the vagi are divided during an inhibitory apnoea caused by periodic inflations, the first inspiratory contraction after the pause was noticeable for its enormous duration. Thus we must assume that division of the vagi not only removes a check upon the rhythmic inspiration, but also upsets the balance of the centre by setting free the potential inspiratory energy stored up during the time the centre was adapted to the inhibitory stimulus.

In conclusion, the vagi produced two effects upon the centre during
normal breathing. Firstly, each inspiratory contraction is checked when it has reached a certain height owing to the stimulus caused by the dilatation of the lungs, and secondly, the inspiratory vitality of the centre is increased owing to these frequently repeated inhibitory stimuli. Removal of these nerves will therefore produce two distinct modifications in the breathing, one of which is permanent, the other more or less transitory. Firstly, the inspiratory contraction will be increased in strength and duration in consequence of the regulating influence caused by the variations in the volume of the lungs. Secondly, the removal of the inhibitory stimuli will set free the greater part of the inspiratory energy stored up in the respiratory centre under the influence of this inhibition, and will cause the appearance of an inspiratory tone, which is most marked immediately after division of the vagi, and gradually passes off as the centre becomes exhausted.

In conclusion it is my pleasant duty to offer my sincerest thanks to Professor Hering for the extremely kind way in which he not only placed his laboratory at my disposal, for nearly two years and a half, but also helped me by every means in his power.