CONTRIBUTIONS TO THE PHYSIOLOGY OF THE LUNGS. PART I. THE BRONCHIAL MUSCLES, THEIR INNERVATION, AND THE ACTION OF DRUGS UPON THEM.

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CONTENTS.

THE experiments we discuss in the present paper have arisen from some work we were conducting upon the circulation in the lungs. In this latter we found it possible to enclose a lobe of the lung in a plethysmograph, and it then became necessary to discriminate between volume changes due to blood on the one hand and air on the other. We therefore studied the movements of air in and out of the lobe; a study we were all the more induced to extend as there were many points concerned with the actions of the bronchial muscles and with the distensibility of the pulmonary alveoli that still required investigation. The present communication deals with the bronchial muscles alone, and we defer to later papers descriptions of our results upon the circulation in the lungs and the distensibility of the alveoli.

Section 1. Experimental methods.

Our aim in the experiments we describe in this paper has been to determine the volume changes of the lung or a lobe of the lung during its movements in normal and artificial respiration. The main number have been concerned with the study of a single lobe, which we have enclosed in oncometers whose general shape is seen in Fig. 1. These were made of gutta-percha, or in the later experiments of sheet copper, which possessed the advantage of lightness and rigidity. They were provided with a wide flange and were thus easily made air-tight by a glass cover. We have usually operated on the right lung because this lung is more subdivided into lobes than the left. The operation

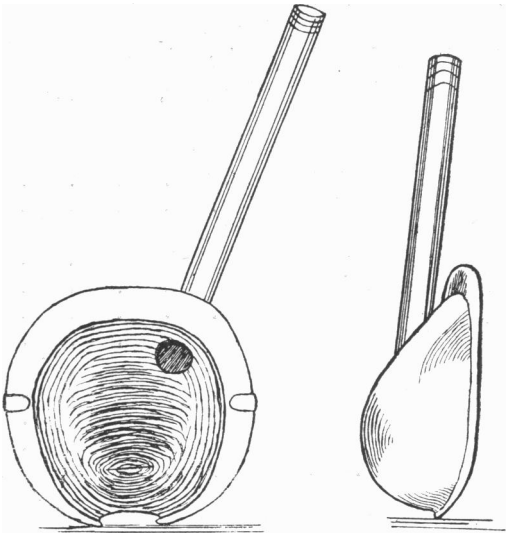


Fig. 1. Front and side views of the metal lung oncometer.

consisted in resecting four or five of the lower ribs—usually the fifth to eighth inclusive—until the lung was sufficiently exposed. The animal was then laid upon its left side and one of the lobes completely freed from its attachments down to the root of the lung. In the cat we have generally found it best to take the larger of the two lower lobes. This is attached by a fold of pleura along its inner edge to the tissues of the posterior mediastinum; when this is cut through the lobe is left free with a short and narrow pedicle. As the pedicle of the lobe is very short we have found it best to have no flange to the orifice of

the oncometer. To make the orifice air-tight when the lobe is in position we use vaseline alone, adding "vaseline-cotton-wool" in those cases only in which the neck of the lobe was much smaller than the orifice of the oncometer. By using vaseline only we avoided any risk of unnecessary pressure upon the structures in the neck of the lobe.

To record the variations in volume we employed either a tambour, a piston-recorder, or the bellows-recorder recently described by one of us[1]; of these the two latter were chiefly used because they do not set up pressure variations in the oncometer. The piston-recorder employed was the latest pattern of the Hürthle model. This instrument has however the great disadvantage that it possesses a very limited range, one quite insufficient for many of our experiments. Later we had the bellows-recorder at our disposal and therefore chiefly used it.

In the preparation of the lobe for insertion into the oncometer we proceeded in one of two ways:—either great care was taken in the handling of the lobe not to compress it in any way, or else by gentle pressure the air was largely expelled from the alveoli. The latter method was the one we usually employed in our earlier experiments; in a lobe compressed in this manner a considerable pressure of air is required to again distend it to its normal inflation. If therefore, during artificial respiration, we employed a pressure just sufficient to produce a normal expansion of the other lobes we only obtained a partial expansion of the lobe experimented upon. By carrying the preliminary compression of the lobe one step further a condition is reached in which practically no air enters this lobe, provided the air pressure employed for respiration is kept so low that it is only just sufficient to inflate the rest of the lungs to a normal extent. By allowing free entrance and exit into the lobe, as in our later experiments, in which we used the bellows-recorder, we were of course studying the condition of the lung under much more normal conditions.

We have used two further methods for recording the volume changes due to the movements of the air in respiration. In the first of these an intercostal space was exposed and a small opening made into the thorax. A flanged glass tube was then introduced into the incision and fixed tightly in position by stitches. It is easy in this way to make the joint perfectly air-tight for low pressures. The tube was now connected to a bellows-recorder, which thus registered the amount

[1] Brodie. This *Journal*, xxvii. p. 473. 1902.

of air driven out of the thorax at each inflation of the lungs. The walls of the thorax thus act as an oncometer, but they are not completely motionless. To keep them as nearly as possible at rest we therefore bandaged the whole of the abdomen and thorax fairly tightly. If, when fixing the glass tube in the thorax, it is tied in position about 4 cms. from the sternum and in the sixth interspace, this method makes a very simple though not very accurate experiment for studying the air volume changes of the lungs in artificial respiration. Care must, however, be taken that the lungs are not so far distended that the edge of a lobe is driven up to cover the orifice of the tube and thus form a valve.

The other method employed consisted in tying a cannula in the trachea and then enclosing the animal in an air-tight box, through one wall of which the tube from the tracheal cannula is led. This is essentially the method of Knoll, modified however in that, by the use of a large bellows-recorder instead of a tambour, volume-measurements were taken instead of pressure changes. In these experiments either the animal was allowed to breathe normally, or respiration was carried on artificially. The latter, for many purposes, is more advantageous on account of the greater regularity of the movements, and because the experiment is then under better control. In several of the experiments of this type we have avoided the error due to any resistance to movement offered by the thorax and abdominal walls by resecting the whole of the sternum and the anterior third of the ribs on each side.

In addition to recording the volume variations of a lobe, or of the whole lung, we have in many cases simultaneously recorded the lateral tracheal pressure. For this purpose a T-tube was tied into the trachea, the lateral branch connected to a tambour covered with rather thick rubber membrane, and the other limb to the ordinary tracheal cannula and respiration pump. The tambour used indicated for each millimetre rise of the writing-point a rise of pressure of 6 mm. of water.

With regard to these records of tracheal pressure we must point out, that the method we used for the artificial respiration is by no means the correct one if we wish to record marked changes in lateral pressure for any variation in the bronchial resistance, for the air space between the respiration pump and the trachea was far too great. We have in nearly all our experiments purposely chosen it so, because we wished to keep the tracheal pressure changes as nearly uniform as possible throughout the experiment. Most of our tracheal pressure

records therefore show no or only minimal changes, and consequently are not reproduced in our figures. It was only when working upon big animals and employing a large blast of air, with a relatively small lateral orifice in the tracheal cannula, that the variations in tracheal pressure became important. When in the few instances we have wished to bring about tracheal pressure changes following changes in the bronchial resistance, we have been easily able to do so by diminishing the thrust of the air-pump and nearly closing the lateral orifice of the tracheal cannula. In such cases we have taken care to allow sufficient time for the lungs to empty themselves through this restricted orifice.

The respiration pump and accessories. In any volumetric experiments upon the lungs one must be particularly careful that the successive respirations are completely uniform. In most of our experiments we used the method of inflating the lung by a blast of air, excess of which is allowed to escape through a side opening in the tracheal cannula. The form of respiration pump used consists of a large piston moving in a cylinder[1]. The piston was worked by a crank attached to a shafting which could be driven at any desired rate. The attachment of the piston-rod to the crank can be changed quickly, so as to alter the amount of air delivered at each thrust. The valves directing the course of the air work easily, but are perfectly air-tight. The upper end of the cylinder is closed in and provided with an inlet tube, so that any gas required can be administered in place of air. On the delivery tube is a specially constructed tap[2], by means of which any desired fraction of the air delivered at each thrust can be diverted into a small bottle containing an anæsthetic. In this way the amount of anæsthetic may be accurately graduated without in any way altering the total volume of air delivered to the tracheal tube at each inflation.

We did not find it any great advantage to moisten the air injected into the lungs, but we consider it of essential importance that it should be efficiently warmed. Several attempts to do this were made, such as by passing the air through several feet of lead piping immersed in hot water, but the ultimate and only really successful method of warming was as follows:—The delivery tube from the respiration

[1] This form of respiration pump is made from the designs of one of us (T.G.B.) by Mr C. F. Palmer, Brixton.

[2] Figured and described in the "Proceedings of the Physiological Society," p. xxxii. This *Journal*, xxvii. 1902.

pump was connected to the lower end of a metal cylinder fixed beneath the operating table. Inside the cylinder two incandescent eight candle-power lamps were fitted, and from the upper end of the cylinder another piece of tubing carried the warmed air to the animal. The connecting tube from the warming cylinder to the tracheal tube was kept as short as possible. The whole of the tubing from the pump to the tracheal tube was of large diameter. By means of this apparatus we could modify the pressure at which the air was delivered to the lungs in one of three ways, viz. (1) by altering the size of the exit from the tracheal tube, (2) by changing the amount of air delivered by the pump without altering its rate, or (3) by altering the rate of the pump. Throughout our experiments we have kept the pressure as low as possible, only allowing it to rise to just the necessary height for the efficient distension of the lungs.

Animals, anæsthesia, etc. The animals mainly used were cats, but the results were controlled by a considerable number of experiments on dogs and rabbits. With the exception of a few experiments, in which the animals were killed by pithing, all were anæsthetised, usually with ether, but at times with chloroform, or with the A.C.E. mixture. In experiments on dogs we generally administered morphia as well. In a few cases we anæsthetised first with ether, and then injected urethane either intravenously or intraperitoneally.

Care was always taken to keep the animal warm. Thus the room in which the operation was performed was always well warmed, and the animal lay upon a bed of cotton-wool supported on a copper box filled with water a little above body temperature. After the operation was ended the animal was covered up with cotton-wool.

In all the experiments an ordinary du Bois coil was used for excitation with a single Leclanché cell. The current could just be felt on the tongue when the secondary coil was at 14 cms. from the primary.

Section 2. Interpretation of the records.

We reproduce in Fig. 2 a tracing[1] obtained in a typical experiment in which the lobe was distended at each inflation to approximately the normal extent. It clearly records simultaneously two variations in

[1] All the tracings in this paper are to be read from left to right. In all cases the time record gives seconds. All the tracings reproduced are from the right lung. L.V. stands for lung volume, B.P. for blood-pressure and T.P. for tracheal pressure.

volume. The wave of large amplitude, *i.e.* each high vertical, is due to the movement of the air in and out of the lobe, and that of small

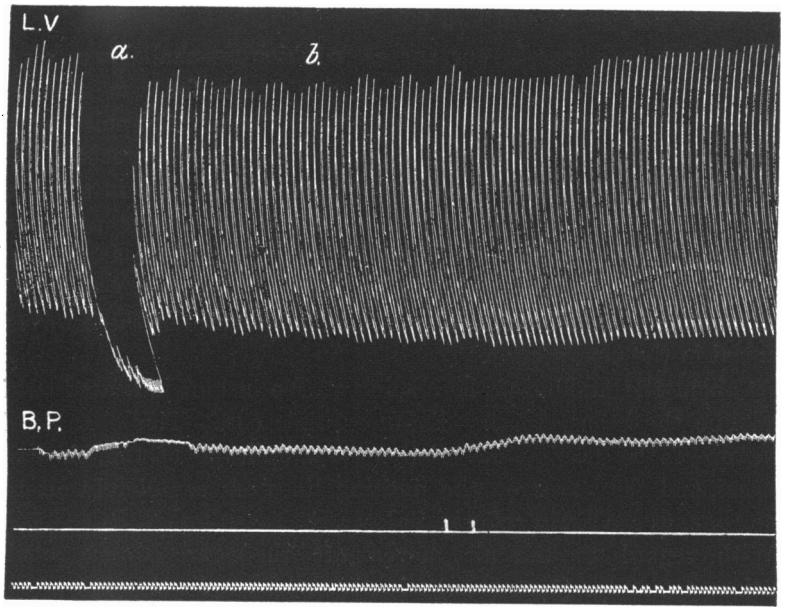


Fig. 2. Cat. Urethane and curare. One milligramme of muscarine previously administered. The zero B.P. is 16 mm. below the abscissa line. Reduced ⅓.

amplitude is the blood-volume pulse. Unless otherwise stated the rise of the lever in all our tracings indicates increase in volume, *e.g.* inflation with air or increase in amount of blood contained within the lobe. An increase in the average amount of blood is represented by a rise in the line joining the bases of the waves, and conversely a rise of this line commonly, but not always, indicates increase in blood-volume. In order to show the various features of this tracing more clearly the artificial respiration was stopped during the part *a*. This brings out two points, namely, the amplitude of the blood-volume pulse and the residual air volume of the lobe. The gradual fall of the tracing after the cessation of the respiration shows that the lobe was nearly able to empty itself completely at each retraction. The amplitude of the volume-pulse (2·2 mm.) is seen to be very small in comparison with that of the air-wave (50 mm.). When the artificial respiration was restarted the amount of distension effected progressively increased for the first four inflations, when its original amplitude was regained. On

account of the slow rate of the recording surface the air-waves appear as almost vertical lines with pointed apex and base. This is so in most of our tracings, for usually we were only desirous of studying the height of the wave, not its general form[1].

There are two lines in our curves to which we shall have to refer frequently and to which we therefore give names for convenience of reference. The first of these is that drawn through the apices of the air-waves and forms the upper border of the volume record. The second is a similar line drawn through the bases, and is the lower border of the record. We will term these the upper and lower limiting lines respectively. In Fig. 2 it is seen that there are waves in both these lines, those in the upper line being the more marked. This is generally true for all our tracings. The significance of these waves is discussed in the next section.

At about the middle of the tracing, at the instant indicated on the signal line the vagus was first ligatured, then cut. This changes the character of the tracing materially, the amplitude of the air-waves increases, and the waves on the limiting lines are completely altered. These changes are again referred to later.

With regard to the air movements there are three possible variations to study, (1) a change in the total amplitude, (2) a change in the rate of rise and fall, and (3) an alteration in the amount of residual air left in the lobe at the commencement of each inflation. The consideration of the second of these factors is deferred to section 8 of this paper. An alteration in the total amplitude of the air-wave, *i.e.* in the volume of air entering and leaving the lobe at each respiratory cycle, may be brought about by an alteration of one of three factors, viz., (1) a change in the air supply, either in the pressure or in the time during which it is allowed to distend the lobe, (2) an alteration in the distensibility and elasticity of the alveolar wall, or (3) an alteration in the resistance between the trachea and the alveoli:

(1.) The first of these is as a rule under direct control, and it is possible to so arrange the apparatus for artificial respiration that an alteration in the other two will produce so small an effect upon the first that it may be nearly always neglected. An instance in which this is not the case is recorded in Fig. 24, p. 136. In our experiments we have as far as possible avoided any error arising from this cause by using a large volume of air for each inflation, and keeping the tubing

[1] This latter we discuss in section 8 of this paper (p. 147).

etc., leading from the pump to the trachea of large calibre, with a large lateral orifice in the tracheal cannula.

(2.) The second factor can only be due, in our experiments, either to a change in the amount of blood contained within the pulmonary capillaries, or to the production of an effusion or secretion in this position. In all the changes we wish to discuss in this paper, effects of this kind either do not occur or are so minute that they may be neglected in face of the very large variations otherwise produced. That we are not dealing with any important change in the distensibility of the alveolar walls is easily determined by allowing a large volume of air at known pressure to distend the lobe before and after any particular observation. We have thus shown that the alveolus ultimately dilates to the same volume under the two given conditions.

(3.) The third factor in these experiments can only come into play in consequence of a change in the diameter of the lumen of the bronchioles. This diminution may be due either to muscular contraction of their walls or to swelling of the mucous membrane, but almost invariably the change has been muscular.

The evidence to be looked for as affording proof of contraction is a change in one of three factors:— (*a*) in the amplitude of the air-waves, (*b*) in an approximation of the limiting lines, or (*c*) a change in the rate of ascent or descent of the air-waves. The production of a constriction may be made to show itself in a simultaneous change of all these three, by altering the rate and force of the artificial respiration so that the air-waves are well marked and possess pointed apices. This latter point indicates that air was entering the alveoli during the whole of the inflation period. A flat-topped curve on the other hand indicates that the pressure of inflation lasted a longer time than was necessary to distend the alveoli to that pressure. In the sensitive state therefore a rise in the resistance of the air passages will be shown by a diminution in the rate of filling, and as the pressure only acts for the same length of time as before, by a diminution in the amplitude and a consequent alteration in the level of the limiting lines. The other method of experiment in which attention is directed to the rate of filling, and not to the total amount of distension, is not so convenient for experiment, and the occasions on which it is of special use are therefore given separately in section 8. A further convenient evidence of bronchial constriction is a rise of tracheal pressure, and we have consequently recorded it simultaneously in many experiments. Experiments of this

class succeed easily when the rate of filling of the alveoli is relatively slow. This latter effect was brought about by using a lobe only partially distended. As previously pointed out gentle handling of a lobe produces a degree of collapse such that, while the remainder of the lungs is normally distended by the respiration pump, this lobe only dilates to about one-half or even less of the extent to which the others are distending. The reasons of this behaviour are by no means easy to determine. One possible explanation is that the compression of the lobe has completely emptied many of the alveoli, and the adhesion of their surfaces cannot be overcome by a pressure of inflation sufficient to fully distend a normal lobe. This condition would be accentuated by the action of the collapsed alveoli in restraining the free movement of the normal alveoli in their immediate neighbourhood.

The alterations in the direction of the limiting lines produced by a constriction may vary considerably, thus we may find rise or fall of either of the lines in all their possible combinations compatible with a diminution in the height of the air-waves. The most typical change is a rise in the lower and a fall in the upper limiting line. These may be of equal extents or much more marked in one than in the other. A common result is a very marked rise in the lower limiting line and a smaller rise in the upper, Fig. 17, p. 128. As to what will happen in any given case depends upon the following factors, (1) the degree of constriction, (2) the force of inflation, (3) the time intervals between successive inflations. By properly modifying the last factor one can accentuate at will any of the possible variations.

The interpretation to be placed upon the changes of level of these lines must be based upon the following considerations. With any given condition of the bronchioles the degree of inflation and its rate depend upon the duration and extent of the change in tracheal pressure. The corresponding features of deflation are due to an elastic recoil of the alveoli—a force which is small in comparison to the force employed in distension. Consequently, the rate of emptying is rather slower than the rate of filling, especially in the later stages. In an experiment arranged with the lobe in a sensitive state, the lobe is filling the whole duration of the inspiratory phase, and emptying the whole duration of the expiratory phase. If the high tracheal pressure at the end of inflation lasted longer the lobe would continue to expand, and also if the expiratory phase lasted longer the lobe would continue to contract. If now a constriction of the bronchioles be produced the rate of filling falls off, hence the height of the air-wave is less. The rate of

emptying also decreases and consequently the fall of the lever is less. There is thus a tendency for the upper limiting line to fall, and the lower to rise. If the expiration time is further shortened we tend to produce a more marked rise in the lower limiting line and conversely. The greater the rise thus induced in the lower limiting line the less becomes the fall in the upper, until at last a stage is reached in which the upper line begins to rise. By still further continuing to shorten the expiratory phase a very considerable rise of this line, indicating marked over-distension, may be produced.

If on the other hand with fixed conditions of inflation and deflation a similar series of changes be produced they will indicate a gradually increasing change in the other main factor, viz., the constriction. The more marked the tendency to the production of over-distension becomes, the greater must be the constriction, but there is obviously yet another reaction possible, viz., one in which the constriction comes on so quickly and so forcibly that no time is allowed for over-distension, and collapse of the lobe is produced with complete absence of air movements.

To recapitulate the main conclusions: it has been shown that in the employment of our method a constriction of the bronchioles is proven by one or more of the following changes in the tracing:

1. A diminution in the amplitude of the air-waves.
2. An alteration in the rate of rise and fall of those waves (especially the latter).
3. The production of an increased and permanent inflation, *i.e.* a rise of the lower limiting line.

Section 3. The cause of the waves seen in the limiting lines.

The waves which occur on the limiting lines (cp. *supra*) are of two varieties. In the first of these the crest and trough of the waves respectively correspond in the upper and lower lines; when this happens the two waves are always of the same amplitude and consequently the total amplitude of the whole tracing does not vary. These waves are relatively rare, and when present are usually rather irregular. We reproduce in Fig. 3 a tracing showing this form. They can only be produced in one of two ways. The first and more usual is a rhythmic variation in the total blood-volume of the lobe, and frequently synchronous variations in the aortic pressure curve are seen. The second possibility, which must always be excluded, is that the lobe was not properly fixed in the oncometer and that rhythmic movements on

the part of the animal (*e.g.*, respiratory) pulled upon the root of the lobe. Waves of this origin are of course excluded by the use of curare.

The second variety of waves is the more common: here the crest of the wave in the one line corresponds in time to the trough of the wave in the other. The waves in the tracing of Fig. 2 belong to this variety. Waves of this form may also be produced in one of two ways. (*a*) By variations in the tonus of the bronchial muscles, or (*b*) By interference effects between the air and the blood-volume.

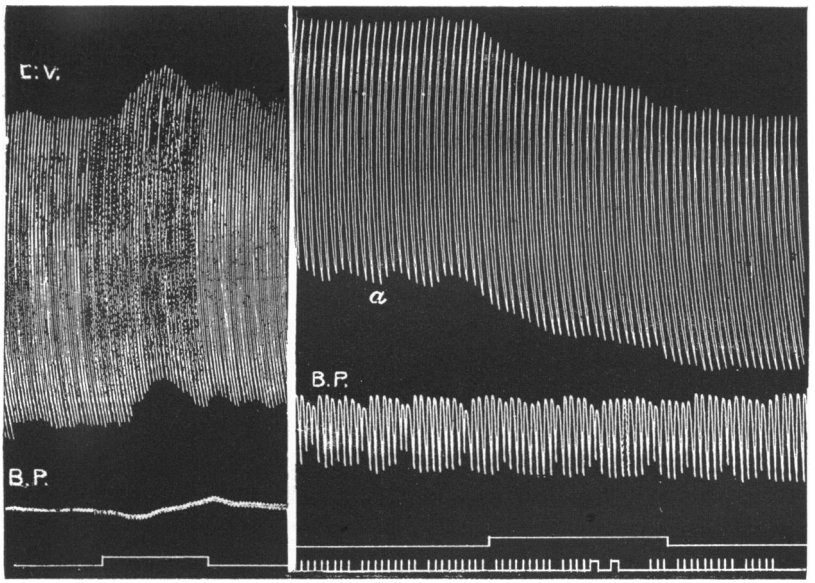


Fig. 3. Cat. A.C.E. The zero B.P. is 38 mm. below the abscissa line. During the interval indicated by the signal the vagus was first ligatured and then cut. Reduced ⅓.

Fig. 4. Dog killed by pithing. Upper tracing tracheal pressure. During the time indicated by the signal the artery to the lobe was clamped. Reduced ⅓.

We have never observed tonus waves in any of our tracings at the commencement of an experiment, *i.e.*, under normal conditions. They only made their appearance as the result of some action, such as vagal stimulation or the use of a drug. Thus in Fig. 20, p. 131, waves are produced by stimulation of the vagus. In Fig. 36, p. 158, a dose of pilocarpine is seen to produce a very marked wave of constriction before completely occluding the bronchioles to the lobe.

But the waves usually seen are interference in character, as may be proved by temporarily arresting either of the two factors producing

them. Thus in Fig. 2, where at *a* the air movements were stopped, the waves disappeared. The three small waves seen just after the tracheal tube was disconnected from the respiration pump are due to accidentally allowing a little of the air blown from the pump to enter the open end of the tracheal tube. If, on the other hand, the blood be excluded from the lobe the interference waves again disappear and we get air-waves of uniform height. This can be done by suddenly clamping the vessels running to the lobe, or as in Fig. 4 by clamping the artery only. In this experiment the artery was clamped during the time indicated on the signal line, and was released at the instant the signal fell, but did not at once fill again, for the lobe was seen to remain bloodless. The waves in the first part of this figure are most marked in the lower limiting line. The fall in this line directly after clamping the artery is due to the emptying of the lobe of blood, the vein having been left untouched. The irregularities in the descending part of the same line are due to slight movements of the clamp pulling upon the lobe: they correspond exactly with similar variations on the upper limiting line. By excluding the blood therefore the waves have again been abolished.

Apart from demonstrations of this type, which are not always possible, we are able to prove from examination of the tracing itself that we are dealing with interference effects, by applying the known tests for waves produced by interference. Thus, if the number of respirations and heart-beats which go to form a complete cycle be counted, it is found that the number of heart-beats + or − 1 is an exact multiple of the number of respirations. Thus for the wave marked *a* in Fig. 4 the number of respirations is 7, and the number of heart-beats 8. Again, for the wave marked *b* in Fig. 2 the number of heart-beats is 31, and of respirations 6.

Yet a further proof exists in that the sum of the total amplitudes of the waves on the limiting lines is double the amplitude of the blood-volume pulse. Thus in Fig. 2 the amplitude of the wave on the upper limiting line is 3 mm., that on the lower line is 2 mm., and the volume-pulse is 2·5 mm. A similar result has been obtained by us in nearly all the waves which so frequently occur throughout our tracings. These waves are always most marked when the lobe is only being partially expanded, a result to expect from *a priori* reasoning, for then the ratio of the volume-pulse to the air-wave is greater. Further, the waves are very variable in length, rarely continuing of the same length for long. This is because the heart rate is continually altering while

the respiratory rate remains constant. This variability is well seen in Fig. 2, and is again exemplified in Fig. 5. For the wave *a* of this

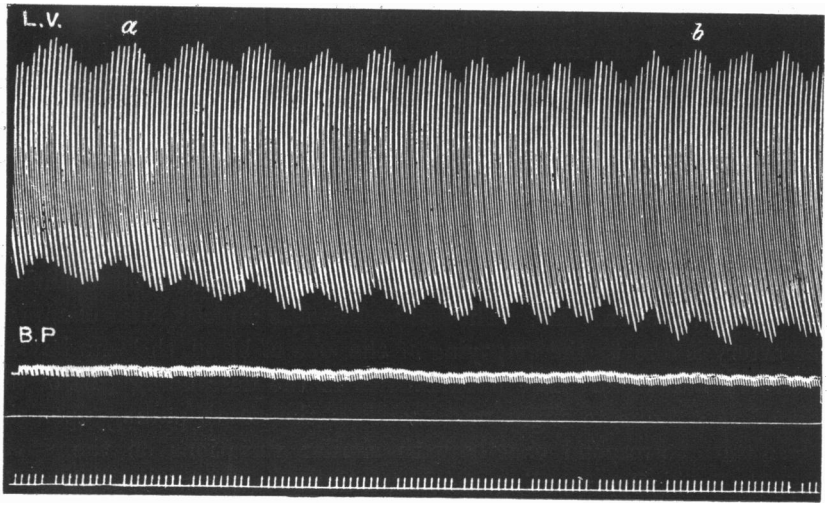


Fig. 5. Cat. A.C.E. R. vagus cut. The animal had previously received 0·01 grm. pilocarpine. Zero B.P. lies 60 mm. below the abscissa. Reduced $\frac{1}{3}$.

tracing the number of inflations is 12, and of heart-beats 25. For the wave *b* the numbers are 8 and 17 respectively, the time interval between the two being only 90 seconds. The difference is due to an

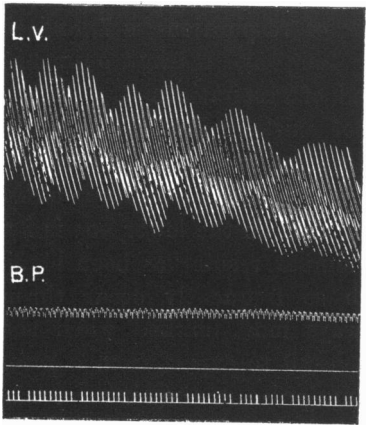


Fig. 6. Cat. A.C.E. Zero B.P. lies 21 mm. below the abscissa. Reduced $\frac{1}{3}$.

alteration in the rate of the heart-beat, which at *a* is 32 in 10 sec., while at *b* it is 34 in the same time.

Another feature of the tracings is that the notches on the air-waves produced by the volume-pulse fall successively later or earlier, as the case may be, upon the air-wave, and that the notch thus appears to travel either up or down the air-wave culminating at a crest or trough of the waves on the limiting lines. This is seen in Fig. 2, but we give another instance in Fig. 6, as it illustrates the point far better. In this figure the wave *a* is produced by 12 respirations, and 37 heart-beats.

To sum up, waves are most commonly due to interference, and their mode of production is exactly comparable to the phenomenon of beats in sound waves. They may also be due to rhythmic contractions of the bronchial muscles; thus we have observed them immediately after the death of an animal, *i.e.*, after the heart has ceased to beat (Fig. 34, p. 154), and in artificially perfused lungs, where the pressure of perfusion was maintained at a constant height.

Section 4. Some experiments on a schematic lung.

In order to exemplify and control some of the results obtained upon the lung we conducted a few experiments upon an artificial pulmonary alveolus represented by an elastic bag. This was enclosed in a bottle and its orifice tied upon a short piece of glass tubing passing through the rubber cork of the bottle. A second glass tube through this cork was connected to a bellows-recorder, which thus registered the volume variations of the sac, the bottle acting as an oncometer. The rubber bag was now distended rhythmically by the respiration pump, to which it was connected through a tracheal cannula. Between the cannula and the bag was a length of rubber tubing provided with a screw-clip. The rubber tubing thus represented the muscular-walled bronchus, the lumen of which could be restricted by the screw-clamp.

In the next two Figures are given the results of experiments in which the tube leading to the balloon was very gradually constricted and then as gradually released. The effect upon the volume per inflation commences directly the constriction begins, progressively increases with it, and falls off as the constriction is relaxed. Both figures show a diminution of the amplitude of the air-wave as the constriction is increased, but the other features of the tracing are markedly different. In Fig. 7 the upper limiting line falls and the

lower rises, whereas in Fig. 8 the upper line falls a little at first, then quickly rises, while the lower rises throughout. In both we get a reversal of the changes as the constriction is decreased, and both show

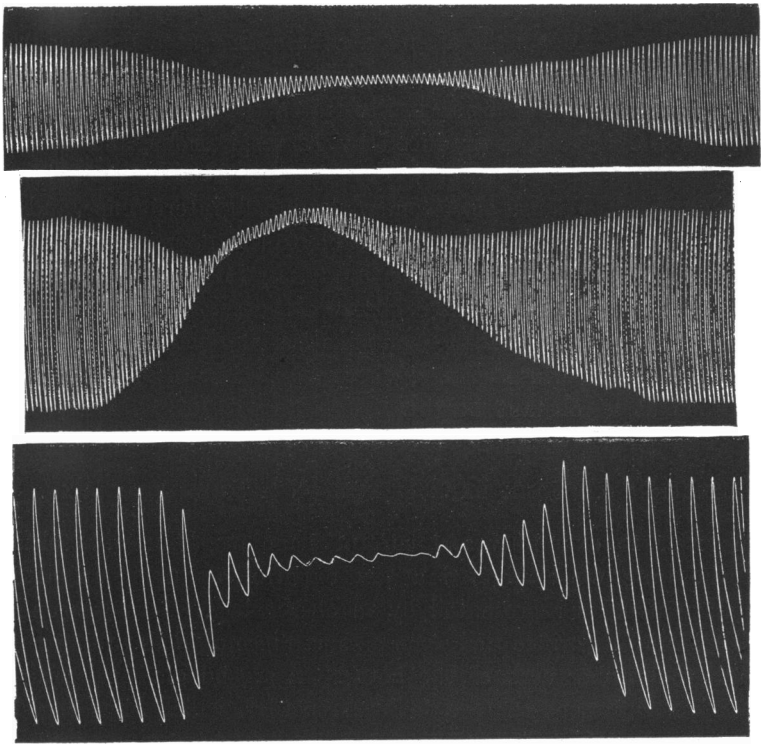


Fig. 7. Tracing obtained from a thin-walled rubber sac rhythmically distended as in artificial respiration. Rate of pumping was 3 in 2 seconds. The inlet tube to the sac was gradually constricted and gradually relaxed.

Fig. 8. Similar tracing to that of Fig. 7. The only change is in the rate of pumping, which now is 1 per second. The rate of movement of the drum has been proportionately changed.

Fig. 9. Similar tracing to the two preceding. The only change is in the rate of pumping, which is now 1 distension in 4·5 secs.

that as the constriction was produced, less and less air was forced through the resistance into the balloon. The variations in the limiting lines illustrate the points already discussed on pp. 106, 107; and the way in which the two effects were produced are therefore of interest in this connection. Both tracings were taken from the same bag within

a short time of one another, the only difference in the experiments being that in the second (Fig. 8) the rate of pumping was decreased to two-thirds the rate used in the first, the rate of movement of the drum being proportionally altered. The maximum pressure of inflation was therefore decreased, but, as measurement showed, only to a slight degree. In spite of the greater maximum tracheal pressure attained during each inflation the curve is of less height, for the variation in height is rather a function of the time-duration of the rise of pressure—in this instance being very nearly directly proportional. Thus the ratio of the times is as 2:3, and the heights are 21 and 32 mm. respectively. A further difference, which however is unrecorded in the Figures, is that the balloon during Fig. 8 was more distended at the end of deflation than in Fig. 7. The reason there is such marked over-distension in the second case and not in the first is therefore clearly due to the relatively greater difficulty of emptying as compared to filling. This greater difficulty is due to two causes, first, because there is more air to drive out, and secondly, because the internal pressure of a thin-walled rubber balloon falls the more it is distended. This is patent from the well-known fact that if two exactly similar balloons, one distended considerably, the other to a less extent, be connected to one another, the less distended one empties itself into the more distended. Whether we have a similar phenomenon at play in the movements of the pulmonary alveoli is a point to which we return later.

It is also possible to convert the first effect of the two preceding figures into the second in yet another way, viz. by increasing the distending pressure so that the movements of the balloon are more marked. In this manner again we attain the same end, that is, the balloon is made to empty a larger volume of air each phase. The emptying being effected by a smaller force than the filling, it is consequently more influenced by an increased resistance, so that as this latter grows the over-distension becomes progressively more marked.

Both these reactions are sensitive in that they show well-marked variations following a small constriction of the inlet tube; they are also sensitive for another reason, not to be gathered from the figures themselves, viz. that the whole of the changes were brought about by a relatively small increase in the resistance, and that a distinct effect was produced immediately the resistance was increased. For comparison with these results we give a third in Fig. 9, which was obtained from the same balloon and shows how the sensitiveness has been lost by

reducing the rate of the respiration pump. The surface was travelling at the same pace as in Fig. 8. The rate of the pump was 4·5 times slower, and the amount of air delivered each inflation was the same. The most important difference is that the change in amplitude does not commence when the constriction was begun. When it is produced it is very marked, and is sudden in onset, not because the rate of increase of the resistance was more sudden than in the preceding cases, but because a marked change could only be produced when the tube leading to the balloon was nearly occluded.

From these experiments on balloons we conclude that working with an artificial system designed in imitation of the lung, it is necessary, if we wish to obtain sensitiveness in the direction of being able to show small changes in the resistance of the tubes leading to the distensible sacs, to employ a force of inflation sufficiently great to give a good distension and worked fairly rapidly. These conditions we have also found to hold true for the lungs with certain reservations which are discussed when considering the action of the vagus on the bronchioles. We should mention that in addition to the two effects we have reproduced in Figs. 7 and 8, yet a third is possible and may be readily produced if desired. This is an entire absence of over-distension, *i.e.*, during the constriction the amplitude falls off as before but the lower limiting line of the tracing remains straight. This is a condition frequently observed in the lungs, and can be at once reproduced by allowing a sufficient time for the sac to completely empty itself at each deflation.

Section 5. Broncho-constrictor nerve-fibres.

The question of the innervation of the bronchial muscles has been the subject of many investigations, but it was not until the papers of Einthoven and of Beer appeared that the existence of constrictor fibres in the vagus was satisfactorily demonstrated. Our observations have been very numerous, extending over more than 100 animals, chiefly because we found so many negative or partially negative results that it was necessary to determine their meaning. One important result of our work is that we are able to satisfactorily demonstrate the existence of broncho-dilator fibres running side by side with the constrictor fibres (cf. p. 138). Their presence was the cause of many of the initial difficulties. In the description which follows we first give a short account of the previous literature, for which we are largely

indebted to the papers of Gerlach, Einthoven, and Beer, and then proceed to our own experiments.

i. Historical.

Williams[1] was the first to investigate the action of the vagus upon the muscles of the trachea, bronchi, and bronchioles. His animals were killed, and a tube, tied tightly in the trachea, was connected to a water-manometer. The trachea and lungs were then removed and a large sheet electrode was fitted around the lower margins of the lungs. A current from a powerful battery was now passed through the lungs to the brass cannula in the trachea. Each time the current was closed the manometer rose considerably (50 mm.), only falling slightly if the current was kept closed. Williams found that though the fibres were easily fatigued the effect could be obtained repeatedly for about an hour after the death of the animal if intervals of rest were allowed. If the lungs were too distended only poor effects were obtained.

Mechanical excitation of the vagus was ineffective, as also was the passage of a constant current through the nerve, although the œsophagus was strongly 'convulsed' by this stimulation. On cutting into the lung he found that the bronchi contracted powerfully to mechanical excitation. He concluded therefore that the bronchial muscles were easily excitable directly, and that the vagus was not their motor nerve. His experiments give evidence which, in the light of our present knowledge, clearly indicate that by his method the bronchial muscles were really being excited indirectly, for he found that it was not possible to register a contraction later than about one hour after death, and further that a dose of strammonium or atropine given just before the death of the animal prevented the occurrence of the reaction. Under both conditions we now know that the muscles are still capable of contracting if suitably excited.

Longet[2] was the first to show that the vagus contained motor fibres to the bronchial muscles. He directly observed the bronchi, exposed by cutting through the lung, in freshly killed large animals (horse, ox), and found that they contracted when the vagus was excited electrically. He points out, however, that his experiments do not permit him to say whether the minute bronchi behave similarly.

Volkmann[3] also obtained positive evidence of the action of the

[1] Williams. *Brit. Assoc. Reports*, 1840, p. 411.

[2] Longet. *Comp. Rend.*, t. xv. p. 500. 1842.

[3] Volkmann. See Article "Nervenphysiologie" in *Wagner's Handwörterbuch der Physiologie*, II. p. 586. 1844.

vagus on the bronchi. His method consisted in tying a glass tube, drawn out to a fine nozzle, into the trachea. The animal was killed and a small flame placed in front of the nozzle. On stimulating the vagi he, in all cases, observed movements of the flame, and in one experiment it was even blown out. He obtained the same result when the thorax was opened, though the movements were then much weaker. Here again the results though positive give us no proof of the influence of the vagus upon the smaller bronchi. They only tell us that the air space contained within the lung has been decreased, but that might well be due entirely to an action upon the trachea and large bronchi. The same criticism must hold for any method that attacks the problem statically. Most of the early observers employed such a method, usually recording the intra-pulmonary pressure by a water-manometer connected to the trachea of a recently killed animal, after the manner employed by Williams. Thus Donders[1] in his classical work upon the force of retraction of the lung recorded the pressure in this manner, and although he investigated the effect of vagal stimulation on several occasions he invariably obtained negative results. A probable explanation of his lack of success may be that the lungs were too highly distended when the vagus was excited. Similarly Wintrich[2] obtained negative results, when the thorax was either opened or intact. Knaut[3] however obtained positive results in the greater number of cases, but the rise in pressure was in no case very great. The results of experiments of this class were criticised by Rügenberg[4], who ascribed the positive results to the movements of the œsophagus simultaneously produced.

Bert's[5] experiments were of the same type, but he introduced the important modification of recording the pressure changes by a tambour instead of by a water-manometer. At first his results tended to confirm Rügenberg, but he later found that the negative result was due to the fact that he was distending the lung to too high a pressure. When working upon collapsed lungs he always obtained positive results. As these experiments were performed upon dogs he pointed out that it was the vago-sympathetic that was excited, and to determine whether the active fibres belonged to the vagus or to the sympathetic, he tested the

[1] Donders. *Ztschr. rat. Med.* III. p. 292. 1853.
[2] Wintrich. *Virchow's Handbuch d. spec. Path. u. Ther.* V. Abt. I. p. 189. 1854.
[3] Knaut. *Dissert. Dorpat.* 1859.
[4] Rügenberg. *Studien des Physiol. Instit. zu Breslau.* Heft 2, p. 47. 1863.
[5] Bert. *Leçons sur la physiologie comparée de la respiration*, Paris, 1870, p. 369.

action of the vagus in reptiles and found it to cause contraction of the lungs both in the case of turtles and lizards. He further found that the right vagus in these animals innervated the right lung only, and conversely.

Schiff[1], accepting the proof that excitation of the vagus caused a contraction of the lung, attempted to determine whether the alveoli or the bronchi were the parts which contracted. For this purpose he removed the lungs with the trachea and vagi from an animal immediately after death. Having slightly distended the lungs the trachea was stopped by a rubber cork, on to which it was tied tightly. The lungs were then laid upon a table, the nerves placed across electrodes which could be worked from a distance, and a thin bright metal disc placed on the edge of a lobe. The edge of this disc was watched through a telescope from a distance. On stimulation of the vagus he obtained negative results in most cases, in five the disc fell a few fractions of a mm., and once it showed slight rotatory movements. He thence concluded that it was the parenchyma of the lung which contracted and not the bronchioles.

Though his experiments may be considered confirmatory to those showing that the lung contracts on vagal excitation, they certainly cannot be interpreted as discriminating between contraction of the bronchioles and contraction of the parenchyma. If the small bronchioles contract in a lung at rest they must pull upon the neighbouring parts, and so can lead to a decrease in thickness of a lobe, without necessarily altering the volume of the alveoli. His readings, moreover, indicated such minute changes that the method cannot be considered delicate enough for the purpose.

Toeplitz[2] returned again to observation of the intra-pulmonary pressure in recently killed animals but could only obtain negative results.

Gerlach[3] repeated these experiments, employing a water-manometer to record the change in pressure. Working upon excised lungs somewhat after the manner adopted by Toeplitz he always obtained negative results, whereas if the lungs were left *in situ* positive results were gained. Thus in a dog he obtained a rise of 6 mm. of water when both vagi were excited, and in a rabbit a rise of 4 mm. This success led him to work upon curarised animals. The pleuræ were opened and the

[1] M. Schiff. *Pflüger's Archiv*, IV. p. 226. 1871.

[2] Toeplitz. *Ueber d. Innerv. d. Bronchialmusculatur. Dissert.* Königsberg. 1873.

[3] L. Gerlach. *Pflüger's Archiv*, XIII. p. 491. 1876.

vagi excited during a pause in the artificial respiration. He again obtained positive evidence, but the rise of pressure recorded was very small, usually about 5 or 6 mm. of water. Though the use of living animals is an obvious advance it possesses two great disadvantages. In the first place, each heart-beat expresses itself upon the manometer and consequently makes it difficult to read with accuracy. Secondly, some or all of the pressure changes might be of vascular origin, a source of error which Gerlach avoided as far as possible by only employing weak stimuli. The latter point is of very serious importance where such small pressure changes are alone produced. Gerlach excluded all possible error which might arise from movements of the œsophagus or stomach or from contraction of the trachea. He concludes therefore that the effects are due to the bronchioles.

The experiments of Bókai[1] were practically of the same type. He excluded the influence of the trachea by employing a long cannula which he pushed down to the bifurcation. This was then connected to a tambour. The animal was killed, and the chest widely opened, the diaphragm cut away, the heart supported, the œsophagus cut through and the stomach removed. After these precautions he always obtained positive results when the vagi were excited, provided the lungs were not too fully distended. He found the left vagus gave better results than the right.

In more recent times Sandmann[2] working upon curarised animals, and recording the tracheal pressure by a tambour, only obtained slight changes. He excluded any error due to movements of the œsophagus as in Gerlach's experiments and gives curves showing a rise of pressure on excitation of the vagus, but, as in all experiments of this type, the changes are very slight. He states that many were negative and that often both positive and negative effects were obtained from the same animal. He employed atropine to exclude cardiac changes and stated that in some instances a dose just sufficient to paralyse the cardio-inhibitors left the bronchial fibres still active. In this we have completely failed to confirm him, but are in complete agreement with both Einthoven and Beer.

As we have already pointed out, experiments by this method are very unsatisfactory for several reasons. Thus, they do not distinguish between the bronchi and bronchioles, and the effects in the best of cases

[1] A. Bókai. *Orvosi Hetilap*, No. 25. 1880. Abstracted in *Hofmann und Schwalbe's Jahresbericht*, IX. p. 79. 1881.

[2] G. Sandmann. *Arch. f.* (*Anat. u.*) *Physiol.* 1890, p. 252.

are quite minimal. It is consequently very difficult, if indeed possible, to exclude influences produced by circulatory changes. One reason why the recorded results are so small is probably because the air driven out of the bronchi during contraction need not necessarily lead to a rise of intrapulmonary pressure of any measurable extent, but may simply distend the alveoli and thus escape recognition. It is suggestive in this respect that all observers failed to obtain a rise if, at the start, the lung was moderately distended, for we know that the pressure difference required to start the distension of a collapsed lung is much higher than that required for an already distended lung.

We must therefore conclude that a satisfactory method of demonstrating the variations in calibre of these small tubes must be dynamical, and one by which we can investigate the amount of air passing through the tubes or demonstrate a variation in the resistance offered by them. One of the first to realise this was MacGillavry[1], who pointed out that a contraction of the bronchioles in a collapsed lung could only produce a minute diminution of volume, and that the resulting rise of pressure, which is the factor measured in those cases in which the problem is studied statically, must of necessity be still less. The ingenious method he employed was to displace air from a large reservoir at a constant rate into the lung. The lung was well pricked over its surface to allow an escape of the air through the alveolar walls and the lateral tracheal pressure was then measured. He found that in one experiment the pressure rose from 70 to 100 mm. of water on exciting the left vagus, and from 70 to 85 mm. on exciting the right. He thus obtained quite conclusive evidence of the existence of broncho-constrictor fibres in the vagus, but stated that he always recorded better results with the left vagus than with the right, a difference he ascribes to a greater number of fibres in the left than in the right. We think it more probable however that the difference is due to his method of experimenting. A freer exit from the alveoli of the left lung for instance would satisfactorily explain the differences he observed. Unfortunately his method can only be applied satisfactorily to a recently killed animal, for when experimenting upon living curarised animals his results were by no means so decisive and the bleeding produced by the pricking materially obscured the interpretations to be placed upon the results.

Riegel and Edinger[2] give a good historical account of the previous

[1] T. H. Mac Gillavry. *Arch. Néerlandaises des Sciences*, XII. p. 445. 1877.

[2] Riegel and Edinger. *Ztschr. klin. Med.* V. p. 413. 1882.

work upon the subject. Their paper is especially valuable in that they record confirmatory experiments performed with the object of testing previous work. Thus they repeated and confirmed Donders and Gerlach, and confirmed MacGillavry, though they did not obtain quite so large a rise in pressure as he had obtained. They conclude therefore that there is no question that the vagi innervate the bronchial muscles, and the rest of their paper deals with the consideration whether the spasm of the bronchioles which can thus be obtained is sufficient, in itself alone, to explain all the symptoms observed in spasmodic asthma.

Roy and Graham Brown[1] investigated the subject by a totally different method, viz., by introducing a narrow glass tube into the trachea of a dog and passing it down until it reached about the middle of the lower lobe of the lung. The bronchial end of this tube was closed by a small oblong bladder of animal membrane, which was distended to fill the small bronchus, and the movements of the bladder were then recorded by an oncograph. The curves they obtained they describe as complex, but as the method only deals with rather large bronchi we need not describe them fully here. It is sufficient for our purpose to state that positive effects on vagus excitation were obtained, that atropine caused complete paralysis of the vagal endings, and that tonus was usually present, dilatation following section of the vagus.

Franck[2] has studied the effect of cortical excitation upon the bronchial muscles, his method consisting in recording the extent of the chest movements during artificial respiration in the curarised animal. He obtained constriction, abolished by section of the two vagi, on stimulating parts of the motor areas of the cortex. The figure he gives shows only a slight change, however, not sufficiently decisive to place the conclusion he draws from it beyond question.

Chauveau[3] states that in the horse the bronchioles show some tonus which disappears on section of the vagus, for he found that if the vagus be cut on one side the vesicular murmur on that side disappears and is weakened on the opposite side.

The method adopted by Lazarus[4] was to distend the lung from a small cylinder, into which water was run at a fixed rate, and record the rate of rise of pressure and the total rise; similarly expiration was effected by running water from a second cylinder into which the lungs

[1] Roy and Brown. *Proc. Physiol. Soc.* p. xxi. This *Journal*, VI. 1885.
[2] Franck. *Fonctions motrices du cerveau.* Paris, 1887, p. 145.
[3] Chauveau. *Semaine med.* 1889, p. 117.
[4] J. Lazarus. *Arch. f. (Anat. u.) Physiol.* 1891, p. 19.

were allowed to empty and recording the rate of fall of pressure. The figures given by Lazarus show changes very slight in amount and therefore open to the objection that they may be to a large extent of vascular origin. He experimented upon curarised rabbits, and obtained positive results on vagal excitation.

Unquestionably the most important work upon the subject that has hitherto appeared is that of Einthoven[1], who attacked the problem by a totally different method. The experiments were conducted upon curarised and morphinised dogs, in which the distension of the lungs was effected rhythmically by injecting air from a syringe of moderate size into the trachea. The syringe was connected by a short length of tubing to the trachea so that the air space from the syringe down to the small bronchioles was practically only that of the upper air passages. It was worked rhythmically, and for a short time at the height of each distension the trachea was connected to a mercury manometer, which thus recorded the maximum pressure attained. A hindrance to the entrance of air into the alveoli means more air retained in the trachea and therefore a higher maximum pressure. By this method Einthoven was able to trace the course of the contraction with considerable accuracy, and if there is any criticism to be made of the excellent results he records it is that the method gives us no indication of the state of distension of the lung. He also gives one experiment in which the movements of the thorax were studied, and in that way shows how the movements of the lungs are limited by excitation of the vagi. The experiment thus recorded agrees in its general form very much with our tracing Fig. 11, p. 123.

In the same year Beer[2] published a long series of experiments in which the question of the action of the vagus was tested by many methods. In all cases he obtained evidence of the existence of broncho-constrictor fibres. We need not enter into a full discussion of his results, it is sufficient for our purpose to record the methods adopted. These were: (1) to record the intrapulmonary pressure in a curarised animal; in these, better results were obtained when the thorax was intact than after it had been opened. (2) To record the full variations of the lateral tracheal pressure in curarised animals in which artificial respiration was regularly maintained. (3) To record the rise in tracheal pressure (Expirationsstoss) produced by the emptying of the lungs into a box with a relatively large opening to the external air.

[1] Einthoven. *Pflüger's Archiv*, LI. p. 367. 1892.

[2] Beer. *Arch. f. (Anat. u.) Physiol.* 1892, Suppl. p. 101

(4) To record the movements of the diaphragm in curarised animals. In these experiments, when carried out during an interval when the artificial respiration was stopped, Beer observed a movement downwards of the diaphragm, which he explains as being caused by the distension of the alveoli by some of the air driven out from the bronchioles. On the other hand when recording the diaphragm movements while artificial respiration was still continued, he observed diminution in the extent of the movements and a permanent lowering in expiration, indicating distension of the alveoli.

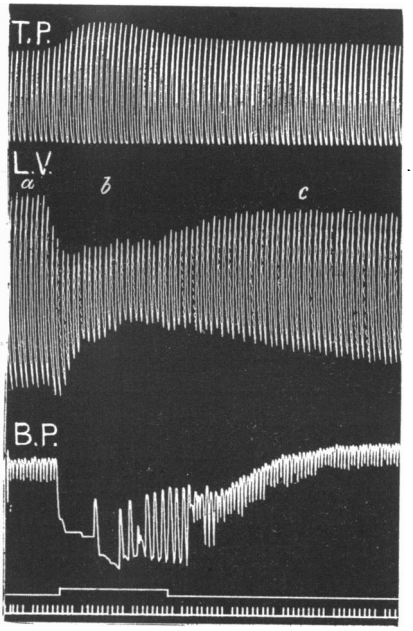
ii. Our own experiments.

A. *Those in which the lobe was normally distended during each respiration.*

The results we give are those which we consider the most typical. Great care was taken that the lobe experimented upon was uninjured, and that it moved quite freely in the oncometer. As showing certain differences we give tracings taken from the dog, rabbit and cat respectively. In all cases the aortic blood-pressure was simultaneously recorded.

Fig. 10 is from the lower lobe of the right lung of a small dog. The upper tracing is that of the tracheal pressure, the middle, the volumetric record of the lobe, and the lower is the aortic pressure. At the time indicated by the signal the right vagus was excited. The effect upon the blood-pressure is typical. The effect upon the lung volume is a very marked diminution in amplitude of the air-waves commencing at once and quickly attaining a maximum. The effect passes off slowly after cessation of excitation. The extent of the change is shown by the following figures. The height of the air-waves at *a*, *i.e.* before excitation, is 51 mm. The heights of the four waves immediately following the commencement of the excitation are 48, 45, 42 and 36 mm. respectively. At *b*, the height is 22 mm., at *c*, 37, and later, 44 mm. At the height of the constriction, therefore, only about two-fifths of the quantity of air enters, as compared to the stage before excitation. The maximum constriction occurs at the fourteenth inflation. Comparing this with the record of the lateral tracheal pressure, we see that this rises quickly and attains its maximum at the eighth inflation. It then remains up during the excitation and falls gradually as the constriction passes off. This tracing indicates maximum pressures of 114 mm. of water at *a*, 192 at *b*, 159 at *c*, and 156 later. There is thus

a distinct difference in time between the positions of the two maxima of constriction, as judged by the volume change on the one hand, or the pressure change on the other. It is difficult to say which gives the course of the bronchial contraction most accurately. A point against the lung volume record in this respect is, that the lung does not immediately come to a position of equilibrium for a sudden change in the conditions of inflation, but takes some three or four respirations to do so. (See Fig. 2 at *a*.) This delay is very little marked if the lung



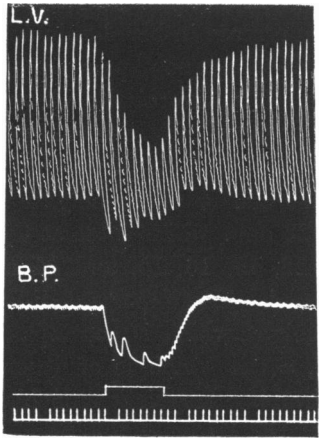


Fig. 10. Dog killed by pithing. Excitation of vagus; coil at 6 cms. Reduced ½.
Fig. 11. Rabbit killed by pithing. Stimulation of vagus; coil at 6 cms. Reduced ⅓.

is being fully distended, but becomes more and more so the greater the collapse. For this reason we must not consider the volume changes as necessarily accurately indicating the relative amounts of constriction at different times. The volume change at once shows any change in calibre of the bronchioles and gives a direct measure of the effect of that change upon the lung. For the study of the course of the constriction, its amount and time relations, the pressure curve is possibly a nearer approximation than the lung volume curve. In this tracing recovery is at first quick, then slow, but never quite complete:

this is a very common phenomenon and apparently an important feature of the physical properties of the lung. It is seen here on both volume and pressure tracings. If in such a state the lung be distended rather more forcibly for two or three inflations, and then the respiration be continued exactly the same as before, it will return with very considerable accuracy to its original state. The lung therefore behaves in this respect in exactly the same way as imperfectly elastic bodies, showing a higher degree of extension if it be brought down from a high tension to a moderate one, and a lower degree of extension if brought up from a lower to the same moderate tension.

The lower limiting line at first falls and only later rises. In spite of this fall the two limiting lines approach one another as we have already seen, and it is the approximation of the two lines—*i.e.*, the diminution in amplitude—which is the sign of bronchial constriction and not the change in direction of the two lines. This fall in the lower line is due to a decrease in blood-volume, a change which is discussed on p. 134.

We may now pass on to an examination of the similar effects observed in the rabbit. A typical tracing is given in Fig. 11, which we see is practically the same result as that just discussed, though the commencement of the change is a little different. This is seen from the measurements of the heights of the air-waves. Before stimulation these are 33 mm., while those at the commencement of excitation are 36, 32, 29, 22, 19, 16, 15, and 14 mm. At this last point the minimum is reached. The important difference is that the first effect is an increase in height, which is accompanied by a sharp fall in the lower limiting line, a fall which is of vascular origin. Either, therefore, there is a preliminary transient bronchial dilatation, or the lobe is more distensible. That the latter is the true explanation was proved, for this animal, by stimulating the vagus immediately after the animal had been bled to death, when the preliminary increase was absent. The result therefore suggests that the empty condition of the pulmonary capillaries renders the lobe more distensible, a conclusion which we later show to be the correct one (*vide* p. 135). The only other notable difference between this and the preceding Figure is the rapid and more complete recovery.

In the third animal, the cat, the results obtained differ materially from those just described in the dog and rabbit, as is seen from Fig. 12. Here again the three tracings represent tracheal pressure, lung volume and aortic pressure. During the time indicated by the signal the right vagus was excited with weak induction shocks. The first effect is a slight diminution in amplitude, immediately followed by recovery to

exactly the same height as before, and this continues during the whole duration of the stimulus; but 10 seconds after it had ceased a marked

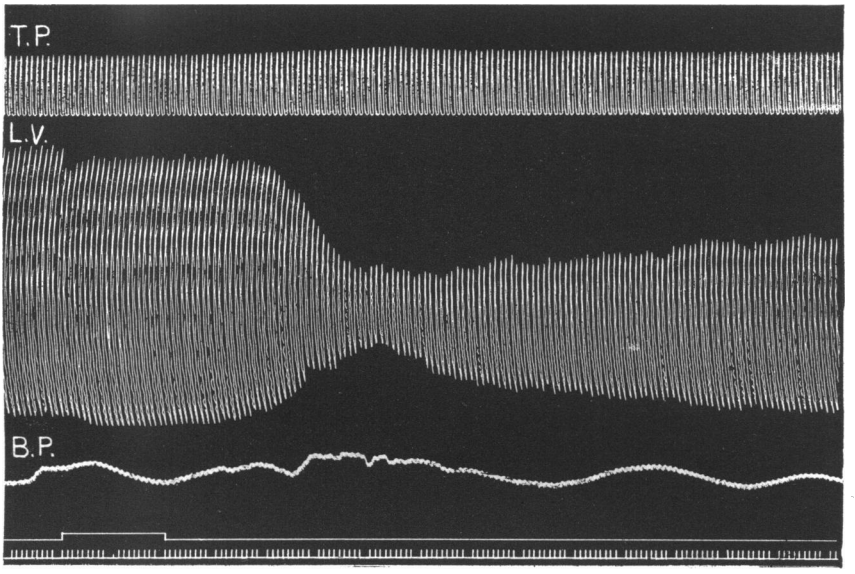
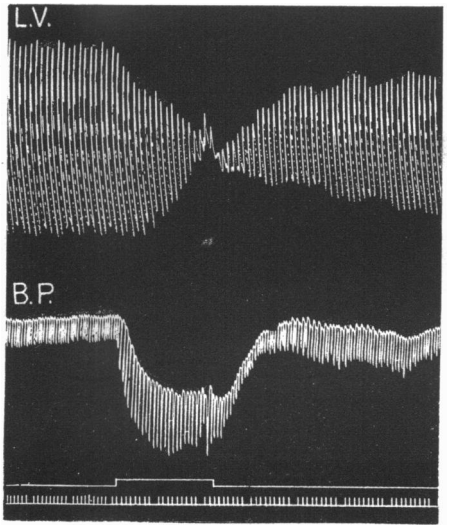


Fig. 12. Cat killed by pithing. Stimulation of vagus; coil at 10 cms. Zero B.P. 17 mm. below abscissa line.

constriction commenced, attained its maximum 10 seconds later, and then gradually disappeared. The tracheal pressure shows analogous changes, though the artificial respiration was not arranged for showing them in a pronounced manner. The final relaxation is particularly slow in this instance, but commonly it is more complete and rather quicker.

Such a response as that figured at once suggests that we are here dealing with two simultaneous effects, the one tending to produce constriction, the other relaxation, *i.e.* that in the vagus there are broncho-dilator fibres as well as broncho-constrictor. The different response in the cat would then imply that the dilator fibres are especially developed in this animal. Although this figure shows the usual reaction obtained when experimenting upon the cat, yet we have observed many variations. A very rare effect is that recorded in Fig. 13, which we see differs in no essential particular from the results typically obtained in the dog and rabbit. The constriction had become practically complete when the excitation was stopped. It is interesting

too to note that in this case the cardiac inhibition is much more pronounced than is usual in this animal. We have at different times observed practically all intermediate stages between these two extremes. Thus, the initial constriction may be more prolonged, but the chief



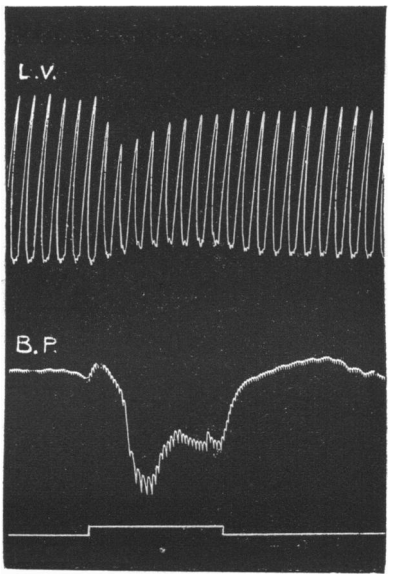


Fig. 13. Cat. Pithed. Stimulation of vagus; coil at 6 cms. Zero B.P. 24 mm. below abscissa.

Fig. 14. Cat. Ether. Stimulation of vagus; coil at 10 cms. Zero B.P. 48 mm. below abscissa line. Reduced $\frac{1}{3}$.

variations were found in the constriction which follows the cessation of the stimulus. This may commence a little earlier and be more marked, but the effect is generally in the reverse direction. As examples of the more commonly observed variations we give the following four figures. In the first of these (Fig. 14) a rapid constriction is produced, which quickly recovers although the stimulation continues, and there is no constriction after the cessation of the stimulus. In Fig. 15 the first effect of the prolonged stimulus is a relaxation, followed by a constriction, but again, the main constrictor effect is observed after cessation of the stimulus. This experiment is of further interest because the animal had, at some time, suffered from a severe attack of pleurisy on the right side and the lobe experimented upon was firmly adherent to the outer pleura, so that considerable difficulty was experienced in separating it

from the chest wall. The lobe was markedly emphysematous and it is seen from the tracing that retraction was very imperfect. Two further tracings taken from this same animal are given as they illustrate other points. In Fig. 16 very considerable distension is produced, which begins about 5 seconds after the stimulus was started. In this

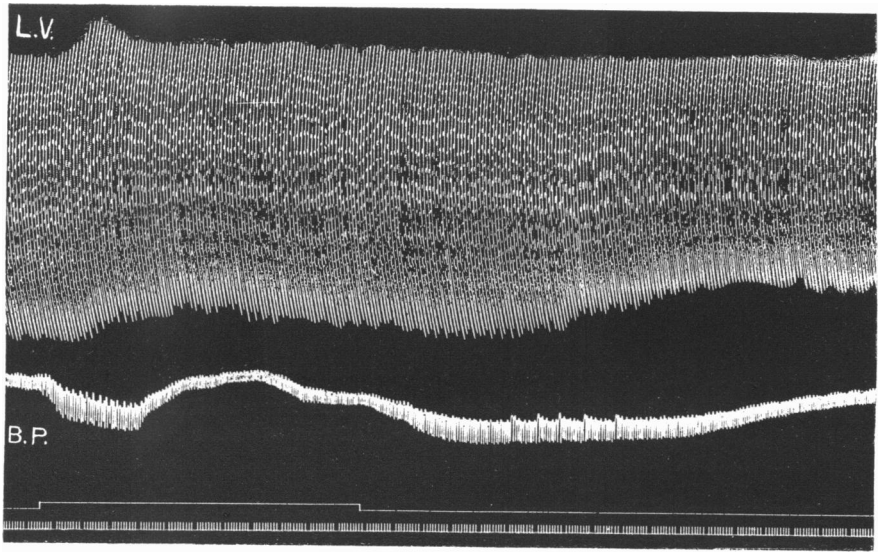


Fig. 15. Cat. A.C.E. Stimulation of right vagus; coil at 8 cms. Reduced $\frac{1}{2}$.

experiment the pressure of distension was kept very low and the time allowed for expiration was shortened. The tracing of Fig. 17 was obtained from the same animal about 1 minute later. The force of inflation had been slightly increased, but the time allowed for expiration remained the same as before. At *a*, the artificial respiration was stopped for a short time, in order to record the amount of residual distension of the lobe, which is seen to be very considerable. The vagus was now excited, and at once the amplitude falls and further over-distension is produced. It is interesting to note that the instant at which excitation ceased is marked on the volume record by a sudden diminution in amplitude of the air-waves, which shortly after are cut out completely. About 2 minutes later the air movements returned spontaneously. The experiment therefore has an important bearing upon the pathology of asthma, for it is one in which we were able to observe the changes in the air movements when the bronchioles

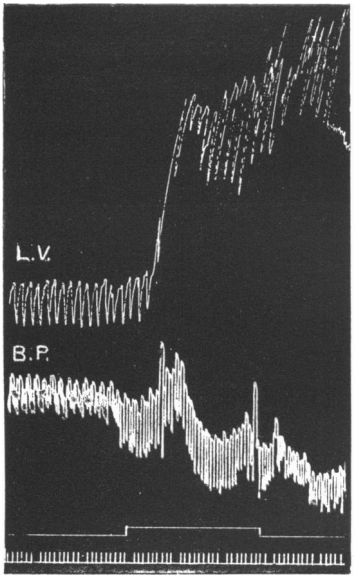


Fig. 16. Cat. A.C.E. Respiration effected by the method described on p. 148. Stimulation of vagus; coil at 8 cms. Pressure of inflation 38 mm. of water. Zero B.P. 38 mm. below abscissa line. Reduced $\frac{1}{3}$.

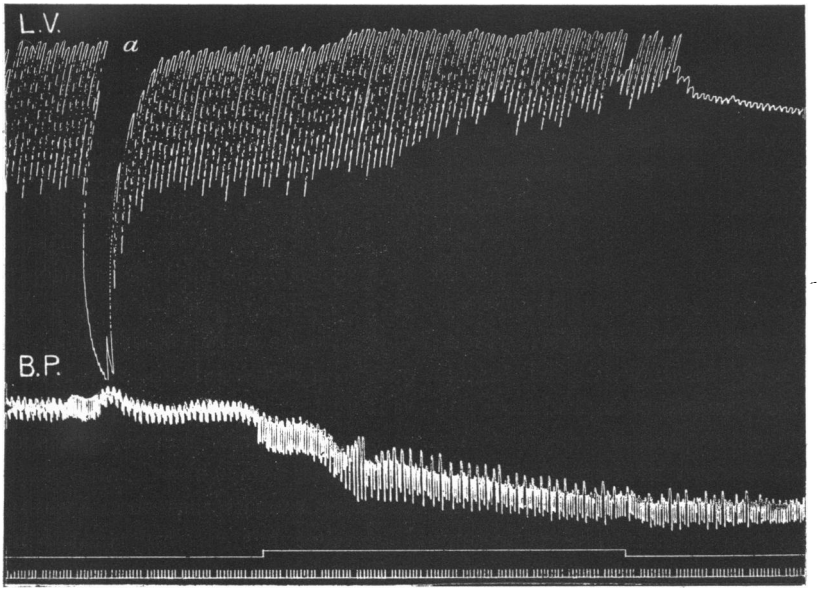


Fig. 17. Same animal as in Fig. 16. The artificial respiration effected by a rather greater pressure of air (50 mm. of water). Zero B.P. 20 mm. below abscissa line. $\times \frac{1}{2}$.

constricted in an emphysematous lobe. Before enclosing the lobe in the oncometer it was watched and noted to expand very easily but to retract slowly and incompletely. In appearance the lobe was much paler than the upper part of the lung, which was apparently normal. The alveoli were very large. The tracing exemplifies the abnormal physical state of the lobe very completely. Its distensibility was if anything rather increased but its elasticity was very imperfect. Lastly, the time required by the lobe to empty itself was much greater than in the case of a normal one.

B. *Experiments upon partially collapsed lobes.*

Experiments upon partially collapsed lobes show certain differences from those already described. Fig. 18 gives one of the commonest results we have observed in the cat, and it resembles in the main

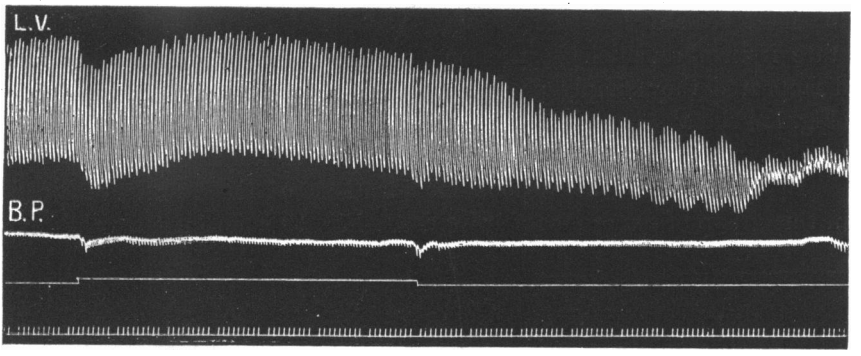


Fig. 18. Cat. A.C.E. Stimulation of vagus; coil at 7 cms. Zero B.P. 73 mm. below abscissa line. Reduced ½.

the usual result obtained in this animal, shown in Fig. 12. A short constriction marks the commencement of excitation; but the air movements are unaltered during the main period of excitation, and the main constriction developes during the 70 seconds after the stimulation was stopped. It results in almost complete blockage of the air movements. The alterations in the lower limiting line seen in this figure are usually present and though of a degree which might readily be caused by blood-volume changes, we do not think this is the true explanation here, for the aortic pressure remains practically unaltered. They are air-volume changes due, probably, to changes in the distensibility of the alveoli caused by variations in the amount of blood in

the pulmonary capillaries. Just before the air-waves are cut out, a few marked waves are seen in the limiting lines. These are not interference waves, for their amplitude is too great in comparison to the volume-pulse, nor does the crest on the one line correspond to the trough on the other. For this latter reason they cannot be tonus waves and must therefore be variations in the quantity of air retained at the end of expiration, due apparently to slight changes in the ease with which the lobe empties itself in expiration, for the fall of the line as the waves descend on the limiting lines is greater than in the ascending portions. The explanation of this variation in rate of emptying is not easy to understand, and a further instance of it is seen in the over-distension produced when the constriction finally cuts out the air-waves. They may possibly be due to variations in inflation of different sets of alveoli. A lobe which has completely collapsed in this way usually remains so, although the bronchial constriction may have passed off. A few inflations, of sufficient force to slightly distend it, are enough to cause a return to the original state if the bronchial constriction has passed off, but if this has not disappeared they simply produce distension. As in the previous case (Fig. 12) the absence of constriction during excitation is to be explained by the simultaneous excitation of the broncho-dilators.

In Figs. 19 and 20 various modifications of the results obtained in this group of experiments are given. Fig. 19 is an instance showing

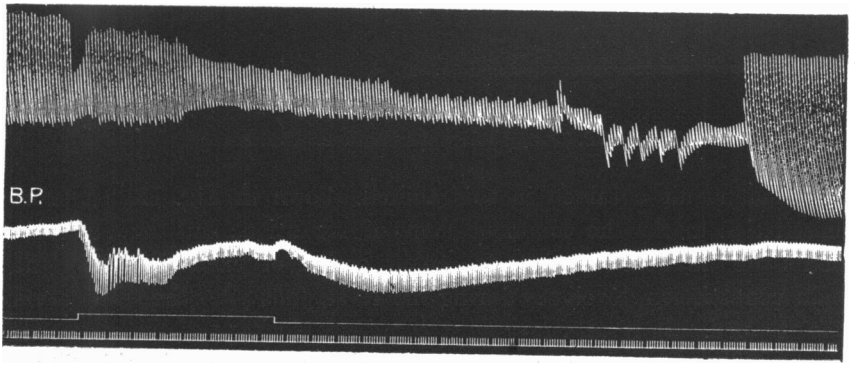


Fig. 19. Cat. Ether. Stimulation of vagus; coil at 8 cms. Zero B.P. 15 mm. below abscissa line. Reduced ½.

slow onset, mainly occurring after excitation had ceased, and followed by spontaneous recovery. In Fig. 20 one other condition is illustrated,

viz. distension, and the course of the constriction is very irregular and in waves. As these occur the lobe becomes more and more distended, the alveoli experiencing considerable difficulty in emptying themselves. The condition lasts a long time after the excitation has

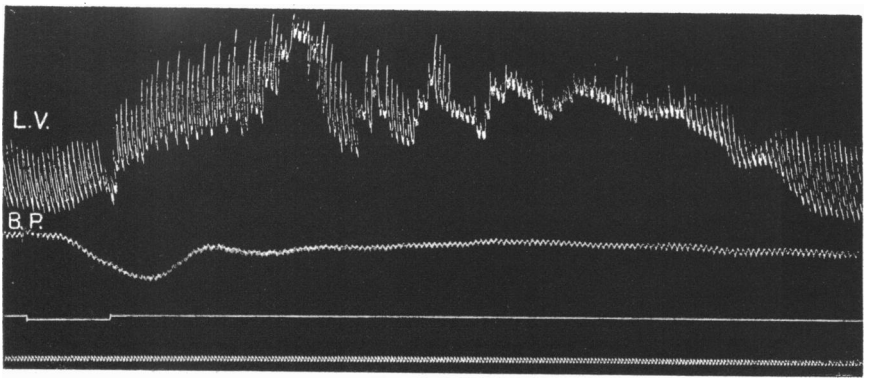


Fig. 20. Cat. Urethane. Curare. Stimulation of right vagus; coil at 7 cms. Zero B.P. 24 mm. below abscissa line. Reduced ½.

ceased, and finally as the distension gradually falls spontaneous recovery occurs. The question as to whether or no distension is produced is largely determined by the way in which artificial respiration is effected. If this is rapid and produces fair dilatation of the lobe while the time allowed for expiration is short, distension is commonly produced. Up to a certain point the greater the contraction of the bronchioles the more readily it occurs, but if the constriction is very marked, quick in onset and prevents the entrance of air almost completely, it is not produced.

C. *The negative results and their cause.*

In our earlier experiments we always worked upon partially collapsed lobes, and in these we usually obtained positive results following excitation of the vagus. When later we began to record the full air volume changes of the lobe, we were surprised to find that the excitation now usually gave poor and transitory effects, and that after the first excitation commonly no results whatever were obtained. Working under exactly the same conditions we at times obtained quite typical results. We never obtained completely negative results on the first excitation, but effects such as that shown in Fig. 21 were extremely

common. It seemed to us that the cause might lie in one or more of the following, viz., (1) that the method was not sufficiently sensitive; (2) that there were broncho-dilator fibres present with the constrictor

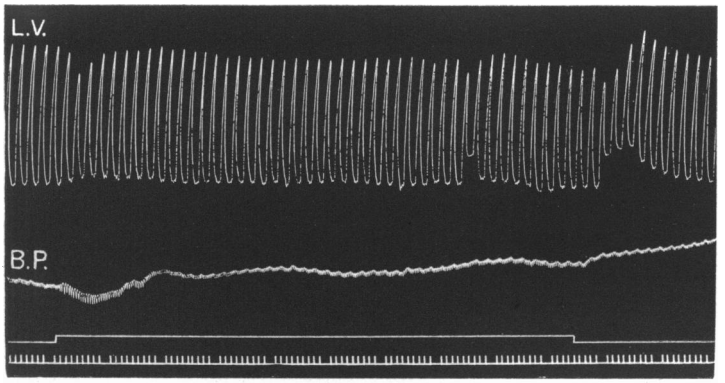


Fig. 21. Cat. A.C.E. Stimulation of right vagus; coil at 5 cms. Zero B.P. 21 mm. below abscissa line. Reduced ½.

fibres in the vagus; (3) that faradic stimulation was not the best for the purpose; (4) that the cat, the animal which usually gave the negative results, only possessed few constrictor fibres in the vagus; (5) that it was due to the anæsthetic employed. We may at once dismiss the first of these, for we now have plenty of evidence that the method is as sensitive as could be desired. With regard to the second we were soon able to demonstrate the existence of broncho-dilator fibres, and for a long time thought this was the full explanation of our negative results. Our experiments upon the third possibility tended to confirm us in this, for having noted how frequently slight positive effects were obtained at the commencement and end of excitation, we tried the effect of repeated short periods of excitation with short intervals of rest. In a great number of instances this was found to be much more effective, but still the number of negative results was very unsatisfactory. We eliminated the possibility of their being due to local fatigue or to the local action of the anæsthetic, as a freshly exposed piece of nerve, thoroughly protected from any possibility of injury, gave the same negative results on excitation. We experimented with mechanical, thermal, and chemical stimuli, again with negative results. We also employed induction shocks in which the make and break shocks were equalised. The Helmholtz and Bernstein modifications gave no different effects, as was also the case when we used the

house-current working through an incandescent lamp, which as has been pointed out by Locke[1] equalises the make and break shocks very efficiently. We tried further the effect of stimulating by single induction shocks repeated at one second and at two seconds interval, but again with negative results. The action of constant currents applied in various ways was equally ineffective. We therefore concluded that excitation in the ordinary manner was on the whole the best. The fourth suggestion mentioned above is important. Negative results were far commoner with the cat than with either the dog or the rabbit, a result which can be readily understood from a comparison of the three typical figures already given (Figs. 10, 11, and 12).

Unfortunately most of our work was completed before we directly tested the influence of the anæsthetic. To avoid all use of anæsthetic the animal was pithed, the medulla and brain only being destroyed. A tracheal cannula was then inserted and artificial respiration started. The operation was then carried out as usual. In these experiments we always obtained good positive effects, no matter how frequently the vagus was excited. In some experiments the nerve was stimulated as many as thirty times and with as good a result at the last excitation as at the first. It is from experiments of this kind that we are able to state that the usual type of reaction yielded by the cat's lung differs from that given by the rabbit or dog. The action of the anæsthetic is a peripheral one and probably at the nerve terminal in the bronchioles. Here the fibrils are exposed to the direct action of the volatile anæsthetic, and they are quickly affected by it. Still it is difficult to understand why the first excitation should cause, as it does, so much better contraction than any of the succeeding ones, although in many experiments we allowed ample time for recovery to take place. We think that the explanation of the negative effects being so much less common when experimenting upon partially collapsed lobes, is that in these the movement of air through the bronchioles was much less, the supply of anæsthetic was thus less frequently renewed, and the nerve endings consequently less exposed to its action.

We may here state that we have tested the branches leaving the ganglion stellatum for broncho-motor fibres with completely negative results.

[1] Locke. *Proc. Physiol. Soc.* p. xvii. This *Journal*, xxviii. 1902.

iii. Some other effects occurring with the excitation of the vagus.

As already pointed out, the first stage of the vagus effect is often, especially in the rabbit, accompanied by a marked fall in the lower limiting line, which as we have seen is caused by vascular changes simultaneously induced by the excitation. In the present paper we do not propose to discuss fully the effects upon the air movements caused by vascular changes, and in what follows only refer to changes of such magnitude that they might interfere with the proper interpretation to be placed upon the recorded effects.

An instance of such a case has already been given in Fig. 11, p. 123, and a further example is given at A, Fig. 22. The second half of this figure (B) was obtained in the following manner. After recovery from

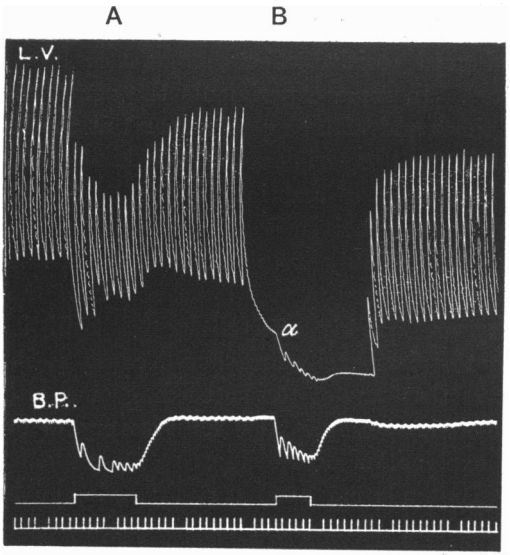


Fig. 22. Rabbit, pithed. Stimulation of vagus; coil at 10 cms. The first stimulation is during the artificial respiration and the second a short time after it had been stopped. Reduced ½.

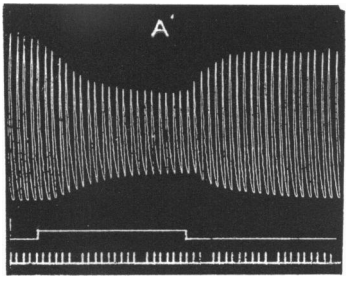
the first excitation the artificial respiration was stopped for a time, when the lobe collapsed considerably, the vagus was then excited a second time (at *a*). A second sharp fall in the tracing occurs, which is therefore due to a diminution in the blood content of the lobe, and there is a partial recovery as the inhibition passes off, and the blood-

pressure once more rises. Though the marked fall seen in the first of these two reactions is therefore partly a blood-volume diminution, the second reaction clearly indicates that this explanation only accounts for a part of the effect. That the whole effect is in fact due to a change in the blood distribution was proved in the following way upon the same animal. A control excitation was first recorded and the animal was then bled to death. When the blood ceased to flow the ventricles were cut across to make certain that no alteration in the amount of blood in the lobe was possible. The vagus was now excited and the reaction given in Fig. 23 was recorded. The result is as typical, as regards the air changes, as before, but differs from the preceding effects in that the lower limiting line begins to rise at once. We have another proof in the behaviour of the lobe in experiments in which the cardio-inhibitory fibres have degenerated. We found that the broncho-constrictor fibres were still excitable and the reaction was similar to one obtained upon the bloodless lung. Similarly too the initial fall in volume is absent if the vagus be excited while the vessels to the lobe are temporarily ligatured. Attempts to exclude the cardio-inhibitory influence by administration of atropine proved as ineffective in our hands as in Einthoven's[1] or Beer's[2], for we invariably found that the minimum dose of atropine sufficient to cut out the vagal action on the heart also abolished every effect upon the bronchial muscles. Beer[3] overcame the difficulty of separating the cardio-inhibitory effects from the broncho-constrictor by the employment of muscarine. As is well known[4] a stage in muscarine poisoning occurs in which cardiac inhibition is present, but no further slowing occurs on exciting the vagus. Working upon animals in which this condition was present, Beer states that he was able to obtain typical broncho-constrictor effects without a simultaneous vascular change as evidenced by absence of change in the aortic blood-pressure.

The effect we are dealing with is therefore due to the altered distribution of the blood, but Fig. 22 tends to show that the full volume change is a decrease partly in blood, partly in air. How then are we to explain the air diminution as consequent to a blood change? As it is due to a decrease in the amount of blood in the lobe, the explanation probably is that the empty state of the pulmonary capillaries enables the alveoli to contract more completely. The

[1] Einthoven. *loc. cit.* p. 428.
[2] Beer. *loc. cit.* p. 123.
[3] Beer. *loc. cit.* p. 150.
[4] Weinzweig. *Arch. f.* (*Anat. u.*) *Physiol.* 1882, p. 527.

erectile action of the capillaries has diminished, and we are in fact dealing with a change in the condition which v. Basch[1] has termed 'Lungenstarrheit.' This change in distensibility[2] together with a diminution in the blood-volume of the lobe therefore explains the sudden decrease in volume of the lobe occurring at the commencement of excitation of the vagus. It is not always present and is usually far better marked in the rabbit than in either the dog or the cat. In the latter it is commonly absent or but very slightly marked[3], a result which



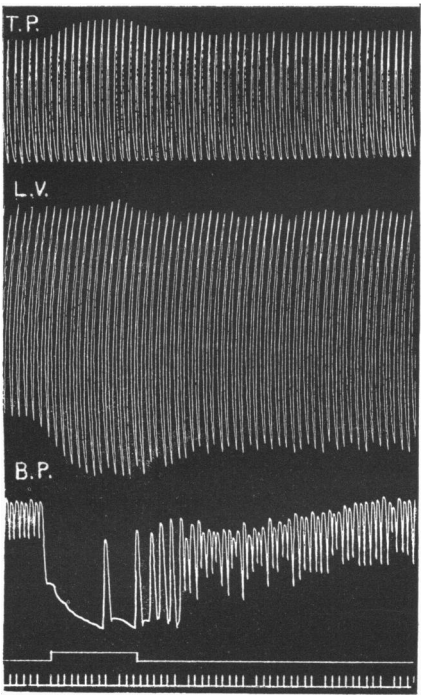


Fig. 23. Same animal as in Fig. 22 rendered bloodless by opening the carotid and excising the heart. Stimulation of vagus; coil at 10 cms. Reduced $\frac{1}{3}$.

Fig. 24. Dog, pithed. Stimulation of left (opposite) vagus; coil at 8 cms.

agrees with the commonly observed slight action of the vagus on the heart. The effect is, as was to be expected, more marked the higher the ratio of the volume-pulse to the air volume. It is of considerable

[1] v. Basch. *Wien. med. Blätt.* 1887, p. 465, also *Wien. med. Presse.* xxix. p. 587. 1888.

[2] The question of distensibility will be discussed by us more fully in a later paper.

[3] See, however, Fig. 18.

value to note that stimulation of the vagus leads to a fall in blood content of the lung. This means either that the output from the left ventricle is greater than that from the right, and therefore that the left ventricle is less inhibited than the right, or that the lung empties itself into the left auricle, which thus becomes over-distended. The reaction is the same on stimulation of either the right or left vagus. Compare in this connection Fig. 24, which records the effect on the right lung of excitation of the left vagus.

Another point, arising from the effect of excitation of the vagus, is the influence of the rise of tracheal pressure, produced in some instances by our method of experimenting, upon the remaining lobes of the lung. It appeared possible that the lobe experimented upon, being placed under very dissimilar conditions from the rest of the lungs, might react differently, and that therefore many of the negative results we have previously described and explained might have been due to this cause. A bronchial constriction may cause a rise in tracheal pressure under the conditions of our experiments, and this rise will tend to diminish the effect upon the amplitude of the air-waves. It must also produce a greater distension of those lobes not involved in the bronchial constriction, which is in fact seen to be the case in Fig. 24. This tracing gives a record of the tracheal pressure, volume changes of a lobe of the right lung, and the aortic pressure curve in a dog. At the time indicated by the signal the left (opposite) vagus was excited. This caused a constriction of the bronchioles of the left lung as indicated by the rise in tracheal pressure. This rise in pressure caused an increase in the amplitude of the air-waves of the record of the right lobe. The maximum tracheal pressure per inflation rose from 144 mm. before to a maximum of 171 mm. of water during the excitation. The increase in the amplitude of the air-waves is from 41 mm. to a maximum of 54 mm. The rise in tracheal pressure and the air volume changes both occur gradually and the maxima coincide in point of time. The increase in amplitude of the air-waves is however proportionately greater than the increase in pressure. Within certain limits we have seen that the amount of distension of the lobe fairly accurately follows the increase in tracheal pressure, in direct proportion. If this were the case in this experiment the amplitude of the air-waves should only have increased to 48·5 mm., whereas actually they increased to 54 mm. The explanation of this further increase is that, as already noted, the extensibility of the lobe is greater because the cardiac inhibition has partially emptied its capillaries. In this figure we may also draw attention to the fact that

excitation of the left vagus has produced a fall in volume of the lung.

This experiment is also of service as tending to show that no constrictor fibres for the right lung ran in the left vagus. It is however possible that some of the increase of distension of the right lung might have been due to the excitation of dilator fibres for the right lung in the left vagus. This is not probable, for we have much evidence to show that in a resting state the bronchioles are completely relaxed. We have, moreover, proved that no crossing of the fibres occurs in the thorax, by first plugging the left bronchus with vaselined cotton-wool and then exciting the left vagus. The blood change alone, *i.e.* decrease in volume and proportionate increase in distensibility, is now produced in the right lung.

iv. Does the vagus exert a tonic effect upon the bronchial muscles?

We have already mentioned (p. 120) the observations of Chauveau and of Roy and Brown on this point. Einthoven[1] was unable to observe any dilatation of the bronchioles on section of the vagi in the dog, unless some tone had been accidentally or artificially induced at some previous time in the experiment. In the dog, cat, and rabbit we have never observed dilatation nor constriction on section of the vagus at the commencement of an experiment. We have however recorded dilatation following section in animals which have been previously injected with small doses of muscarine or pilocarpine. The dilatation in these rare cases has never been very great and could quite well be explained as due to excitation of the dilator fibres by the section of the nerve. We have also observed dilatation in animals which have been previously receiving large doses of carbonic acid. This dilatation is often very marked, and as will be shown later (see p. 167) is due to the cutting off of impulses from the centre in the medulla.

Section 6. Broncho-dilator nerve-fibres.

Whether dilator fibres are supplied to the bronchial muscles has been studied by many previous workers. Thus Sandmann[2] comes to the conclusion that such fibres are present in the vagus, but the figures he gives are far from conclusive, especially as he has not properly

[1] Einthoven. *loc. cit.* p. 411.

[2] Sandmann. *loc. cit.*

eliminated the effects of vascular changes. Roy and Brown[1] describe dilator fibres as being present with the constrictor in the vagus. They rely mainly upon reflex dilatation of the bronchioles, but give no evidence to show how they eliminated the possibility, that the result was due to an inhibition of the tonus maintained by the medullary centre, for in their method of experimenting tonus is always present. It must be remembered too, that their experiments refer to bronchi of some considerable size. Einthoven[2] comes definitely to the conclusion, that there is no evidence in favour of the existence of dilator fibres which cannot be better explained upon other grounds. In this conclusion he is confirmed by Beer[3], who however in an addendum[4] to his paper states that in two experiments upon animals previously treated with muscarine he observed increase in the amplitude of the phrenographic curve following excitation of the vagus. His records show a small but definite increase which gradually dies away after stimulation ceases. He suggests that possibly this may mean a broncho-dilatation, although he does not commit himself so far as to regard the result as evidence of the existence of broncho-dilators.

Our attention was drawn early to the possibility of the presence of dilator fibres in the vagus by the irregularity of the reaction of the bronchioles, when the vagus was excited in the cat. It was useless attempting to prove their existence by trying to find a form of stimulus that would leave the constrictor fibres unexcited, because the bronchial muscles when at rest show no tonus. In our first attempts we therefore threw the muscles into tonic contraction and then excited the vagus in the ordinary manner. We induced the tonic contraction of the bronchioles by injections of muscarine or of pilocarpine, and at once obtained positive evidence of the presence of dilator fibres, as will be seen from Fig. 25. Excitation of the vagus is here seen to produce a big effect upon the volume record of the lobe, which begins to increase in amplitude after a short latency, quickly attains a maximum at which it persists while the stimulation lasts, and dies away after its cessation. A reaction of such magnitude as this can only be due to the one cause, namely, a relaxation of the bronchial muscles. This conclusion is strengthened by the record of the tracheal pressure, the maximum height of which per inflation is seen to fall as the lung record increases and to rise as the lung again diminishes. It is most striking to watch

[1] Roy and Brown. *loc. cit.* p. xxiii.
[2] Einthoven. *loc. cit.* p. 417.
[3] Beer. *loc. cit.* p. 133. [4] Beer. *loc. cit.* p. 208.

the quick recovery of the whole lung which previously may have been almost quiescent. The reaction may be repeated an indefinite number of times. The fibres are not easily fatigued and the lung may be kept relaxed for a considerable time by continuing the excitation of the

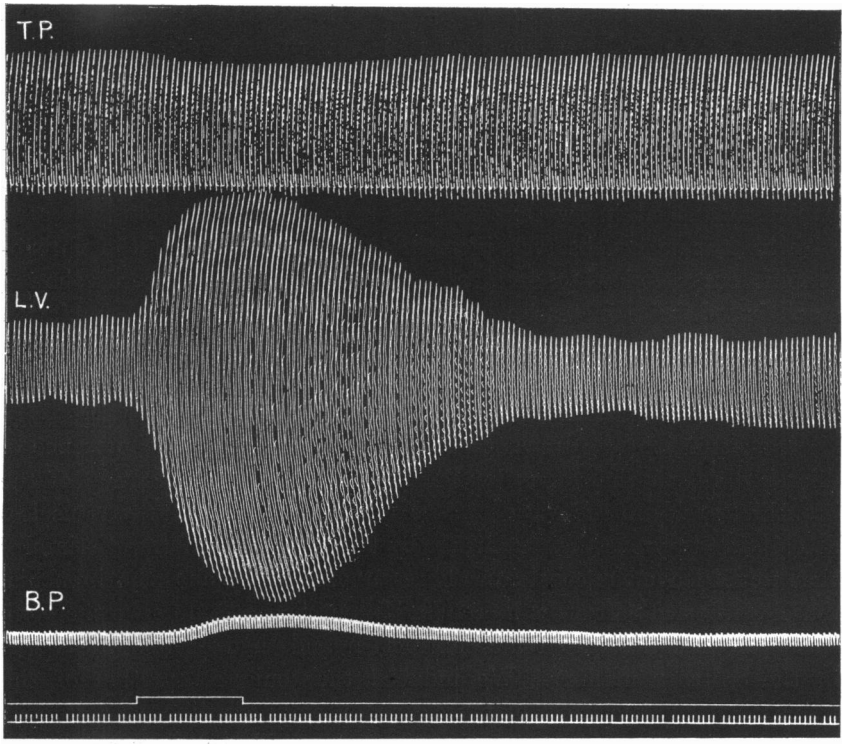


Fig. 25. Cat, pithed. Excitation of right vagus, coil at 4 cms. during the bronchial tonus produced by 0·01 grm. pilocarpine.

nerve, but as soon as the stimulation is stopped the dilatation quickly passes off, and the constriction gradually returns. The behaviour of these fibres shows many points of similarity with that of the constrictor fibres, more particularly in regard to their sensitiveness to anæsthetics administered by inhalation. Quite a small dose of the latter markedly diminishes the effect.

We have attempted to separate the constrictor from the dilator fibres by the degeneration method. The vagus was cut in the neck and the peripheral end excited 4, 7, 14, and 56 days after section. Stimulation of the vagus 4 days after section gave a typical reaction similar to

that of Fig. 12. Pilocarpine caused constriction in the usual way and good dilator effects were then obtained. The animal in which the nerve had been cut 7 days previously gave less marked results. The constrictor effect was distinctly weaker but the muscles reacted to pilocarpine well and the subsequent dilator effects were nearly as good as those obtained from a normal nerve. In the animal in which the nerve had been cut 14 days the changes were more pronounced. The constrictor effect on vagal excitation was very weak, even though interrupted excitations were employed. Pilocarpine still caused a fairly typical constriction and the dilator fibres were apparently well preserved, being still nearly as good as in a normal animal. The animal whose vagus had been cut 56 days previously gave most interesting results. We could not obtain constriction by any mode of excitation of the nerve. Pilocarpine produced absolutely no constriction of the lung on the same side, although it produced the typical effect upon the opposite (intact) side. Excitation of the nerve after the administration was also without effect. We therefore conclude from these degeneration experiments that the constrictor fibres degenerate somewhat earlier than the dilator, and that both take a considerable time to completely degenerate. As pilocarpine produced no effect upon the last animal we further conclude that the drug acts upon the nerve terminals of the constrictor fibres. Our results upon the degeneration of the broncho-constrictor fibres are thus somewhat different from those obtained by Bert[1], who found them degenerated in the same time as the cardio-inhibitory fibres, *i.e.* in 4 to 5 days. He found too that the pulmonary contractility had entirely gone in 2 weeks and that it had not returned after 4 months.

In considering whether our experiments really prove the existence of dilator fibres in the vagus, we have to eliminate the possibility that the effect might be due to an inhibition of the stimulating effect of the pilocarpine upon the constrictor nerve terminals and not to an action of a separate set of nerve-fibres upon the muscles themselves. Also it is well known that there are many ganglionic masses scattered along the bronchi and it is therefore possible that the inhibition may occur here. Our degeneration experiments, however, show that the constrictor fibres do not connect with these ganglia. We think, moreover, that the magnitude of the effect, and the regularity of its course in successive stimulations, are points which prove the existence of dilator fibres. This conclusion is greatly strengthened by the behaviour of the animals

[1] Bert. *loc. cit.* p. 370.

in which the vagi had been cut some time previously, for in these, as already stated, we succeeded in partially separating the two sets of fibres. Again, the form of reaction which is typically presented by the cat is one which is difficult to interpret except on the supposition that we are here dealing with the simultaneous excitation of two opposing sets of nerve-fibres. The question is one to which we hope to return at some future period.

In connection with the question of broncho-dilator fibres some of Grossmann's[1] experiments with muscarine are of importance. He states that the restriction of the air movements in animals treated with muscarine, which in his first paper he entirely ascribed to vascular changes, may be annulled by stimulating the cardiac accelerators. In the tracing Grossmann reproduces (Fig. 7, Pl. vi.) the pressure changes in the aorta and pulmonary artery are very slight and had already commenced before the excitation was started, but the effect upon the respiratory movements was most marked. Before we read his paper we had tested the nerves leaving the ganglion stellatum to see whether they contained broncho-constrictor or dilator fibres with completely negative results. After reading his paper we again returned to those experiments, for we thought that the most probable explanation of his result was that some broncho-dilator fibres passed through the ganglion stellatum. Our results were again absolutely negative. We were not able to confirm his experiments in any of the few instances we repeated them.

We conclude that no dilator fibres to the bronchial muscles pass through the ganglion stellatum.

Section 7. Reflex broncho-motor phenomena.

Many previous observers have obtained evidence of bronchial constriction following various sensory stimulations. Thus Gerlach[2], by exciting the central end of the cut vagus or superior laryngeal, obtained a rise of tracheal pressure which was abolished by section of the second vagus: excitation of the recurrent laryngeal was without effect. Riegel and Edinger[3] showed that ammonia vapour blown into the lung caused constriction and that the effect was abolished by cutting the vagi. Roy and Brown[4] found that excitation of the central end of one vagus

[1] Grossmann. *Ztschr. klin. Med.* xii. p. 579. 1887.
[2] Gerlach. *loc. cit.* [3] Riegel and Edinger. *loc. cit.*
[4] Roy and Brown. *loc. cit.* p. xxiii.

usually caused slight contraction, though at times and especially if the animal was etherised it caused a marked expansion. In these latter cases stimulation of the uncut vagus usually caused expansion. From excitation of the central end of a sensory nerve they very rarely observed any effect, and if any change occurred it was very slight. Stimulation of the stomach, intestine, pleura, tracheal mucous membrane or nostrils also proved ineffective. Franck[1] obtained positive results on exciting the central end of the vagus. The tracing of pleural pressure and of the respiratory movements, which he gives, only shows quite small changes, and he had not sufficiently excluded vascular alterations to enable us to definitely conclude that the effects were of bronchial origin. In a later paper[2] he describes the production of bronchial spasm following endo-cardial and endo-aortic irritation, but he gives no figures illustrating his experiments. Knoll[3], moreover, showed that the reflexes Franck observed were due to irritation of the pulmonary nerves and not of those arising from heart or aorta. Sandmann[4] obtained reflex constriction from irritation of the nose, larynx, and even of the cornea, but the curves he gives in support of this are not very convincing. Lazarus[5] obtained reflexes by stimulating the nasal mucous membrane mechanically or electrically; they were abolished on section of the vagi. He found that the most sensitive spots were the nasal septum and the turbinals.

The conclusions thus far enumerated are all based upon experiments in which the method employed was not very sensitive. Vascular changes may therefore have played a great part in their production and certainly had not been sufficiently eliminated. Einthoven's[6] method is much more trustworthy, and he describes the reflex results he was able to obtain as very inconstantly produced. Stimulation of the central end of the vagus gave nothing; of the sciatic usually nothing, but in one case he recorded marked constriction and in one other marked dilatation. In both these two exceptional cases the effect was cut out by dividing the two vagi. In the animal in which dilatation occurred he concluded that the result was not due to excitation of dilator fibres but to inhibition of a tonic action of the constrictor centre.

[1] Franck. *Fonctions motrices du Cerveau*, p. 145, and *Arch. de Physiol.* xxi. p. 544. 1889.

[2] Franck. *Arch. de Physiol.* xxii. p. 546. 1890.

[3] Knoll. *Wien. Sitzungsber.* iii. p. 479. 1884.

[4] Sandmann. *loc. cit.* [5] Lazarus. *loc. cit.*

[6] Einthoven. *loc. cit.* pp. 413 and 419.

He found that this was the one animal, out of all he experimented upon, which showed considerable constrictor tone.

We have in many experiments attempted to obtain reflex constriction or dilatation of the bronchioles by stimulating afferent nerves, but while the direct excitation of the vagus gives very constant results reflex excitation is disappointingly irregular. The most important nerves we have stimulated for this purpose are the sciatic, the vagus, the laryngeal branches of the vagus, and the nasal branches of the fifth cranial nerve. In studying these reflexes we have found it of the utmost importance to avoid the use of chloroform or ether as the anæsthetic. The experiments must therefore either be performed upon unanæsthetised animals, upon animals anæsthetised with morphia, or upon decerebrate animals. Our experiments were usually conducted under one of the two latter conditions, but in a few instances were repeated upon animals lightly anæsthetised with chloroform.

In no instance have we obtained any effect by exciting the central end of the sciatic in a curarised animal, but the experiments are not numerous.

Stimulation of the central end of the vagus divided about the middle of the neck also produced no change, a result which confirms Einthoven's experiments of a similar character. In one instance however, we observed a slight but distinct dilatation (Fig. 26.) This result would seem to indicate the presence of some tonus in the

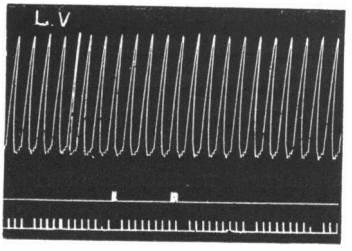


Fig. 26. Cat. A.C.E. Tie and cut right vagus.

bronchial muscles, a condition which may have existed here, for we had just previously excited the opposite vagus in its continuity in the neck. There is one other possible explanation of the result, which we think to be the more probable one. Although omitted from the tracing the excitation caused a marked fall in blood-pressure. This leads, as we have already seen, to an increase in distensibility of the alveoli by the emptying of the pulmonary capillaries and can well account for the

small increase in amplitude of the tracing recorded. Excitation of the superior laryngeal has in the three instances we have tried it given no result.

The most important reflexes we have obtained are from the nasal mucous membrane. Excitation of this either electrically, mechanically, or chemically usually produces some degree of constriction, which, as a rule, comes on very gradually (Fig. 27) and is very persistent. In the

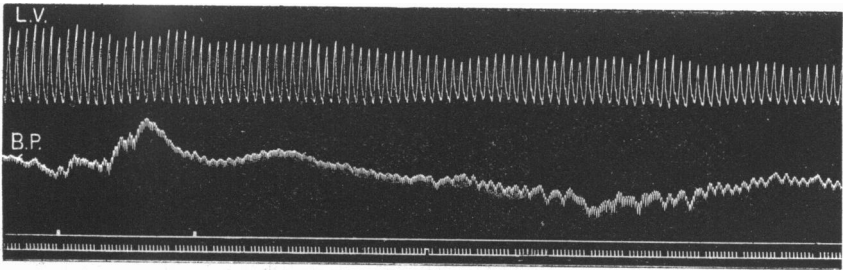


Fig. 27. Cat, decerebrate. Between the two signals the left nostril was mechanically excited. Zero B.P. 32 mm. below the abscissa line. Reduced nearly $\frac{2}{3}$.

instance given the stimulus was mechanical, but we found that in most cases chemical excitation gave the best results. A most effective stimulus for this purpose is bromine vapour blown in a diluted form over the nasal mucous membrane. It, however, has the great disadvantage that the stimulation cannot be repeated, for the first administration apparently kills the nerve terminals. In one instance only, this form of excitation produced an increase in the air-waves (Fig. 28). We have already pointed out that there is little or no tonus in these muscles and we are therefore inclined to attribute its presence in this instance to some accidental cause, though we were unable to discover its origin.

Seeing that the existence of broncho-dilator fibres is now certain, there must be a double medullary centre, and it should be possible under appropriate conditions to set either of them into activity separately.

Broncho-reflex effects are of considerable importance as tending to elucidate certain points in the pathology of spasmodic asthma. We hope to return to them again later, but we may point out that those observers who have excited the nasal mucous membrane, all describe this as the most effective position from which to obtain reflex-bronchial constriction, and in this we agree. It has long been known that many cases of spasmodic asthma have been permanently cured by operations

upon the nose. Recently Francis[1] has published remarkable results in which most cases of spasmodic asthma have been permanently cured by cauterisation of a certain area of the nasal septum. This area is a spot high up and towards the back. As confirming this we have found that the most effective spot for bringing about the reflex in cats and dogs is

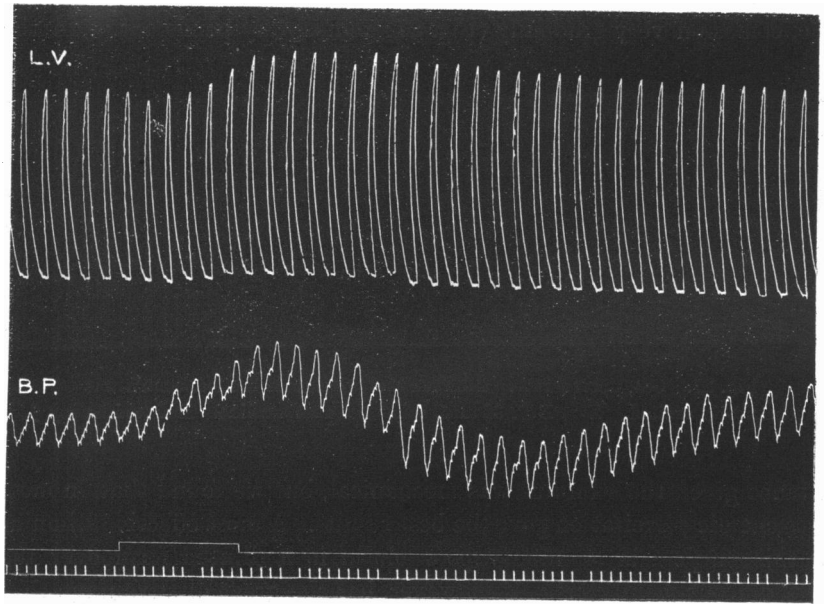


Fig. 28. Dog. Ether. Morphia. Bromine vapour blown into left nostril. Zero B.P. 30 mm. below abscissa line. Reduced ½.

a small area well back upon the nasal septum. The reflex constriction from the nasal mucous membrane must be of a protective nature. We know that by excitation of this membrane the following reflex effects have been obtained[2]. (1) Closure of the glottis; (2) arrest or slowing of the respiration; (3) cardiac inhibition; (4) dilatation of the peripheral arterioles. Chemical or mechanical excitation of the laryngeal mucous membrane leads to arrest of the heart and of the respiration, and finally excitation of the pulmonary nerves leads to most pronounced cardiac inhibition. All these reflexes appear to be protective and for the purpose of saving the animal from the effects of

[1] Francis. *Lancet*, Oct. 18th, 1902, p. 1053.

[2] See Brodie and Russell. This *Journal*, xxvi. p. 92, 1900, where an account of the earlier literature is given.

irritant particles or vapours entering with the air in respiration. All the reflexes upon the respiratory tract tend to stop the entrance of any irritant, effects which are all the more perfectly realised because the first part of the respiratory tract is so sensitive to these forms of excitation. A still further protection is reached by the vascular effects, for these in the first place tend to make the animal faint and thus reduce the activity of the respiratory centre, and secondly tend to retard the absorption of any irritant vapour that may have gained admittance and thus prevent serious toxic effects by a sudden access of a large dose of poisonous material. Perhaps too the respiratory reflexes are of especial value in the case of the entrance of irritant particles, for the changes all result in decreasing the rate of admission of air and thus give greater time for the particles to fall on the mucous membrane, where they will be held.

SECTION 8. SOME EXPERIMENTS IN WHICH THE RATES OF DISTENSION AND COLLAPSE WERE INVESTIGATED.

In the experiments hitherto described we have been examining the total volume changes of a lobe of the lung which is inflated by the delivery of a large volume of air, the tracheal tube being provided with a big lateral outlet. The object aimed at by this method is to be sure that the maximum tracheal pressure at each inflation shall always reach the same height, so that no change in the result can be due to an alteration in the mechanical conditions of the distension. To attain this end the lateral exit from the trachea must possess very little resistance in comparison with that offered by the lungs. If in an experiment of this kind the record of the tracheal pressure changes be taken upon a rapidly moving surface (Fig. 29) it will be seen that the pressure rises fairly quickly and regularly, remains up for a very short time and then falls, the fall occupying only about one-half the time of the rise. Obviously, for many purposes this form of artificial respiration is not ideal, and this is especially the case if we wish to study the rate of distension and of collapse. For this purpose we should rather aim at inflating the lung with a constant pressure acting for a definite time. This can never be actually attained although we can approximate to it by conducting the artificial respiration differently. We have aimed at this in some experiments by rhythmically connecting the trachea, for a definite, short time, to a very large chamber containing air, constantly maintained at a fixed pressure. In expiration, the tracheal tube was

freely opened to the external air, but, of course, the emptying was not effected in quite so satisfactory a manner, because the force producing it—the elasticity of the lung—is one which varies as the lobe empties.

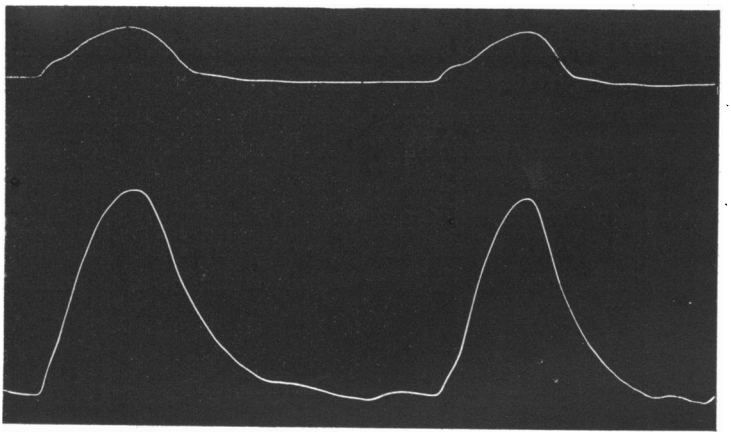


Fig. 29. Tracheal pressure (upper line) and lung volume tracings taken by the usual method but on a rapidly moving surface. (Surface moved by hand at about 48 mm. per second.)

Although the method is therefore only approximate, it yet offers certain advantages over the ordinary one. To apply it, it was necessary to employ a means of alternately connecting the trachea to the compressed air chamber and then to the external air, in regular rhythm. As in many instances it would further be of great advantage to be able to alter the duration of the filling and emptying, we devised the apparatus represented diagrammatically in Fig. 30. It consists of a short brass cylinder cut into three compartments by two perforated discs. Into each compartment a short wide tube opens, two, I and O, from one side of the cylinder, the other, *c*, from the opposite side. This latter tube is connected by a short piece of wide rubber tubing to a glass tube tied tightly into the trachea. The two ends of the cylinder are closed by two tambours, T_1 and T_2. When both tambours are undistended as in the figure, there is a free air passage from *c* through the two perforated discs to both I and O. If now the tambour T_1 be blown up, the rubber distends until it reaches the nearer disc, covers the holes in it, and thus closes the communication between I and *c* to all ordinary air pressures. Similarly the distension of the tambour T_2 closes the communication between O and *c*. The mode of working is as follows:—Starting

with both tambours distended, the tube I is connected to a large reservoir containing air under pressure, the tube O being left open to the exterior. If now T_1 is suddenly deflated, air passes from I through *c* and distends the lungs until the pressure there is the same as in the main reservoir. T_1 is now again distended, thus closing the connection between the reservoir and the trachea. T_2 is next deflated and the lung

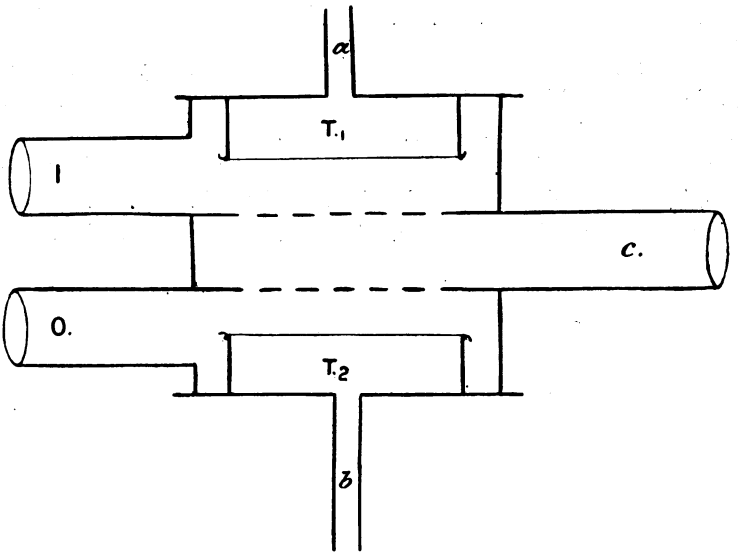


Fig. 30.

at once empties itself through O. T_2 is then once more closed. The alternate distension and emptying of the tambours is effected rhythmically by a separate piece of apparatus which consists of two valves, one for each tambour. The valves are connected, respectively, to the two tubes *a* and *b* of the tambours and to a small reservoir of compressed air. When the valve is at rest the tambour is distended with air from the high-pressure reservoir. When the valve is depressed it first closes this connection, and then opens a passage to the exterior, and allows the tambour to empty. The rhythmic movement of the valve is effected by a sector fixed on a revolving axis driven at constant speed, so that by varying the length of the sector the time during which the tambour is empty is proportionately lengthened. In this way the time allowed for distension of the lobe and for its recoil can be conveniently and rapidly altered and the time intervals between the two can also be adjusted. The pressure in the high-pressure reservoir

was kept up by the ordinary artificial respiration pump, and was maintained approximately constant by a mercury valve. The pressure used was about ten times that required for distension of the lungs. The pressure in the low-pressure reservoir was kept constant by hand, air being pumped into it by a pump whenever the pressure fell. This reservoir was of very large size so that the fall of pressure with each inflation was quite insignificant, and air was only pumped in during the intervals between two inspirations, *i.e.*, when the tambour T_1 was distended and blocked the connection to the lung. Further, the reservoir was provided with a water-manometer and water valve, and the tube connecting it to the tracheal cannula was of large diameter and as short as possible. A tracing, recorded upon a rapidly moving surface, in an experiment of this kind, is given in Fig. 31. In line A the air pressure used was 50 mm. of water. The increase in volume of

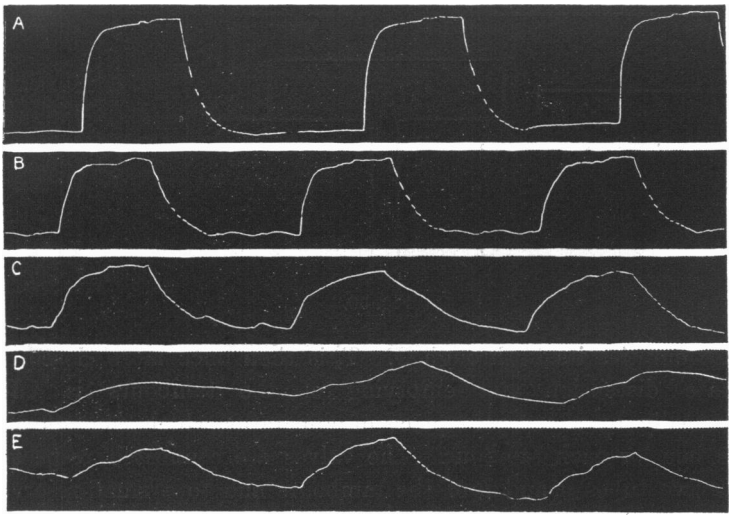


Fig. 31. Lung volume record only. In tracing A the pressure was 50 mm. of water and in the others 38 mm. In the four last the drum was moving at the rate of 15 mm. per sec.

the lobe is at first rapid but becomes very slow towards the end. The top of the curve is nearly flat, only showing a very slight tendency to rise. The fall in volume during expiration is much more gradual, especially in its later stages. The instant of opening of the valve, allowing the compressed air to enter the lung, is of course indicated by the sudden rise of the volume curve; the instant of closure is marked

by a slight rise in the curve seen on the summit. Similarly the end of the time during which the trachea has been open to the external air is marked by the slight notch on the lower horizontal line. In the second line, B, taken about 2 minutes later the distending pressure was reduced to 38 mm. of water, all the other conditions remaining unchanged. The general features of the record are the same as before, only differing in that distension and contraction are a little less rapid and that the successive volume changes are not quite so uniform. The latter difference is due to the low pressure employed, which, in a collapsed lobe, is only sufficient to produce slight distension, and it is easy to see, therefore, that if several of the alveoli are collapsed they will not be opened so promptly as by the higher pressure. The lung therefore will not behave exactly as a distensible elastic sac, some of the distending force being used up at the start to separate the alveolar walls. This adhesion retards free inflation more easily if the force employed is only a little above that required to start the distension.

In this condition the lobe is however in the best and most sensitive state to show any further impediment to the entrance of air such as an increase in resistance in the bronchioles.

The result of excitation of the vagus, upon a lobe under these conditions, is given in the next three records of this figure. Line C followed immediately after line B, and gives the first three inflations after the commencement of the excitation. The effect is most marked, and shows itself both in the rate of distension and contraction, but especially in the latter. The second distension after the commencement of the stimulus, shows the change most markedly, but the third line D shows a tendency to recovery, a condition frequently observed when experimenting upon cats. The fourth and fifth waves are very small, and are affected in rate of both rise and fall. Line E gives the three waves following the cessation of stimulation, and shows the recovery in a very marked way. In several of these waves we see that the curve continues to rise although the tambour has closed the connexion between the distending pressure and the trachea. This rise is unquestionably due to the fact that the distending pressure had not acted long enough to completely distend the alveoli to that pressure, and thus when the tracheal orifice was closed the pressure in the trachea was still higher than that in the alveoli, and the latter were therefore still further distended. The effect of vagal excitation as studied in this method very clearly brings out the marked effect upon emptying. In other words, the act of filling

even when this low pressure is employed is effected much more efficiently than the act of emptying.

It is obvious that this method of experimenting can be of great service when studying the distensibility of the alveoli under different conditions. The method has also proved of considerable service, in that by it we could conveniently watch the behaviour of the lung when varying the times allowed for distension or for collapse. It has proved especially useful in studying the production of over-distension, and was for instance the method employed when taking Figs. 16 and 17, p. 128.

Section 9. Effects obtained after the death of the animal.

Many of the earlier workers upon the bronchial muscles obtained indications of bronchial constriction in animals which had been recently killed. We have therefore made a few observations of this nature, usually at the end of an ordinary experiment. These were mainly of

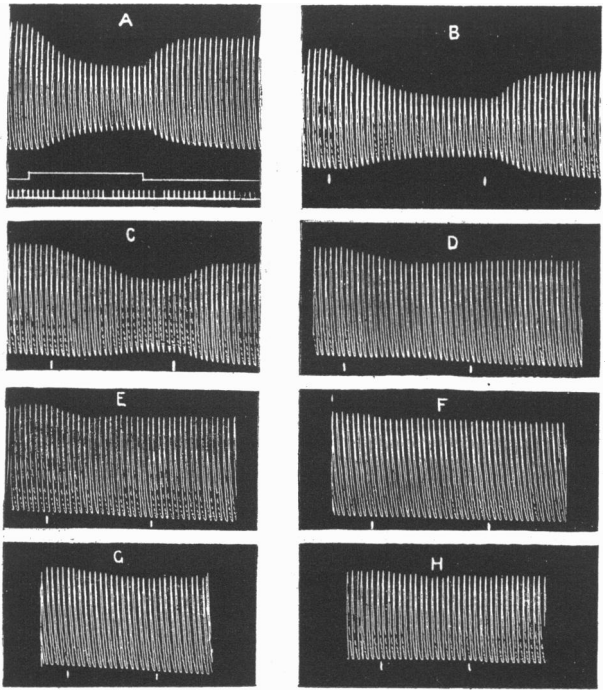


Fig. 32. Rabbit. A series of excitations of the vagus taken after the animal had been bled and the heart excised. A immediately after, B 5 mins., C 10 mins., D 14 mins., E 16 mins., F 20 mins., G 24 mins. and H 28 mins. after.

two kinds. In the first we studied the action of the vagus post-mortem, and in the second, recorded changes which gradually developed spontaneously after death. In Fig. 32 we reproduce the results of a series of excitations of the vagus. In this experiment a rabbit was pithed, and a series of observations, some of which have been given in Figs. 11 and 22, recorded. The animal was then bled from the carotid artery, and the series of records given in Fig. 32 obtained. Tracing A was taken immediately after death, and should be compared with that of Fig. 11, which had been obtained some time previously from the same animal. The stimulus was a weak one, but a perfectly typical bronchial constriction was obtained. Tracing B was obtained 5 minutes later, and only differs from the first in that the onset of the constriction was somewhat slower. C was taken 10 minutes after death, and already the effect is very much weakened, the greatest difference being a still slower development of the constriction than in B. Records were then taken every 2 minutes, and some of these are given. Thus D was taken 14 minutes, E 16 minutes, F 20, G 24, and H 28 minutes after. They show a gradual diminution of effect, but there is still a slight contraction even in the last. The vagus therefore can cause some contraction of the bronchioles half-an-hour after the death of the animal. The nerve terminals are still excitable for a longer period, for pilocarpine caused a very pronounced contraction a few minutes after electrical excitation of the vagus had ceased to produce an effect. It is noteworthy that in this animal very little post-mortem contraction had occurred 30 minutes after death, though as a rule this is very pronounced at a much earlier time.

In a further series of observations the animal was killed by bleeding, and the volume record continued for some time after death. In all instances a slow and prolonged constriction of the bronchioles was recorded. This usually commenced within a minute after the death of the animal, and became so marked as to nearly occlude the bronchioles completely. In a few instances this was followed by relaxation, but in most cases the constriction persisted during the whole time of observation, which in some instances amounted to more than an hour. In Fig. 33 are reproduced short lengths of the tracing taken in one of these experiments. The maximum constriction was recorded 7 minutes after death, and then relaxation commenced and was complete 41 minutes after death. No further contraction was recorded. Fig. 34 shows another instance which is of interest, because the course of events

differs from any of the others we have observed, in that there is a preliminary constriction followed by relaxation and a subsequent second constriction. Maximum constriction was attained in this instance in

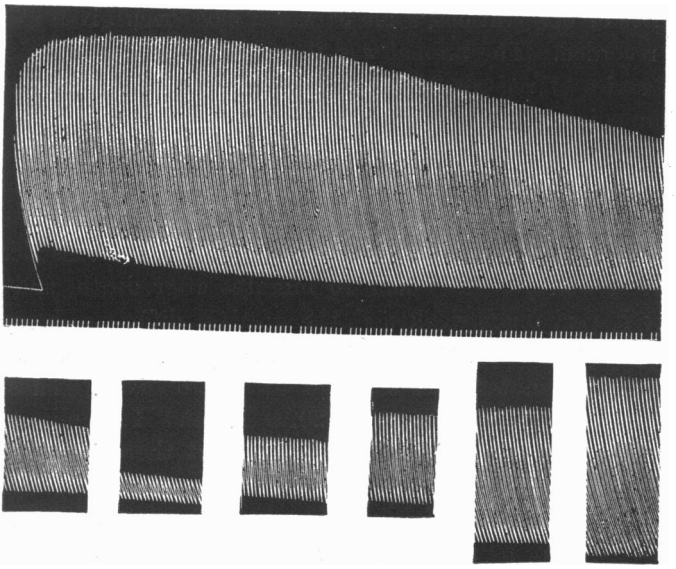


Fig. 33. Cat. Record of air movements after death by bleeding. The later short pieces of tracing are at intervals of 2 mins., with the exception of the last, which followed an interval of an hour.

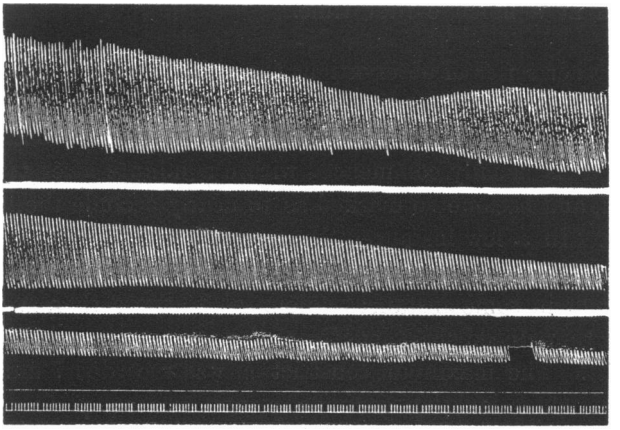


Fig. 34. Cat. A.C.E. Post-mortem contraction of the bronchioles: the three lines follow one another in succession.

10 minutes, and no relaxation occurred. In other cases the course of the contraction was much slower, only reaching its maximum in from 20 to 40 minutes. We think the cause of this contraction is asphyxial.

In a few experiments we volumetrically recorded the air movements of a lobe of an excised lung artificially perfused with blood at constant pressure. Such lungs did not show the contraction just described. These experiments are again referred to in the section dealing with the action of drugs.

Section 10. Action of drugs upon the bronchial muscles.

I. *Muscarine and Pilocarpine.* The action of these two alkaloids upon the bronchial muscles is so similar that it will be convenient to consider them together. They may be used as types of that class which produces bronchial constriction. The discoverers of muscarine, Schmiedeberg and Koppe[1], observed the marked dyspnœa which followed its injection, but ascribed it to an action upon the respiratory centre. Brunton[2] relying upon observation of the exposed lungs and heart, considered that the dyspnœa was due to constriction of the pulmonary arteries, for he observed that the lung became paler in colour, the right side of the heart engorged, and the left empty. This cannot however be the true explanation, for it has been shown that there is no rise of the pulmonary blood-pressure, whereas there is one of the pulmonary venous pressure. (Grossmann, confirmed by ourselves.) We consider the true explanation of the colour change to be partly that the amount of blood in the lung is decreased, just as we have seen is the case in cardiac inhibition produced by vagal excitation, and partly that the contained blood becomes venous, and thus when seen in thin layers the depth of colour is less pronounced than if it were arterial.

Grossmann[3] studied the action of muscarine upon the lungs more particularly with respect to the mode of production of the œdema which he describes as following the injection. He concluded that the whole of the effects were of cardiac origin. He found that the pulmonary venous pressure rose considerably and that the pulmonary arterial pressure at first fell and later rose. From these results he argued that a considerable congestion of the lung capillaries is produced,

[1] Schmiedeberg and Koppe. *Das Muscarin.* Leipzig, 1869.

[2] Brunton. *Brit. Med. Journ.* Nov. 14, 1874.

[3] Grossmann. "Das Muscarin-lungenödem." *Ztschr. f. klin. Med.* XII. p. 550. 1887.

which leads to "Lungenstarrheit," and thus to a great diminution of distensibility with its consequent dyspnœa. Against this we must argue that in our hands muscarine has usually caused a very marked fall in the pulmonary pressure, and that our direct volumetric examination of the blood-volume of the lung has shown that the amount of blood does not as a rule increase but remains practically constant, and if a change is produced it is usually a diminution. Again, "Lungenstarrheit" cannot possibly explain the great hindrance to the entrance of air into the lungs, which is always observed. Even by producing a most marked congestion, as by temporarily clamping the pulmonary vein issuing from a lobe, the restriction in the air movements of that lobe is inconsiderable, and altogether out of proportion to the marked effect on the air movements produced by a small dose of muscarine. We may further point out that in the curves Grossmann published, the development of the dyspnœa takes place during the early marked cardiac inhibition caused by the drug, *i.e.* at a time when the pulmonary artery pressure is extremely low.

In a later paper Grossmann[1] takes into account a possible effect upon the bronchial muscles, but still considers that the main cause of the dyspnœa is due to the action of the drug upon the heart and that the bronchial constriction only plays a subordinate part.

It is well known that muscarine and pilocarpine produce tonic contraction of involuntary muscle (*e.g.* stomach, intestines, bladder, etc.) throughout the body, and our experiments show that the bronchial muscles are no exception to this rule. A small intravenous injection of muscarine produces after a very short latent period a rapid diminution in the quantity of air passing in and out of the lung, and if the force of inflation is not too great and the amount injected sufficient, a complete block is set up so that no air can either enter or leave. This effect is perfectly shown in Fig. 35, where 0·001 grm. muscarine was injected at the indicated mark. The movements of the recording lever after the muscarine has produced its effect are purely vascular.

During this action the animal tends to become asphyxiated, and to prevent death it is necessary to increase the force of inflation. The effect of this is seen in the same figure. When the force is sufficiently great the block is overcome and more air passes into the lung, but the elastic recoil of the lung is unable at first to expel this, and the lobe becomes rapidly over-distended.

[1] Grossmann. *Ztschr. f. klin. Med.* XVI. pp. 161 and 270. 1889.

In many cases the bronchial constriction produced by muscarine or pilocarpine is attained much more gradually, and the latent period

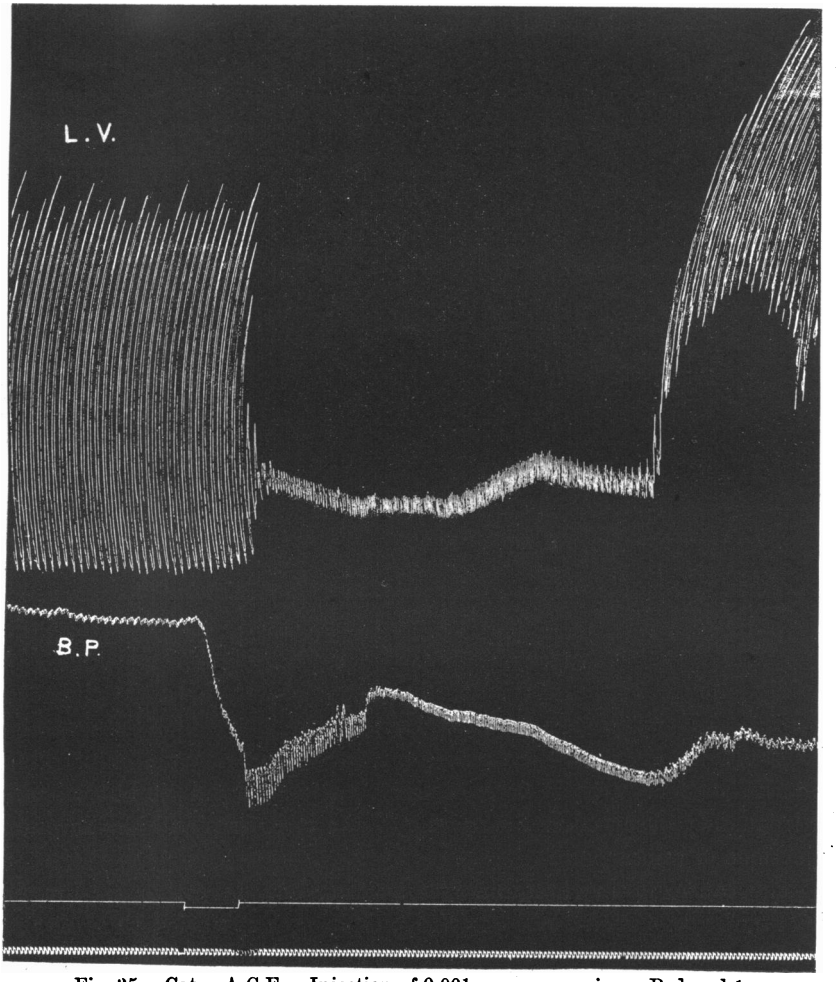


Fig. 35. Cat. A.C.E. Injection of 0·001 grm. muscarine. Reduced $\frac{1}{3}$.

up to the time of complete obliteration of the air movements may extend to even two or three minutes, although such a very prolonged period is exceptional. In these cases the constriction often occurs as a series of waves of alternating contraction and dilatation, a condition shown in Fig. 36, where, although some contraction occurs soon after injection, complete obliteration is not attained until after a latent period of a minute and a half from the time of administration.

Quite commonly, instead of producing immediate constriction, muscarine gives rise to an initial and well-defined dilatation, which is

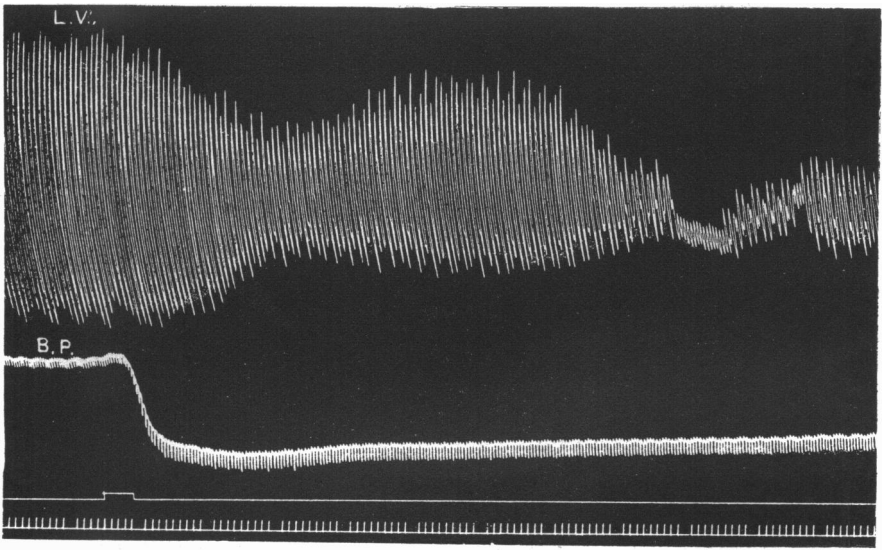


Fig. 36. $\times \frac{1}{3}$. Cat. A.C.E. Right vagus cut. Shows the effect of injecting 0·0075 grm. pilocarpine nitrate.

rapidly followed by the more important constriction : this is clearly shown in Fig. 37, in which the over-distension of the lung which obtains with the gradually increasing bronchial constriction is also well illustrated. This initial relaxation is not peculiar to bronchial muscle but can also be frequently observed in the muscle of the intestines and bladder after injections of pilocarpine.

The cause of this preliminary dilatation may be, either (i) diminution in the amount of blood in the pulmonary capillaries, thus causing greater distensibility, or (ii) relaxation of the bronchial muscles. We do not think the first can completely account for the effect, for it is sometimes very marked, and at other times it is absent although the vascular changes are produced as usual. The true explanation probably is, that the drug excites the broncho-dilator fibres as well as the broncho-constrictor, and that the former react more quickly or more powerfully at first, and the reason the effect is not always present is that tonic constriction of the bronchioles is as a rule absent.

In all these experiments A.C.E. or ether were the anæsthetics usually

employed. In a few cases the experiments were performed on pithed animals when identical results were obtained.

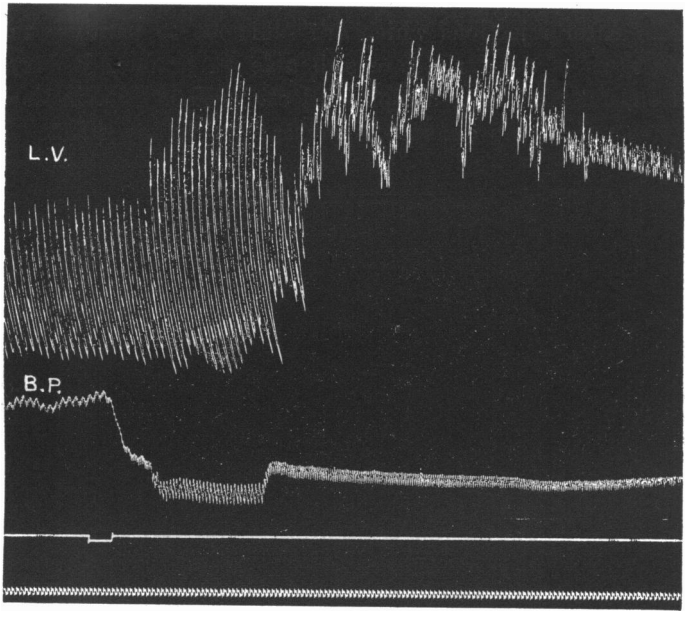


Fig. 37. × ⅓. Cat. Urethane. Shows effect of 0·001 grm. muscarine.

That this broncho-motor effect is peripheral was conclusively shown by perfusion experiments. The heart and lungs were taken from a cat and defibrinated blood at the body temperature was then perfused through the pulmonary artery, warm air being simultaneously and regularly blown into the lungs by the respiration pump: a lobe of one lung was made to record its volume in the usual manner. The addition of a small quantity of muscarine to the perfusing fluid produced an immediate constriction of the bronchioles. The results thus obtained clearly show that "Lungenstarrheit" can have little or nothing to do with the production of the effect.

In most experiments, the animal experimented upon was the cat, but in many the dog and rabbit have been used, and the results in all respects agreed with those above described.

II. *On certain conditions which modify the action of the drugs which produce broncho-constriction.* After section of both vagi muscarine still produces its normal effect. The vexed question as to

whether muscarine and pilocarpine can produce any effect on involuntary muscle after the administration of atropine, seems to depend, at least as far as bronchial muscle is concerned, on the amount of atropine employed. After injections which are sufficient to paralyse the vagi, large injections of muscarine are still able to produce a very slight constriction, but after large atropine injections (0·08 grm. in the case of a medium-sized cat) no amount of muscarine has any effect. Fig. 38

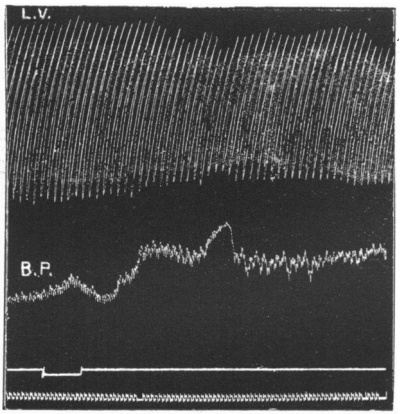


Fig. 38. × ½. Cat. Urethane. Shows effect of injecting 0·004 grm. muscarine after atropine.

shows the result of the administration of 0·004 grm. of muscarine to a cat which had previously received an injection of 0·0055 grm. atropine; some bronchial constriction is apparent.

In some of our experiments urethane was employed as the anæsthetic; in these a distinct difference in the response of the bronchial muscles to muscarine could be determined in most cases. Not uncommonly, after complete anæsthesia with urethane, moderate injections of muscarine failed to produce any constriction, and larger injections only did so after a much prolonged latent period. Fig. 39 shows the effect of muscarine on an animal anæsthetised with urethane, where it will be observed that it is not till after a two minutes interval that any very marked constriction is induced, and this is no exceptional case, indeed sometimes a latent period of five minutes has been noted. Urethane also behaves as a complete antidote to muscarine as regards the involuntary muscle of the alimentary canal. The antagonism of urethane to muscarine is nothing like so complete with bronchial muscle

as with intestinal, and its action in small amounts is rather to delay the muscarine effect than to eliminate it.

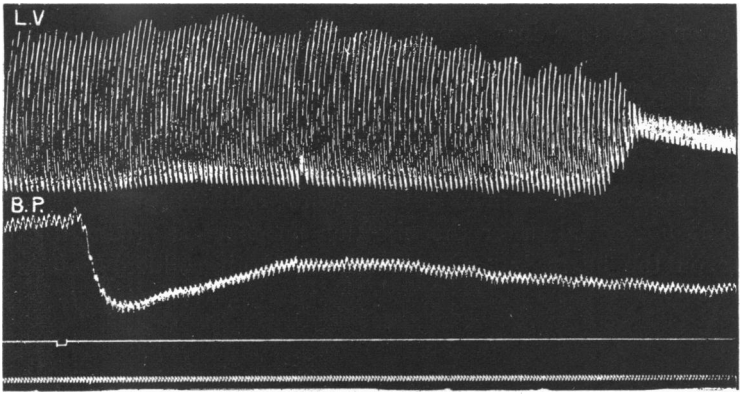


Fig. 39. $\times \frac{1}{2}$. Cat. Urethane. Injection of 0·001 grm. muscarine.

Curarised animals behave very similarly to non-curarised as regards their response to muscarine, in some cases, however, the latent period is slightly prolonged. Fig. 40 shows this condition.

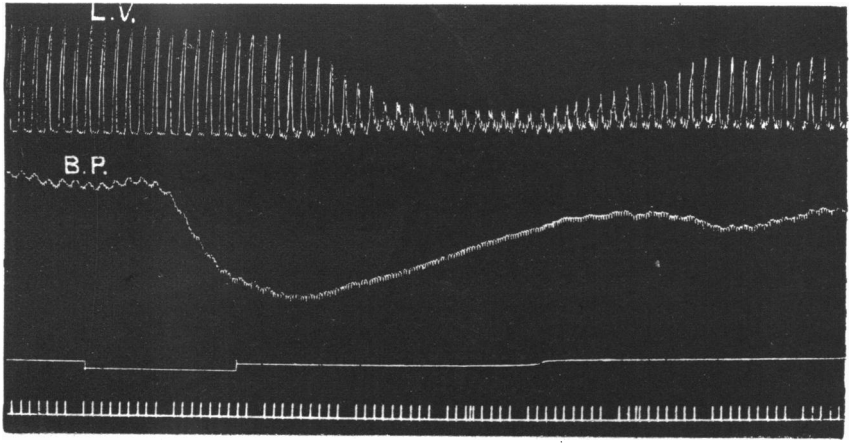


Fig. 40. $\times \frac{1}{3}$. Cat. A.C.E. Curare. Injection of 0·001 grm. muscarine.

III. *The effect of atropine after muscarine.* If atropine is injected into an animal in which moderate broncho-constriction has been induced as the result of a previous injection of muscarine or pilocarpine, an immediate dilatation usually results; this is well shown in Fig. 41. If however the bronchi are so constricted as to produce a complete

block to the air of inflation, the effect of atropine is only seen after a more or less considerable latent period: the explanation of this being that when a complete state of collapse is produced by bronchial constriction, the lobe in the oncometer does not expand directly the constriction passes off but requires a rather higher pressure to produce the initial expansion, a condition we have already discussed (p. 130). Fig. 42 shows the effect of atropine in such a condition. Before the injection there is a markedly slow heart and no air enters or leaves the experimental lobe—the movements recorded being purely vascular. For about 50 seconds after the injection no effect is produced except the one on the heart, but after this interval air suddenly enters the

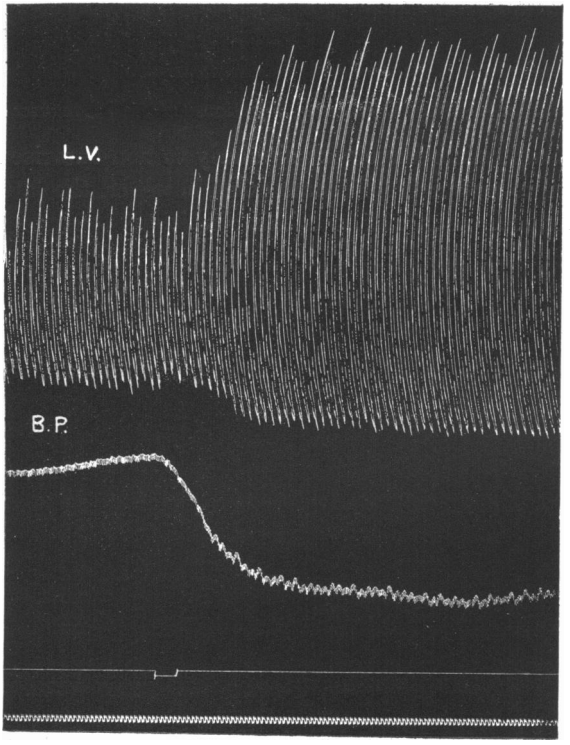


Fig. 41. $\times \frac{1}{3}$. Cat. A.C.E. Injection of 0·01 grm. atropine sulphate after muscarine.

lung, and as this is repeated three or four times while no air escapes the lungs become gradually over-distended. In about 80 seconds from the time of injection a considerable amount of air has been driven into the chest and the elastic recoil of the distended lungs suddenly over-

comes the resistance due to the bronchial constriction; an expiration results, which is the prelude to a very rapid recovery. In many cases

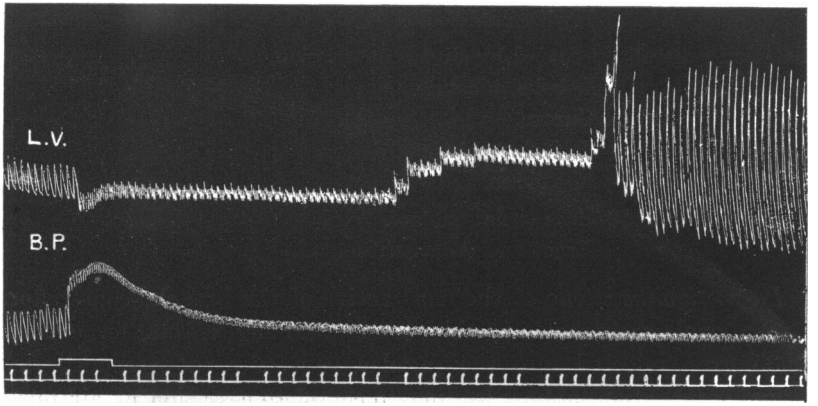


Fig. 42. $\times \frac{1}{3}$. Cat. Urethane. Injection of 0·01 grm. atropine sulphate after muscarine.

the latent period between the administration of atropine and recovery is greater than that shown in the Figure and may reach three minutes or even longer.

In only one case in our experiments did atropine produce any initial constriction of the bronchi; this was in a cat which had been anæsthetised with urethane.

IV. *The action of some other drugs on the bronchioles.* These will be briefly considered, and for the convenience of description it will be advantageous to divide them into groups.

Broncho-constrictors.

A, acting on nerve-endings.	Muscarine, pilocarpine.
	Digitalin.
	Neurine.
	Aspidiospermine.
B, acting on muscle.	Barium chloride.
	Veratrine.
	Salts of many heavy metals.
	Bromine.
C, central and peripheral.	CO_2.

Broncho-dilators.	Atropine, hyoscyamine, hyoscine.
	Chloroform and ether.
	Urethane.
	Hydrocyanic acid.
Dilatation generally preceded by slight constriction.	Lobelia, nicotine.
	Curare.
	* * *
	Morphine.
Relatively inactive.	Suprarenal extract.
	Ergot and its constituents.

Physostigmine is one of the most active of the broncho-constrictors; in very small amounts it is able to produce big effects, for example 0·0005 grm. injected into the jugular vein of a cat produced well-marked constriction, almost leading to complete cessation of air movements. The latent period after injection is usually a little longer than that of muscarine and the constriction frequently begins as a series of waves, which, becoming more and more pronounced, culminate in tonic contraction and obliteration of all air movements. The effect is still obtained after section of the vagi and after moderate injections of atropine. Physostigmine can still produce a contraction of the bronchi in animals which have received so much atropine that muscarine has no effect. After very large doses of atropine, however, physostigmine produces no broncho-constriction although drugs which act on muscle directly such as barium still give rise to constriction. We therefore believe that physostigmine acts on the peripheral vagal endings, but that its antagonism to atropine is much more complete than is the case with muscarine. This effect harmonises with the action of physostigmine on the iris.

Digitalin (Merck) produces a very rapid broncho-constrictor effect and complete occlusion may occur. The reaction is not produced in the atropinised animal (*i.e.* one in which the vagi are paralysed to electrical excitation) to the same extent, although some slight constriction still commonly occurs. Digitalis is not a suitable drug with which to demonstrate bronchial constriction on account of its powerful effect on the heart, for a dose sufficient to produce well-marked bronchial constriction is frequently sufficient to kill the animal.

Neurine gives rise to an immediate and decisive constriction of the bronchial muscles although by no means of so powerful a type as that

observed after muscarine. We consider it possible that the exacerbation of the respiration noted by Halliburton and Mott, and others, when small amounts of neurine are injected into the circulation, may be explained in this manner. The constriction is very persistent but is not produced in the atropinised animal.

Barium chloride is taken as a typical example of a drug which produces its effect by acting directly on plain muscle. Small injections lead to a slow increase in blood-pressure, partly cardiac, but mainly vasomotor, and associated with this is a gradual constriction of the

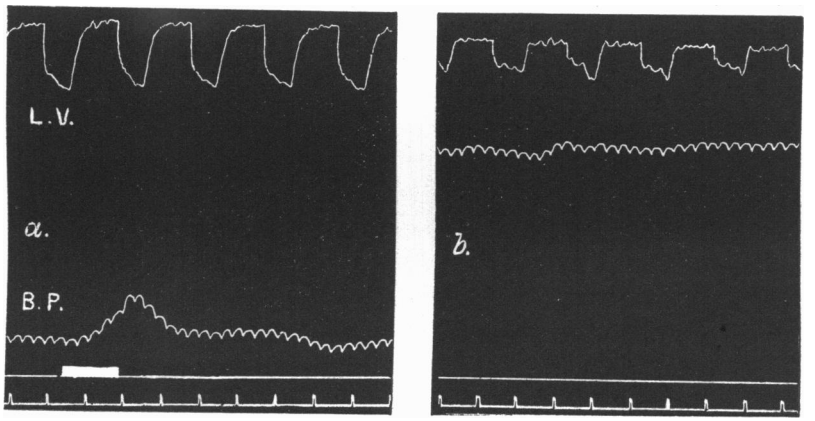


Fig. 43. × ½. Cat. A.C.E. Vagi cut. Tracing by method described on p. 148. Zero B.P. 35 mm. below abscissa line. Injection of 0·03 grm. $BaCl_2$.

bronchial muscles, ultimately attaining to the well-defined asthmatic condition. This effect can be obtained equally well on the atropinised animal. Fig. 43 is an experiment on a cat with vagi cut. The lungs are being inflated from a large reservoir at a constant pressure. (*a*) Shows the normal condition of affairs. (*b*) The condition one minute after the intravenous injection of 3 c.c. of 1 % $BaCl_2$: the blood-pressure is now much higher, the residual air in the enclosed lobe is increased, and less air enters and leaves during each respiration. This condition is developed slower than with drugs acting on nerve, but is much more persistent.

Veratrine has an effect similar to barium; 1 c.c. of a 0·1 % solution will give rise to typical constriction.

Gold chloride. Most of the heavy metals when injected directly into the circulation give rise to increased movements of plain muscle throughout the body. These effects are not however usually obtained

when the metallic ion is administered by the mouth because, with the exception perhaps of arsenic, mercury and lead, so very little is absorbed. Gold chloride is taken as an example of this class. When it is injected into a vein a slow but clearly defined constriction of the bronchioles developes. It rarely obliterates the air movements and is never of so intense a character as that seen after barium. The effect is probably mainly on plain muscle and not on the nervous mechanism.

Bromine. This drug also produces contraction of the bronchioles whether administered by inhalation of the vapour or by injection of a weak saline solution. According to the dose given the constriction may be slight and transitory (Fig. 44), or may lead to complete occlusion

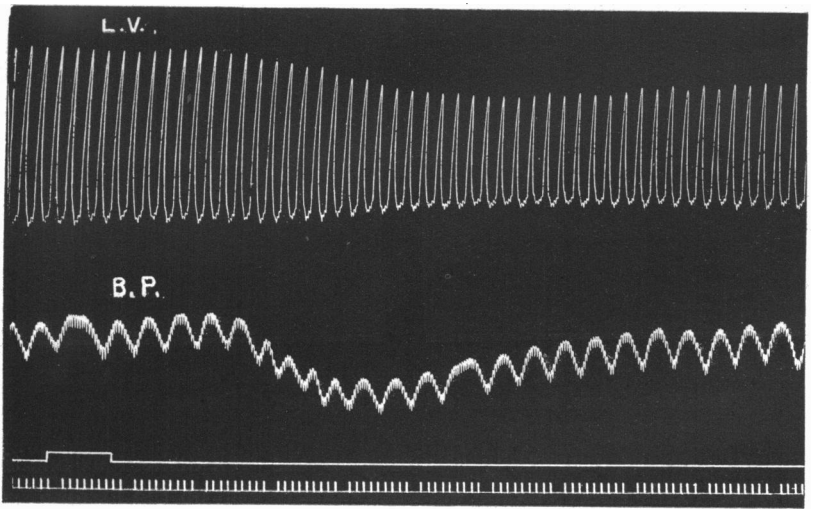


Fig. 44. Cat. A.C.E. Injection of 3 c.c. of a dilute solution of bromine in saline solution. Zero B.P. 49 mm. below abscissa line. Reduced $\frac{1}{3}$.

from which recovery is extremely slow. It acts peripherally and upon the muscle fibres, for it is produced equally as well if both vagi be divided, or after a large dose of atropine. Bromine we know powerfully excites nerve endings and then kills them, but whether in these cases of bronchial constriction the drug also excites the nerve endings we are not able to say.

Carbonic acid. The inhalation of carbonic acid gas has already been shown by Einthoven[1] to lead to a tonic constriction of the bronchi. He showed that in his experiments this was brought about

[1] Einthoven. *loc. cit.* p. 423.

through the medullary centre, for the increased tonus disappeared on division of the vagi in the neck. Einthoven therefore concluded that the gas acted directly upon the centre in the medulla, but did not consider the possibility that the result might have been reflexly produced through excitation of the nerve terminals of some afferent fibres of the vagus (*e.g.* the pulmonary). Einthoven found that no contraction was produced if both vagi had been divided, even if pure carbonic acid were used. We can, on the whole, confirm Einthoven's results, but in one experiment, in which fairly concentrated carbonic acid was used, we observed marked constriction which was not abolished by section of the vagus upon that side (Fig. 45). In connection with

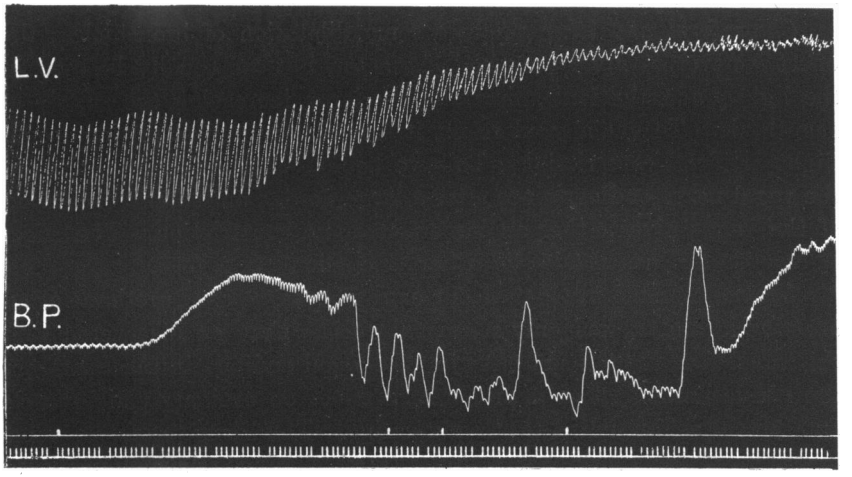


Fig. 45. Cat. Ether. At the first signal a strong dose of CO_2 was added to the respired air, at the second the right vagus was tied, at the third cut, and at the fourth the administration of CO_2 was stopped. Zero of B.P. 27 mm. below abscissa line. Reduced nearly $\frac{1}{2}$.

this figure we must point out that we have frequently proved that vascular changes such as are indicated in that figure are not sufficient of themselves to account for the marked air changes produced. We conclude therefore that carbonic acid as a rule acts by excitation of the centre in the medulla but whether directly or reflexly we are not yet in a position to definitely decide. In some cases the gas can act peripherally, but whether upon nerve or muscle we have no evidence.

Atropine, hyoscyamine, and hyoscine all act in the same way. The action of atropine has already been discussed. It only remains to add

that in the cat atropine gives rise to no dilatation unless some initial constriction has been induced, there being apparently little or no normal tonus of the bronchioles in this animal. Dreser first conclusively showed that stimulation of the pneumogastrics did not cause contraction of bronchial muscle after atropine.

It is not our intention here to deal with the treatment of spasmodic asthma, the radical cure of which consists in removing the source of peripheral irritation; but we desire to point out the impossibility of an attack whilst the patient is under the influence of atropine. During an attack an injection of atropine will quickly abort it. This is of course well recognized by clinicians and the inhalation of strammonium fumes forms the routine method of treatment.

Chloroform and ether produce some dilatation of bronchioles; the effect is never of a very marked character, but can usually be seen in the lightly anæsthetised animal by suddenly increasing the supply of anæsthetic. To get a good result it is necessary to first produce some slight artificial constriction. This we believe is probably an action on the vagal nerve-endings since after a large dose of anæsthetic excitation of the vagus gives either an imperfect or no constriction. The effect of anæsthetics has received further discussion on p. 133.

Urethane. In a number of our experiments we used urethane as an anæsthetic, and it was only after many trials that we discovered that this substance, though not affecting the vagal endings in the heart nor the cardiac muscle, had a pronounced effect on ordinary plain muscle and acted as an antidote to muscarine. This drug produces some dilatation of the bronchioles, if administered to animals showing increased bronchial tonus as, for example, after a dose of muscarine.

Hydrocyanic acid. This substance was employed on account of its marked stimulant effect on the medulla, and it was therefore considered possible that it might produce some constriction by direct stimulation of the vagal centre. Such however has not been found to be the case nor have we succeeded in finding any substance which will produce this result with the exception of CO_2, although the effect may be brought about readily enough reflexly by such substances as veratrine acting on the peripheral ends of the fifth nerve.

Small inhalations or injections of HCN produce a gradual relaxation of the involuntary muscle which is peripheral and probably due to a weakening of both nerves and muscles.

Nicotine has an excito-motor effect on bronchial muscle resulting in constriction, which however soon gives place to dilatation. Initial

dilatation with small doses of nicotine is not usual, but when large quantities are injected dilatation may occur immediately, and this is especially the case after the previous injection of small quantities of some broncho-constrictor body. Fig. 46 shows a typical effect where

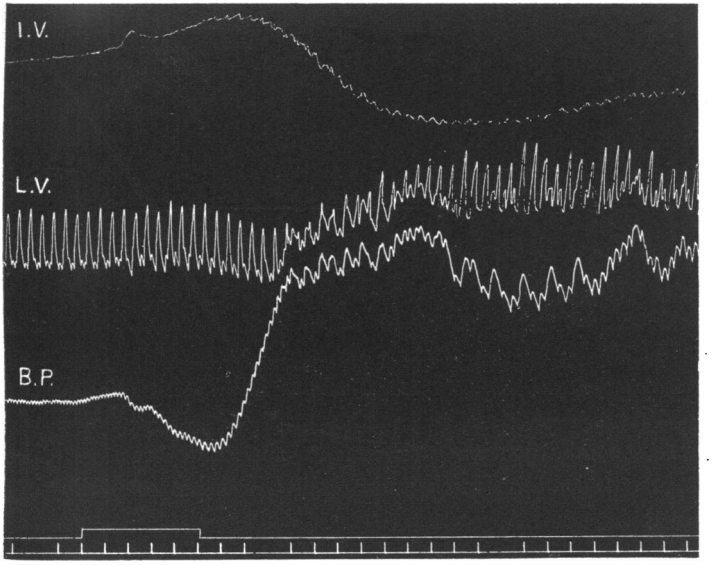


Fig. 46. Cat. Urethane. Injection of 0·003 grms. nicotine. Zero of B.P. is 20 mm. below the abscissa line. Reduced $\frac{1}{3}$.

the upper tracing represents the intestinal volume, the second the air volume of the lobe of the lung, and the lowest the blood-pressure. The lung undergoes a considerable increase in blood-volume as shown by the rise in the lower limiting line. Distinct constriction of bronchi can be seen which is beginning to pass off on the right of the tracing.

Lobelia was tried in a few cases on account of its reputation as a specific in spasmodic asthma. Dreser[1] found that after lobelia, stimulation of the vagi no longer narrowed the calibre of the air passages. We employed two preparations, (1) lobeline, which we found inactive, (2) the ethereal tincture (B.P.). This latter was mixed with half its volume of normal saline, the ether evaporated off, and the solution then filtered. This solution produces a marked rise in blood-pressure, and some slight constriction of bronchi. But if the bronchial tubes are at all constricted, lobelia produces a quick dilatation which rapidly passes off, and the original constriction returns and may be dispelled by another

[1] Dreser. *Arch. f. exp. Path. u. Pharm.* XXVI. p. 237. 1890.

injection of lobelia. Fig. 47 shows such a condition where the bronchi were first constricted by means of pilocarpine, and the lobelia is here seen to induce almost instantaneous dilatation, which however soon dies

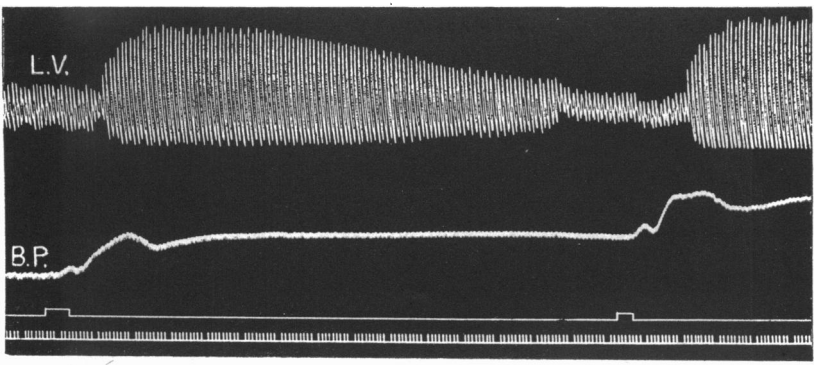


Fig. 47. Cat. A.C.E. Injection of two successive doses of lobelia prepared as described in the text. Zero of B.P. is 25 mm. below the abscissa line. Reduced ½.

away. A second injection is shown on the same tracing. The effect may be repeated many times, and recalls the dilatation following vagal

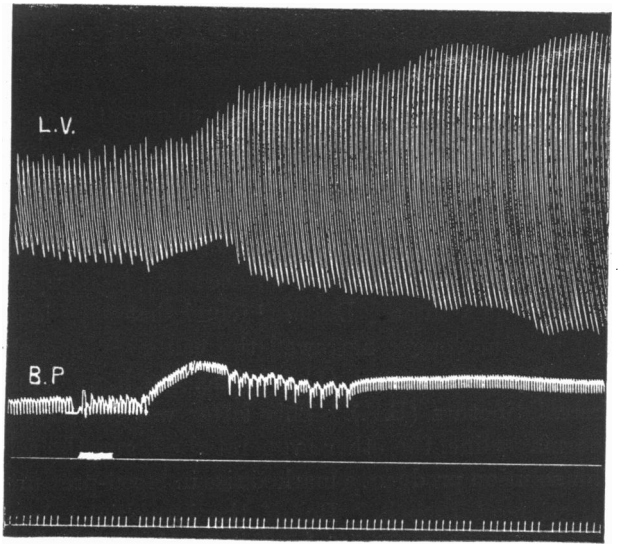


Fig. 48. Cat. A.C.E. Injection of 1 c.c. of a 1% solution of curare. Pilocarpine has been previously administered. The zero of B.P. is 20 mm. below the abscissa line. Reduced ½.

excitation after pilocarpine. This effect is in marked contrast to atropine, where the dilatation is absolutely permanent.

Curari has an action on the bronchi agreeing in the main with those of nicotine and lobelia. If it be injected into the vein of a normal animal there is slight and gradual constriction. This effect is probably analogous to the increased splenic movements noted by Schäfer and Moore and the stimulation of the intestinal movements described by Nasse. When administered to an animal in which the bronchi are already in a condition of some tonus, well-defined dilatation results (Fig. 48). This effect is not permanent, and the bronchi assume their previous condition in 2 or 3 minutes. Curari in no way prevents an injection of muscarine producing its full effects. Its action is produced equally well after the section of the vagi.

Morphine. Large injections in the case of the normal cat lead to very considerable constriction of the bronchial muscle after an initial transitory small dilatation, and this after the vagi are cut. Small doses, on the other hand, are followed by a slight dilatation only, which is the better marked if the bronchi are in a condition of increased tonus. Fig. 49 shows the effect of injecting into the jugular vein of a cat 4 c.c. of a 2 % solution of morphine. The injection caused a great fall of blood-pressure.

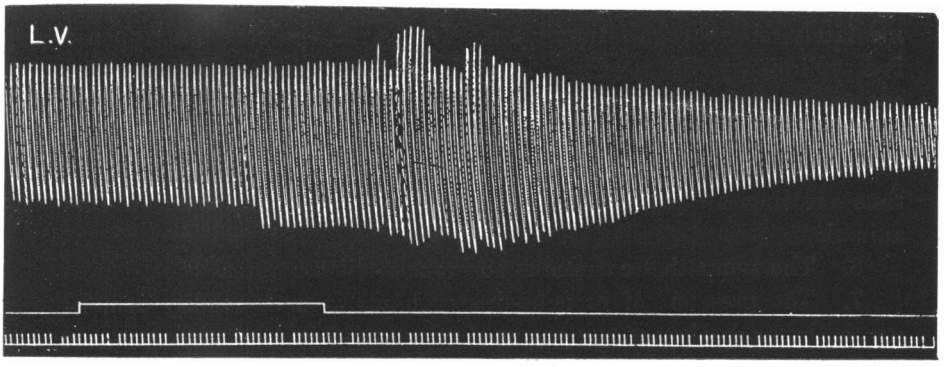


Fig. 49. Cat. A.C.E. Injection of 0·080 grms. morphine acetate.

Suprarenal extract produces very little effect on the bronchi, small doses generally giving rise to neither constriction nor dilatation. With large injections, however, constriction of a temporary character has in a small percentage of cases been observed. It is possible that in this case the free movements of the air are interfered with by the great vascular engorgement which is present.

Ergot. We have employed two preparations of this substance, (1) commercial ergotin, which probably contains all the active ingredients present in the fungus, and (2) sphacelotoxin of Jacobj—the gangrene-producing body. In no case was any immediate effect observed on the bronchi. The ergotin produces an immediate fall of blood-pressure associated with splanchnic dilatation. The calibre of the bronchioles remains apparently unaltered, but increase in the blood-content of the lung is evidenced by a rise in the lower limiting line.

Conclusions.

1. The degree of contraction of the bronchioles can only be satisfactorily demonstrated by some method which directly or indirectly estimates the volume of air passing through them. The plethysmographic method fulfils this condition.

2. The broncho-constrictor fibres run in the vagus; none are found in the sympathetic: there is no central tonic effect.

3. Contraction of the bronchioles may lead to collapse or over-distension of the lung, depending upon the force of the inflation on the one hand, and the time allowed for deflation on the other.

4. In the dog and rabbit, typical bronchiolar constriction immediately follows vagal stimulation. In the cat, the common response is a preliminary slight constriction followed by recovery, and the typical constriction only comes on some seconds after the stimulus has ceased.

5. The vagus contains broncho-dilator fibres, as well as broncho-constrictor, and the former are particularly well developed in the cat, thus yielding an explanation of the anomalous results seen in this animal.

6. The sympathetic contains no broncho-dilator fibres.

7. The presence of broncho-dilator fibres is most readily demonstrated by excitation of the vagus, after an artificial tonus has been set up by means of muscarine, pilocarpine, etc. The broncho-dilatation dies away soon after the stimulus ceases.

8. Both the constrictor and dilator fibres in the vagus supply the lung on the same side only.

9. The inhalation of ether or chloroform for anæsthetic purposes abolishes the effect of the vagus on the bronchioles. This is due to the paralysis of the nerve-endings by direct absorption through the mucous membrane.

10. Excitation of the vagus leads to a diminution in amount of the blood in the lungs. This produces increased distensibility—diminished "Lungenstarrheit" in v. Basch's sense.

11. Reflex bronchiolar constriction is best obtained by exciting the nasal mucous membrane. Little or no result has been obtained by stimulating the sciatic, central vagus, superior laryngeal or cornea.

12. The condition of the bronchioles and any alteration in their contraction can also be determined by recording the rate of distension or of retraction of the lung.

13. Typical bronchiolar contractions by stimulation of the vagus, can be obtained in animals recently killed by bleeding. Some constriction can even be obtained 30 minutes after death.

14. Gradual constriction of bronchioles followed by dilatation is usually seen post mortem.

15. Muscarine, pilocarpine, and physostigmine excite the vagal endings and induce typical bronchiolar constriction. The effect is abolished by atropine.

16. Barium, veratrine, bromine, and the salts of many of the heavy metals (*e.g.* gold) produce constriction which is not influenced by atropine.

17. Inhalation of CO_2 leads to constriction of the bronchioles which is not altogether central in origin.

18. Chloroform, ether, urethane, lobelia, and atropine induce dilatation of the bronchioles when constriction is present. The dilatation produced by lobelia is quite transient, whilst that by atropine is permanent.