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MECHANISM OF STIMULATION OF TYPE J PULMONARY RECEPTORS

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SUMMARY

1. The responses of type J pulmonary receptors (identified according to existing criteria) were studied in anaesthetized cats by recording impulses in individual vagal afferent fibres whose conduction velocity ranged from 0·8 to 7 m/sec.

2. Measurements of actual latencies between insufflation of halothane or ether into the lungs and the excitation of the endings, and the latencies before and after circulatory arrest have established that the endings are located in the interstitial tissues close to the pulmonary capillaries. Mainly for this reason, the term juxta-pulmonary capillary receptors (i.e. type J receptors) has been applied to these endings in preference to the term K deflation receptors used hitherto.

3. The endings were stimulated by pulmonary congestion produced by occlusion of the aorta or left a–v junction for short periods. They were markedly stimulated during pulmonary congestion following injection of alloxan (150 mg/kg) or the addition of chlorine to the inspired air. This excitation was associated with a marked rise in pulmonary artery pressure and the occurrence of pulmonary oedema. However, the actual onset of excitation occurred some time after the rise in pressure and it was in fact more closely related to fall in pulmonary compliance. The frequency of discharge averaged over about 10–20 sec (in order to take the periods of relative inactivity into account) was 7·5 impulses/sec in 10 fibres (range 0·6–19 impulses/sec; S.D. 6·3). This is intense stimulation of the endings and the congestion so produced is therefore regarded as a severe stimulus for the endings.

4. The pattern of excitation was variable. In some fibres the activity consisted of periodic bursts of impulses which seemed to be set off during the deflation phase of artificial respiration, sometimes during the inflation phase. This periodic activity was not due to contraction of smooth muscle as the endings are not stimulated following injection of histamine

(into the right ventricle) which is known to stimulate smooth muscles in the alveolar ducts and respiratory bronchioles.

5. It is postulated that the actual stimulus for the endings is a rise in interstitial pressure or volume produced by a rise in pulmonary capillary pressure. Evidence has been gathered to show that the latter rises during muscular exercise; this rise must stimulate the endings. It was therefore postulated that stimulation of the endings should cause reflex inhibition of limb muscles (for terminating exercise).

INTRODUCTION

So far there are only two reports on the responses of deflation receptors stimulated by phenyl diguanide (Paintal, 1955; 1957*a*). In these papers it has been shown that the endings are weakly stimulated by deflation of the lungs. Infrequently a discharge, that approaches in intensity the discharge following phenyl diguanide, can be produced by releasing the inflated lungs of a cat with intact chest (Paintal, 1957*a*). Moreover, there are many endings that behave like deflation receptors in all respects except that they are not stimulated by deflation of the lungs (Paintal, 1955).

It was also concluded that the endings are located near the alveoli close to the pulmonary capillaries since they were rapidly stimulated following insufflation of ether into the lungs and also by intra-right atrial injection of phenyl diguanide (Paintal, 1957*a*). In view of the further evidence that will be presented in this paper it is therefore considered desirable to refer to these endings as juxta-pulmonary capillary receptors. However, for convenience they will be referred to as type J receptors hereafter.

METHODS

Experiments were carried out on cats anaesthetized with chloralose (75 mg/kg) after induction with ether or trichlorethylene. The results reported herein were obtained from forty-one such cats. The basic techniques used have been described before (Paintal, 1953, 1955, 1957*a*). For example, impulses were recorded and the conduction velocities of individual fibres determined using techniques described earlier (Paintal, 1953). In addition, since under certain conditions (e.g. Fig. 7) the discharge in type J receptors tends to be irregular (as in the case of chemoreceptors) it was necessary to record the natural impulses on a relatively fast oscilloscope sweep (2 msec/cm) triggered by the impulse in order to identify the impulses belonging to a particular fibre as done in a previous investigation (Paintal, 1967*a*). An example of this is given in Fig. 1 to illustrate the assistance derived from this technique. Here in Fig. 1*D* the continuous record shows that the impulses apparently belong to one fibre, but it is clear from the sweeps of the impulses (inverted and showing only the latter part of the impulse) that there are two fibres: fibre no. 1 has a prominent after potential (upward hump) which is missing in fibre no. 2. Only fibre no. 2 is stimulated by injection of phenyl diguanide into the right ventricle.

In some experiments impulses were recorded in two separate filaments simultaneously through two pairs of electrodes and two preamplifiers. Usually, the purpose of this was to be able to compare the effect of a chemical substance on a type J receptor with that on a pulmonary stretch receptor simultaneously. In all cases the impulses were recorded monophasically using differential amplifiers (Tektronix type 122) with a frequency response of 8 c/s to 10 kc/s. Use of wide bandpass facilitated the identification of impulses of individual fibres.

The aortic blood pressure was recorded using a pressure transducer (Statham type P 23 G) connected to a nylon catheter whose tip lay in the ascending aorta. The position of the tip was always confirmed at post-mortem. Injections of substances into the aorta were also made through this catheter. For injection of drugs into the right side of the heart a catheter was inserted through the right external jugular vein. In about half the experiments the tip of this catheter was in the right atrium and in the other half it was in the right ventricle. Right ventricular pressure was recorded, using another pressure transducer (Statham type P 23 Db), through this catheter. This provided an indirect but correct measure of the systolic pulmonary artery pressure, since the latter is only a little less than the right ventricular pressure during systole. In some experiments with open chest the pulmonary artery pressure was recorded instead of right ventricular pressure.

The intratracheal pressure (or the intrapleural pressure) was recorded with another pressure transducer.

Pulmonary congestion. In the initial experiments attempts were made to produce pulmonary congestion by occluding the left a–v junction. In subsequent ones, the ascending aorta was occluded instead and the pulmonary artery pressure or the right ventricular pressure recorded simultaneously. By this method, congestion can be produced only for brief periods and it was not severe enough. Therefore, marked pulmonary congestion leading to the production of pulmonary oedema was produced either by injecting alloxan (150 mg/kg) as described by Peralta (1945) or by ventilating the lungs with chlorine (about 0·5 % in air) for 1–3 min. In some experiments the animal was exposed for a few seconds to chlorine by injecting about 3–6 ml. pure chlorine into the inlet tube connecting the tracheal cannula.

Chlorine gas was prepared by dropping concentrated HCl over potassium permanganate and collecting the gas in a 100 ml. syringe after washing the syringe with chlorine gas. Known concentrations of chlorine were made by introducing measured volumes of pure chlorine into an 11 l. bottle. This mixture of chlorine in air was pumped into the cat with a respiratory pump (Starling) and since the mixture had to pass through the pump and length of rubber tubing the concentration of chlorine appearing at the tracheal cannula was much less than that in the bottle. The concentration of chlorine arriving at the tracheal cannula or in the expired air was measured by mixing known volumes of the mixture (or expired air) with a solution of starch and potassium iodide (soluble starch 0·5 g; KI, 10 g; distilled H_2O, 1 l.). The intensity of blue colour produced was compared with that produced by known concentrations of chlorine in air.

In order to determine the precise location of the endings, halothane or ether was insufflated into the lungs rapidly. For this purpose in the majority of experiments halothene was kept in a bottle at 0° C by surrounding it with ice, and air at room temperature was rapidly bubbled through it by pressing a rubber bulb. The mixture of halothane in air led directly into the tracheal cannula. The intra-tracheal pressure (intrapleural pressure in a few experiments) was recorded simultaneously while the mixture was insufflated. In most experiments the interval between the start of the insufflation and the peak rise in intratracheal pressure (or intrapleural pressure) was about 0·1 sec (Figs. 1*C*, 11*D*, 11*E*). The volume insufflated was about 60 ml.

In some experiments the conduction time from the ending in the lung to the recording electrodes was determined by stimulating the lung locally near the ending with electric pulses of about 1 msec duration. This involves a slight underestimate of the actual con-

duction time, since it is probable that a more proximal part of the fibre was stimulated. In other fibres, the conduction time was estimated from measurements of the cervical conduction velocity and the conduction distance. Again this is likely to underestimate the actual conduction time since the conduction velocity might fall in the distal lengths of the nerve fibres as has been found by Iggo in the case of gastro-intestinal fibres (Iggo, 1958).

Solutions. The concentrations of the solutions used were: phenyl diguanide, 100 μg/ml. in NaCl (0·9 g/100 ml.); histamine acid phosphate (British Drug Houses) 100 μg/ml. in 0·9 % NaCl; alloxan (Sigma Co.) 2–3 % solution in distilled H_2O.

Selection of fibres. Since the discharge in type J fibres is produced within 2·5 sec following injection of phenyl diguanide into the right atrium, this response was used as the main criterion for isolating and identifying these fibres as described earlier (Paintal, 1955). Accordingly, only those fibres have been studied in the present investigation in which the injection–discharge time following 150 μg phenyl diguanide was less than 2·5 sec (Fig. 1*B*). In this connexion selection was greatly simplified by triggering the sweep of the oscilloscope (which lasted 2·5 sec) by the injection signal and observing the appearance of the discharge before the end of the sweep.

Two more tests were applied before studying the responses of the fibre further: the effect of intra-aortic injections of phenyl diguanide was then noted since aortic chemoreceptors and gastro-intestinal receptors are also stimulated by phenyl diguanide although with a greater latency (Paintal, 1954, 1967*a*); only fibres that did not yield a discharge of impulses following intra-aortic injection of phenyl diguanide were chosen for study (Fig. 1*A*). Finally, since it is conceivable that there may be endings anywhere in the pulmonary vascular tree and that these may also be stimulated by phenyl diguanide, the response of each ending to rapid insufflation of a volatile anaesthetic was examined; only those endings were accepted as type J receptors in which a discharge of impulses was produced within 0·3 sec following the insufflation of a volatile anaesthetic (Fig. 1*C*) (cf. Paintal, 1957*a*). For this purpose halothane was used most frequently, but ether was also used in some experiments. It so happened that practically all the fibres that fulfilled the first criterion also fulfilled the second and third. In the earlier experiments of this series, the second criterion could not be applied as an aortic catheter was not inserted.

RESULTS

Location of the endings. The evidence already available (i.e. the responses following insufflation of anaesthetics and injections of phenyl diguanide) has demonstrated that the endings are located in the alveoli close to the pulmonary capillaries (Paintal, 1957*a*). However, Daly & Hebb have cast doubts on this conclusion, since they felt 'that the mechanical interactions of ventilation and circulation are such that they need not be in or near the alveoli although it seems more probable that they are' (Daly & Hebb, 1966). It is now possible to dispel these doubts.

Unlike the earlier investigation (i.e. Paintal, 1957*a*), the actual conduction time from the endings to the recording electrodes was determined in the present experiments. Table 1 shows the latency of the responses obtained in nine fibres following insufflation of halothane or ether. Column 2 of Table 1 gives the recorded minimum interval between the start of insufflation of the anaesthetic and the appearance of the first impulse at the recording electrodes (see Figs. 1*C*, 11*D*). In no case did insufflation of air

alone stimulate the endings. In column 3 are given the conduction times from the endings in the lungs to the recording electrodes (cf. Methods for likely errors). The last column gives the difference between the two, i.e. the maximum interval between the start of insufflation and the excitation of the ending. In about half the fibres this interval is between 78 and 98 msec. It is clear that if an appropriate allowance is made for the transit

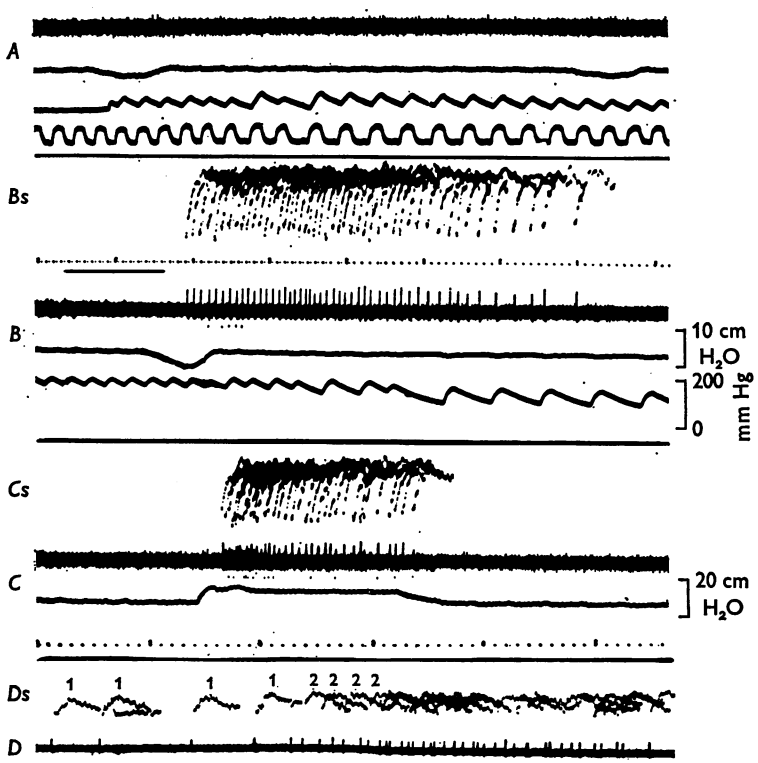

Fig. 1. Criteria used for isolation and identification of impulses in individual type J fibres. *A*, *B* and *C* show respectively the effect of intra-aortic injection of 150 μg phenyl diguanide at signal, intraventricular injection of 100 μg phenyl diguanide (showing the typical reflex effects), and insufflation of halothane (0° C) at sudden rise of intrapleural pressure. Conduction velocity of the fibre was 1 m/sec. *Bs* and *Cs* show the impulses on an expanded sweep; these were recorded simultaneously with the records *B* and *C* and they indicate that the impulses arise from the same fibre. This is not so in *Ds* (another experiment) which shows that the impulses originate in two different fibres 1 and 2 even though the continuous record *D* shows that the impulses are of the same size. Here, 200 μg phenyl diguanide at signal stimulated fibre no. 2 and not no. 1. From above downwards in *A* and *B*, injection signal, impulses in the fibre (none in *A*) intrapleural pressure (inspiration downwards), aortic blood pressure and in *A*, right intraventricular pressure. The 0·1 and 1·0 sec time marks in *B* apply to *A* and *D* as well.

time of the vapours from the tracheal cannula to the alveoli, the actual interval between the arrival of ether or halothane at the alveoli and the excitation of the endings will be still less and it is therefore highly unlikely that the endings can be at any significant distance from the alveolar wall.

TABLE 1. Intervals between start of insufflation of halothane or ether (first three fibres) and excitation of type J receptors

Serial no.	Recorded latency* (msec)	Conduction time (msec)	Max. interval between insufflation and excitation (msec)
3	279	162	117
6	225	131	94
12	296	156	140
16	244	129	115
19	298	205	93
23	356	200	156
27	246	168	78
28	212	116	96
31	100	20	80

* Interval between start of insufflation and appearance of impulses at recording electrodes.

TABLE 2. Minimum and maximum latencies between start of insufflation of halothane or ether (first two fibres) and arrival of impulses at recording electrodes before and after circulatory arrest. Only minimum values are given where just one observation was made

Serial no.	Latencies before circulatory arrest (msec)		Latencies after circulatory arrest (msec)		Difference between two minima (msec)
	Min.	Max.	Min.	Max.	
3	279	529	294*	317*	+15
10	282	382	299	—	+17
6	225	320	226*	266*	+ 1
13	300	397	312*	—	+12
16	286	—	244†	—	−42
19	314	364	298*	362*	−16
20	242	286	259	—	+17
23	356	413	370	—	+14
37	218	254	268	340	+50‡

* Observations made after cutting great vessels and removing ventricles.

† Observations after cutting pulmonary artery following cardiac standstill.

‡ The latencies recorded before and after circulatory arrest were recorded with closed and open chest respectively.

However, in spite of such brief excitation times it is still arguable that ether or halothane is transported downstream by the circulating blood and thus endings at some distance from the pulmonary capillaries are stimulated. Table 2 provides unequivocal evidence that this is not so. In this Table are given the latencies following insufflation of ether or halothane before and after complete circulatory standstill, i.e. after the heart had stopped beating and in some experiments after cutting through the large

vessels and removing the ventricles so that, compared with normal conditions, practically no forward movement of blood took place in the pulmonary capillaries during insufflation. It is clear that there is hardly any difference between the minimum latencies following insufflation before and after circulatory standstill in all the fibres except in the case of fibre no. 9. In this case, unlike the others, the observations before and after circulatory standstill were made under different conditions, i.e. with the chest intact and after opening the chest. The increased latency in this case is most probably due to increased intrathoracic conduction time because of the fall in mediastinal temperature after opening the chest. Since the Q_{10} for conduction velocity of mammalian non-medullated fibres is 1·6 (Paintal, 1967*b*) and the intrathoracic conduction distance is of the order of 80 mm, a reduction in temperature by 1° C will increase the conduction time by 13 msec. In the other fibres both sets of observations were made either with the chest intact or after opening the chest, i.e. the mediastinal temperature was the same in both sets of observations.

In all the other fibres of Table 2, the minimum latency following insufflation of ether or halothane after circulatory standstill is less than the maximum latency recorded with a normal circulation. Moreover, in three fibres the minimum latencies after circulatory standstill were either the same or less than those before circulatory arrest. Such observations show conclusively that the circulation of the blood in the pulmonary capillaries plays no part in influencing the speed of excitation of the endings through the gas phase by volatile anaesthetics. This makes it certain that the endings are not located downstream or upstream from the pulmonary capillaries but at the pulmonary capillaries themselves. It is therefore quite appropriate to refer to these endings as type J receptors.

The rapid excitation of these endings by volatile anaesthetics stands in sharp contrast to the responses of pulmonary stretch receptors which are sensitized by volatile anaesthetics (Whitteridge & Bülbring, 1944; Paintal 1957*b*, 1964; Whitteridge, 1958). The effect of rapid insufflation of halothane was tested on six pulmonary stretch receptors. In none of them was there any early excitation by halothane (Fig. 11*D*), the effects of insufflation with air being essentially similar to that following insufflation with halothane. It was only after a lapse of several seconds or after subsequent insufflations that the effects of sensitization which is known to occur make its appearance. This is consistent with the fact that pulmonary stretch receptors are accessible through the bronchial circulation (Widdicombe, 1954; Paintal, 1964).

Conduction velocities. Figure 2 shows the distribution of the conduction velocities of the fibres of type J receptors which confirms the earlier impression that, on the whole, the conduction velocities of the fibres are

less than 6 m/sec (Paintal, 1955). Although most of the fibres are non-medullated (i.e. with conduction velocities less than 2·5 m/sec), there are some that are medullated (i.e. with conduction velocities > 5 m/sec). This is similar to the conduction velocities of aortic chemoreceptors (Paintal & Riley, 1966).

Effect of pulmonary congestion. It is known that congestion of the lungs stimulates some of these endings (Paintal, 1955), but since there is no

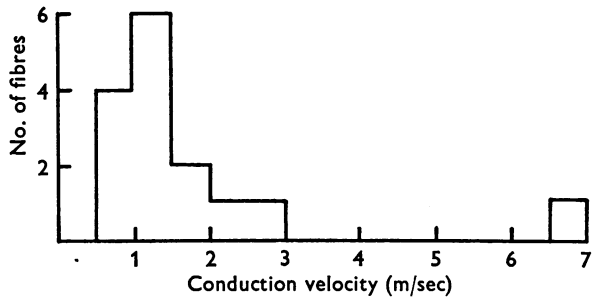

Fig. 2. Frequency distribution of the conduction velocities of type J fibres. Fibres with conduction velocities < 3 m/sec are non-medullated and those with velocities > 5 m/sec are medullated (Paintal, 1967*b*).

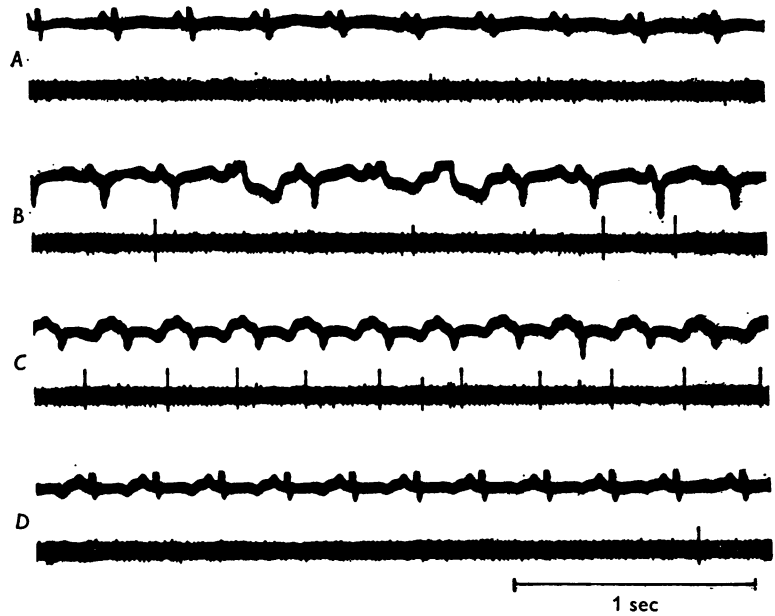

Fig. 3. Moderate stimulation of a type J receptor after occlusion of the left a–v junction. *A* shows no activity before occlusion. *B* and *C* show the activity 4 and 25 sec after start of occlusion, and *D*, 3 sec after end of occlusion. Note, the impulses in *C* do not have a cardiac rhythm (e.c.g., upper trace).

quantitative information about the degree of excitation, this aspect has been studied further.

Occlusion of the ascending aorta or the left a–v junction stimulated eight endings about 5–10 sec after start of the occlusion and this discharge returned to zero within 1–20 sec after releasing the occlusion in different endings (Figs. 3 and 4). In the case of two other endings this procedure had no effect. The intensity of stimulation was variable. In two fibres the stimulation of the endings during occlusion of aorta was quite

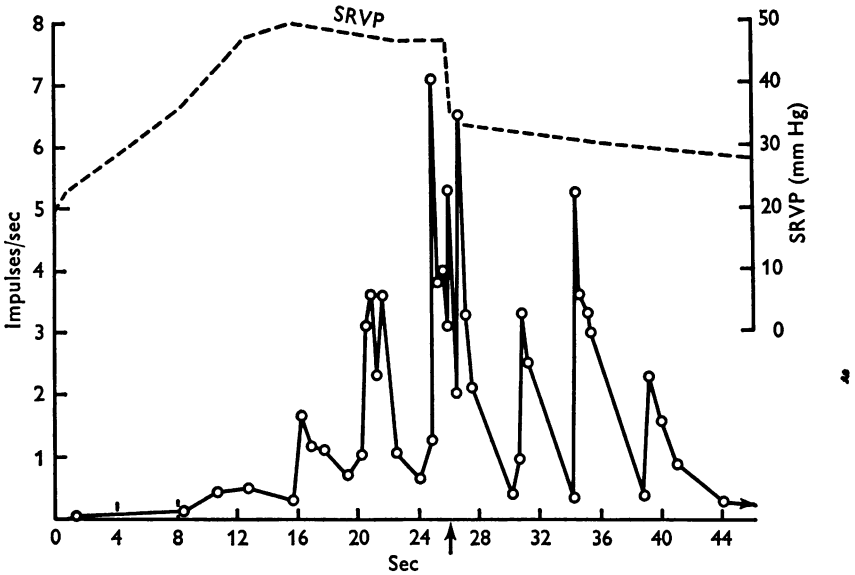

Fig. 4. Response of a type J receptor to occlusion of the aorta at zero time. Note the lag between the rise in systolic right ventricular pressure (SRVP) and the excitation of the ending. There is a similar lag at the end of occlusion at arrow. The ordinate (impulses/sec) represents the reciprocal of the interval between individual impulses.

marked; the peak frequency rose to 7 impulses/sec in one fibre (Fig. 4) and to about 20 impulses/sec in the second one at a time when the systolic right ventricular pressure had risen to 54 mm Hg. In one cat, occlusion of the aorta produced only a small rise in pressure (< 10 mm Hg) but three endings were stimulated, two weakly (< 1 impulse/sec) and one moderately (1·2 impulses/sec).

The interval between the start of the rise in systolic right ventricular pressure and the onset of stimulation in different fibres varied considerably. In some fibres it was as little as 2 sec, and in others about 15 sec or more. Perhaps the two endings that were not excited even 30 sec after occlusion may have been excited had the occlusion been maintained for longer periods. This is what one would expect from the effects of profound

congestion produced by alloxan in which the latency for excitation was a minute (Fig. 6) or more (cf. below).

Since pulmonary congestion produced by occlusion of the aorta or left a–v junction can only be of short duration and the effects are short-lived (Figs. 3 and 4), two other methods were used for producing severe pulmonary congestion leading to pulmonary oedema, namely alloxan and chlorine gas. It is known that chlorine in adequate concentrations produces pulmonary oedema (Goodman & Gillman, 1941) and that alloxan injected intravenously (150 mg/kg) leads to pulmonary oedema in cats (Peralta, 1945).

The effect of alloxan was tried on eight endings while the cat was ventilated with a respiratory pump; contractions of respiratory muscles were prevented by adjusting the level of anaesthesia. Alloxan apparently did not stimulate the endings directly since intraventricular injections of alloxan had no effect for several seconds (> 10 sec in most fibres) after injection, i.e. long after the arrival of the drug at the endings. As indicated by the short injection–discharge times following phenyl diguanide (1·5 sec in these endings), alloxan should have arrived within 1·5 sec following the start of injection. In one exceptionally excitable ending, a discharge of 7 impulses appeared 5 sec after injection of alloxan at about the same time as the rise in systolic right ventricular pressure (Fig. 5*A*). This excitation was not unexpected because the same ending was stimulated markedly and quickly by occlusion of the aorta.

In the case of three endings, 25, 50 and 120 sec respectively elapsed before the endings were excited. In these it can be argued that alloxan does not have a direct action of the endings as is the case with phenyl diguanide; clearly the excitation must be secondary to some other changes. An evident stimulus is the pulmonary congestion produced by alloxan, owing to the great rise in pulmonary artery pressure and the increased permeability of the pulmonary capillaries produced by alloxan (Aviado, 1965; Staub, Nagano & Pearce, 1967).

In all experiments injection of alloxan was followed by a marked rise in mean pulmonary artery pressure (when recorded) or in systolic pulmonary artery pressure as revealed by the records of right ventricular pressure. This rise in pressure started within 10–20 sec following the injection and it reached a peak within 1–2 min (Figs. 5*A* and 6). This level was maintained for about 2–15 min after which it fell with the appearance (or just before the appearance) of oedema fluid in the tracheal cannula.

The increased activity in the endings did not bear a direct relation to the rise in pulmonary artery pressure. Thus, as shown in Fig. 6, there was a considerable lag between the rise in the pressure and the excitation of the endings. In fact, in most cases, peak rise in pressure was attained several

seconds or minutes before peak increase in activity (e.g. Fig. 6). Similarly, the fall in pressure and the fall in activity in the later stages of the experiments were not coincident in some experiments (e.g. Fig. 6). All these results suggest that the rise in pulmonary capillary pressure *per se* is not the direct stimulus for the endings. Most probably it is the pulmonary

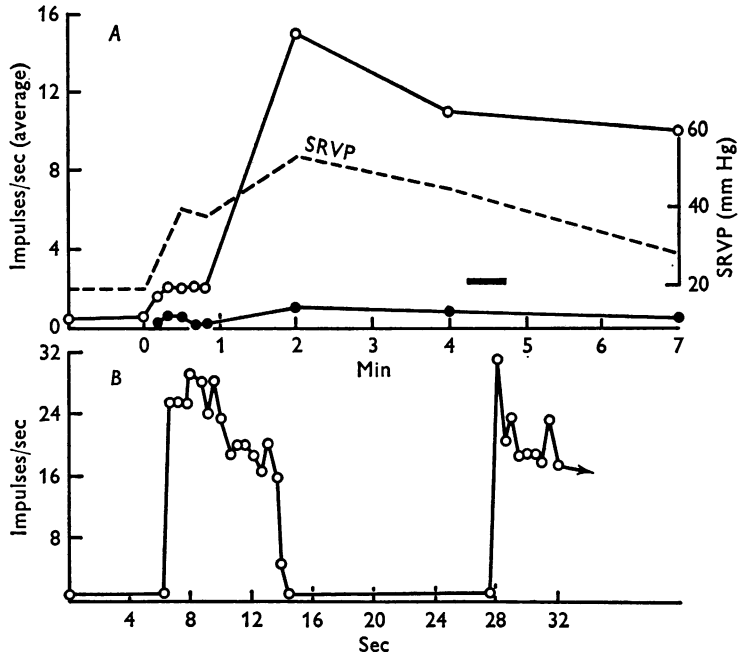

Fig. 5. Activity in two type J receptors following injection of alloxan (150 mg/kg) at zero time. The ordinate in *A* represents impulses/sec averaged over 10 sec periods initially up to 1 min and over 50 sec periods thereafter to take the periods of relative silence shown in *B* into account. Note, the marked difference in the intensity of activity in the two endings no. 1 —○—○— and no. 2 —●—●—. Also that the initial rise in activity coincides with the initial rise in systolic right ventricular pressure (SRVP). The intratracheal pressure was unchanged throughout. *B* shows the activity of fibre no. 1 during the period represented by the bar in *A*. The frequency of discharge (reciprocal of impulse interval) is indicated every half second. This is much higher than the average frequency of discharge (11/sec) shown in *A* because the relatively silent intervals shown in *B* were taken into account while averaging the discharge in *A*.

congestion (due to raised pulmonary capillary pressure) leading to the production of interstitial oedema with the consequent rise in interstitial pressure or volume (see Discussion) which stimulates the endings. This view is consistent with the observation that the increase in activity of the endings seemed to coincide roughly with the increase in intratracheal pressure (Fig. 6). However, in one experiment (see legend to Fig. 5*A*)

there was no such correlation. The appearance of oedema fluid was not associated with any further enhancement of excitation. In fact in a few fibres (e.g. Fig. 6) the discharge fell for variable periods while the fluid started pouring out of the tracheal cannula.

As expected, the degree of stimulation of the endings after alloxan varied widely in the eight fibres tested. The responses of the two fibres shown in Fig. 5*A* represent the two extremes; intermediate responses are shown in Fig. 6.

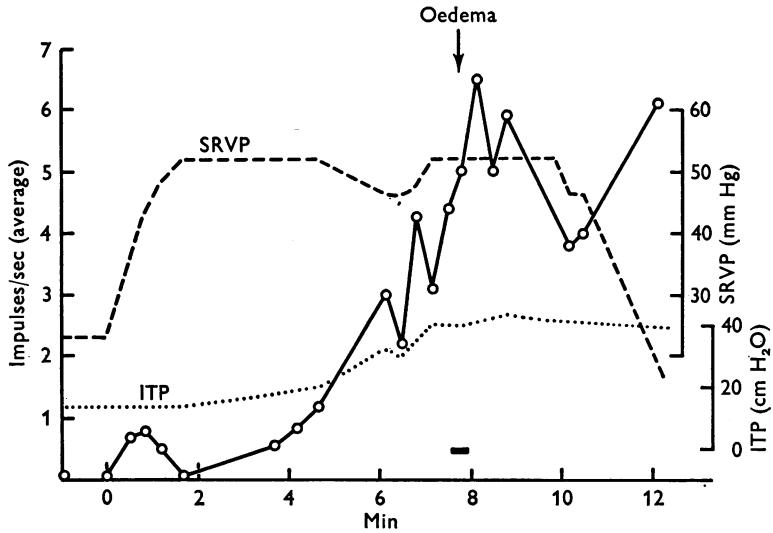

Fig. 6. Graph showing response of average intensity in a type J fibre following alloxan at zero time. The ordinate on the left represents impulses/sec averaged over 20 sec periods. Oedema fluid appeared in the tracheal cannula after the 7th minute at arrow. Cat on artificial respiration. ITP, intratracheal pressure.

The pattern of excitation presented certain interesting features. Thus in some fibres, the discharge was irregular (e.g. Fig. 7), somewhat like the discharge in chemoreceptors. However, in most fibres the discharge seemed to appear in the form of periodic bursts of activity (Figs. 5*B*, 7, 8). As the total activity increased the periods of relative inactivity between the bursts became shorter and the bursts of activity longer. In some instances these bursts seemed to be set off during the deflation part of artificial respiration (as shown in Fig. 8 after chlorine). This was not uncommon. In other fibres the activity seemed to be set off during the phase of inflation. The bursts seemed to have a regular discharge of impulses (similar to those after chlorine in Fig. 8), and occasionally during the periods of intense activity the discharge seemed to start and end suddenly (Fig. 5*B*).

The consistent excitation of type J receptors during pulmonary congestion following alloxan contrasts with the variable response in pul-

monary stretch fibres whose activity was recorded simulataneously in some experiments. Thus in one fibre which was normally active only during inflation, a discharge appeared during the expiratory phase of the pump cycle after alloxan and the peak frequency attained during inflation of the lungs was a little higher than normal. On the other hand there was practically no effect in another fibre whose activity was recorded simultaneously through a second pair of recording electrodes. In two fibres there was obvious increase in activity after alloxan and in one fibre the increase was

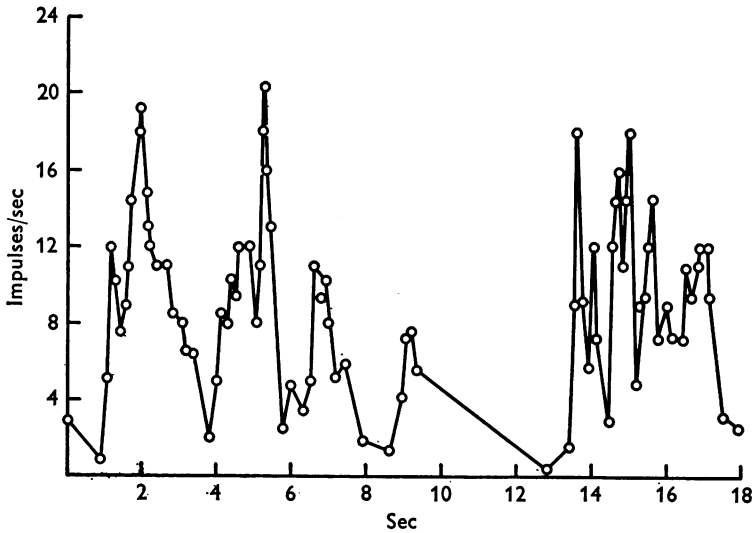

Fig. 7. Pattern of discharge of the fibre of Fig. 6 during the period represented by the bar in Fig. 6. Ordinate represents impulses/sec as the reciprocal of impulse interval. Note periodic variation of activity.

related to the rise in intratracheal pressure which rises considerably after alloxan. On the whole these results are consistent with those of Widdicombe (1961) on the effects of pulmonary oedema on pulmonary stretch receptors. Actually it is difficult to assess the effects of pulmonary oedema on pulmonary stretch receptors because under such conditions it is not certain which parts of the lungs are ventilated.

The effects of chlorine, which produces pulmonary congestion and oedema (Goodman & Gillman, 1941), were similar to that of alloxan. Four out of the 5 type J receptors tested were markedly stimulated after administration of chlorine; in one there was only weak stimulation after the initial excitation. It was found that 0·5 % chlorine given for about 1–3 min was adequate to produce marked excitation of the endings and this lasted till the cat died of pulmonary oedema. The excitation set in about 15–30 sec after starting the administration of chlorine.

A very convenient way of stimulating these endings was by merely injecting about 3 ml. pure chlorine into the inlet tube near the tracheal cannula. This stimulated the endings instantly presumably by a direct action on the endings. After this initial intense stimulation, there was a period of relative silence followed by the gradually increasing stimulation as seen after alloxan. In one experiment the mean pulmonary artery pressure rose to 43 mm Hg within 1 min following administration of 0·5% chlorine, and similarly in another, the systolic right ventricular pressure

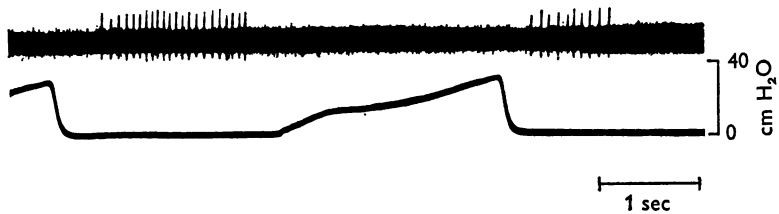

Fig. 8. Record showing significant activity during periods of deflation in a type J receptor 24 min after chlorine. Peak intratracheal pressure (2nd trace) is 32 cm H_2O; before chlorine it was 12 cm H_2O. Volume of inflation with pump was about 65 ml. throughout.

increased to about 52 mm Hg. It is possible therefore that the delayed marked excitation of the endings was due to the pulmonary congestion produced by the rise in pulmonary capillary pressure as well as to the increased permeability of the pulmonary capillaries (Goodman & Gillman, 1941).

The pattern of activity a few minutes after administration of chlorine was similar to that following alloxan, i.e. there were periodic bursts of impulses interspersed by periods of relative silence; in some fibres these bursts seemed to be set off during deflation (Fig. 8). On other occasions they appeared to be set off during the inflation phase of artificial respiration. As with alloxan this activity continued until the cat died, after which no further observations were made.

Intensity of discharge. During the periods of greatest activity after chlorine or alloxan the frequency of discharge averaged over 10–20 sec periods (so as to take into account the periods of relative silence) ranged from 0·6 to 19 impulses/sec in ten fibres; the mean was 7·5 impulses/sec (S.D. 6·3).

Histology. In ten cats the lungs were examined histologically after administration of alloxan or chlorine. In all of them there was evidence of capillary engorgement with presence of interstitial oedema, haemorrhages into the alveolar septa and intra-alveolar oedema. However, there was considerable variation in the extent of pathological changes in different parts of the lungs. In view of this it was difficult to correlate the activity

of the endings in one part of the lung with the pathological changes in another part from which the sections were made.

Responses following phenyl diguanide and histamine. Much is already known about the responses of these endings following intra-right atrial injections of phenyl diguanide (Paintal, 1955, 1957*a*). However, in view of the fact that proof of single unit activity was not present in the earlier papers, but has been obtained in the present one, it is important to compare the present results with those of the earlier papers. In the present

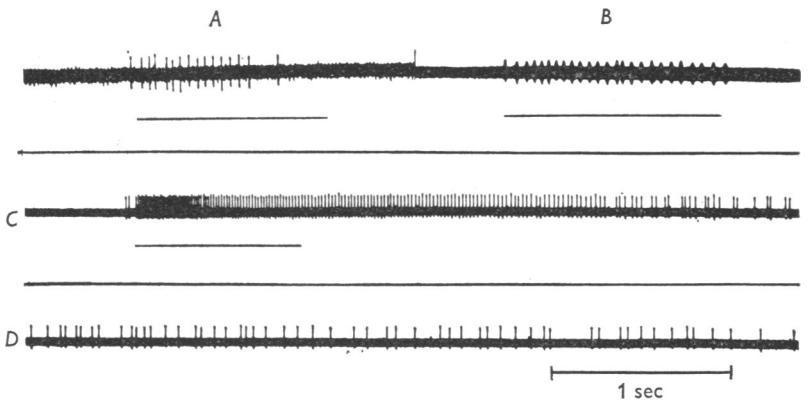

Fig. 9. Responses of three type J receptors, shown respectively in *A*, *B* and *C*, to application of local pressure on the lung in the region of the ending in three cats. The duration of application of pressure is indicated by the signal. *D* is a continuation of *C* and it shows the persistence of the discharge set off by the stimulus.

experiments in thirty-two fibres, the peak frequency averaged 19 impulses/sec (range 4–39 impulses/sec; S.D. 7·9) following injections of phenyl diguanide. The duration of discharge averaged 4·6 sec in twenty-four fibres (range 1·1–8·5 sec; S.D. 2·3). These values are similar to those reported earlier. The injection–discharge time (from beginning of injection to start of discharge) following intra-ventricular injections averaged 1·5 sec in nineteen fibres (range 0·5–2·3 sec; S.D. 0·5). This is just a little less than that following intra-atrial injection of phenyl diguanide, i.e. 1·8 sec (Paintal, 1957*a*), which is to be expected. These results are of significance in the interpretation of the time course and intensity of the reflex effects produced by the endings.

The effects of intraventricular injections of 100–160 μg histamine were observed on three type J endings. In no case was there any early (within 3 sec) or late (up to 30–60 sec) stimulation after injecting histamine.

Effects of local pressure. Application of local pressure on the lungs was an effective method of stimulating the endings (Fig. 9) so that it became possible to localize the endings in the individual lobes. All the eighteen

fibres of the right vagus from which impulses were recorded with open chest had endings in the right lung. Some endings could be stimulated by stroking the surface of the lungs; others needed strong pressure in order to stimulate them. The peak frequency of discharge was, in every ending examined, greater than that following phenyl diguanide, being above 50/sec (Fig. 9). The discharge ceased either before or with the end of the stimulus (Fig. 9*A*, *B*). However, in some cats, particularly in those with

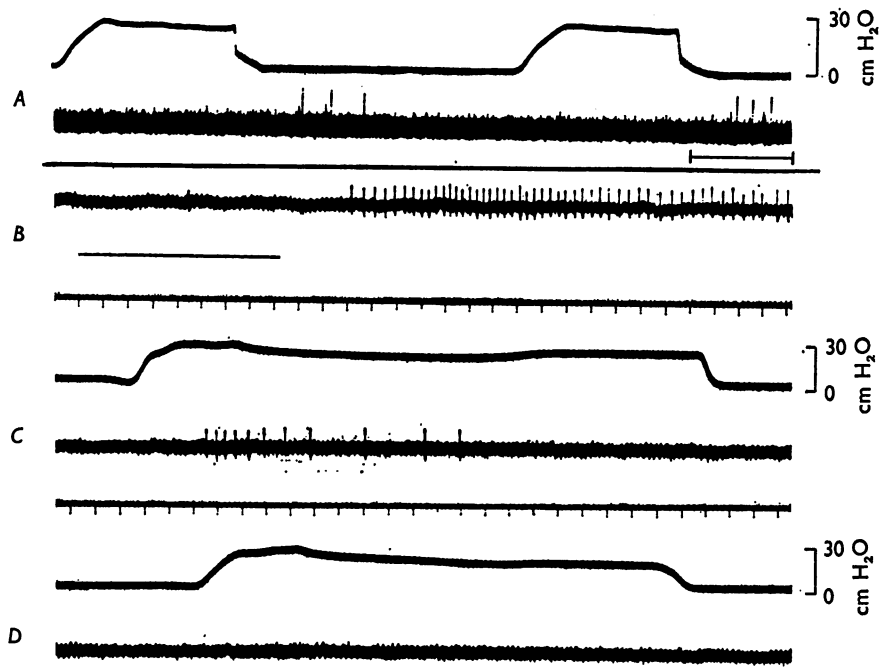

Fig. 10. Responses of two type J receptors to very large inflations of the lung. *A* shows the typical response of one ending following release of 160 ml. inflation (i.e. deflation) described earlier (Paintal, 1955, 1957*a*). *B* shows the typical response of another ending to intra-atrial injection of 225 μg phenyl diguanide at signal and *C*, the response of the same ending to inflation of the lungs with 130 ml. air. In *D* a similar inflation had no excitatory effect. The chest was intact in both experiments. The upper trace in each record (except *B*) is of intratracheal pressure.

pulmonary oedema after alloxan or chlorine, it was found that mechanical stimuli set off a relatively prolonged discharge of impulses which continued for several sec after the mechanical stimulus had been withdrawn (Fig. 9*C*). Apart from the clinical significance, such results indicate that under these pathological conditions, excitation of the ending persists after the withdrawal of the stimulus perhaps due to poor elastic recoil on account of fluid accumulation.

Resting discharge. A characteristic feature of these endings is that they

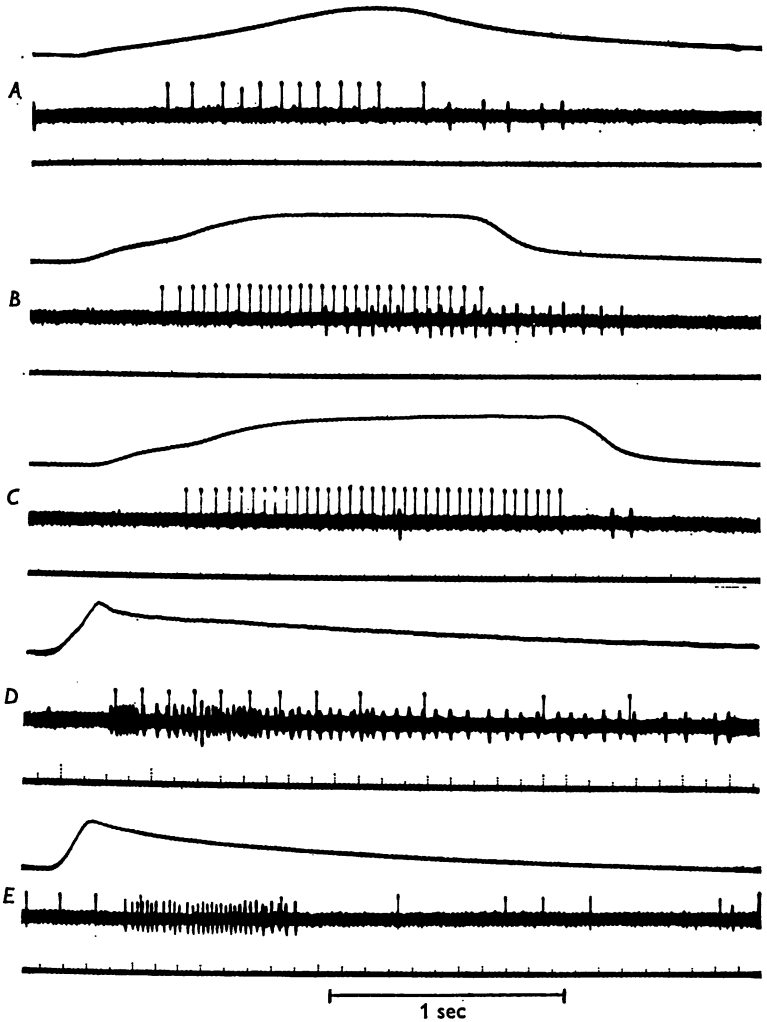

Fig. 11. Responses of type J receptor (small diphasic spike) to inflation of the lung (*A*, *B* and *C*) with open chest and insufflation with halothane (60 ml.) in *D* and *E*. The large monophasic spikes in *A*, *B*, *C* and *D* are those of a pulmonary stretch fibre and these show the consistent response to inflation of the lung with 60 ml. in *A* and about 150 ml. in *B* and *C* in contrast to the variable response in the type J fibre which is excited during the deflation phase in *A*, during inflation in *B* (but after a significant delay); there is comparatively little effect in *C* (again about 150 ml. inflation). Insufflation of halothane had no excitatory effect on pulmonary stretch fibre in *D* (normal circulation) in contrast to the marked excitation of the type J receptor which is excited with a similar latency in *E* after cutting the great vessels and removing the ventricles. From above downwards in each record, intratracheal pressure, impulses in filament and 0·1 sec time marks. Gain of amplifier for intratracheal pressure in *A*, *D* and *E* is twice that in *B* and *C*.

are normally inactive in cats with intact chest (Paintal, 1955, 1957*b*). This has been confirmed again in general but occasionally one comes across certain endings with a discharge of the order of 0·2 impulses/sec. In one ending there was a resting discharge of 1·2 impulses/sec and this ending was also stimulated by deflation of the lungs. Considering that the average discharge during stimulation of the endings during congestion is 7·5 impulses/sec, resting discharge of the order of 0·2 impulses/sec acquire some significance, although direct mechanical stimulation drives them at more than 50 impulses/sec.

Effect of inflation. It was reported earlier (Paintal, 1955) that inflation of the lungs does not stimulate the endings that are stimulated by deflation (Fig. 10*A*). This has been confirmed provided the inflation is of the order of 100 ml., i.e. about four times the normal tidal volume of the cat. In fact many endings were not stimulated even by large inflations (150 ml.). However, one came across occasional endings that were stimulated if the volume used was large, i.e. > 100 ml. Such excitation was poorly related to the actual inflation itself because sometimes the discharge set in after a significant delay (e.g. Fig. 11*B*). Moreover, the responses were highly variable in the same fibre (Figs. 10 and 11). Such responses resemble those reported by Coleridge, Coleridge & Luck (1965) in the dog and by Coleridge, Coleridge, Luck & Norman (1968) in the cat.

DISCUSSION

The results obtained with volatile anaesthetics before and after circulatory standstill (Table 2) and the effects of phenyl diguanide demonstrate that these endings must be located close to the pulmonary capillaries. In this position they are influenced by whatever reaches them via the gas phase on the one hand and the pulmonary circulation on the other. Unlike the pulmonary stretch receptors (Widdicombe, 1954) these endings must be sufficiently far away from the capillaries of the bronchial circulation to be unaffected by intra-aortic injections of phenyl diguanide (Fig. 1*A*). In view of these results it has been considered desirable to term these endings as juxta-pulmonary capillary receptors (i.e. type J receptors) in preference to deflation receptors used hitherto (Paintal, 1955, 1957*a*, 1963, 1964, 1968) because, although deflation by itself stimulates some of these endings (Paintal, 1957*a*), it is far less effective than pulmonary congestion. In fact the congestion following alloxan or chlorine is to be regarded as a severe stimulus because of the intense activity of the endings during such congestion. Lesser degrees of congestion which might be expected to occur during exercise (see below) would produce correspondingly smaller degree of stimulation of the endings.

It is now necessary to define the precise nature of the stimulus. One possibility is that movement of fluid out of the pulmonary capillary during congestion (i.e. rise in pulmonary capillary pressure) causes an increase in pressure or volume of the interstitial tissue spaces and it is this increase in interstitial pressure or volume that constitutes the actual stimulus for the endings which perhaps function as interstitial stretch receptors. The greater the rise in pulmonary capillary pressure, the greater the rise in interstitial pressure (or volume) and the greater the excitation of the endings. It is conceivable that the endings may be located in the peribronchial and perivascular interstitial tissue that is close to the pulmonary capillaries since it has been found by Staub *et al.* (1967) that the earliest manifestations of pulmonary oedema are to be found in this region. On the other hand they could also be located in the interstitial tissue between the alveolar epithelium and the endothelium. It is important to note that the endings are unaffected by capillary pulsations themselves (i.e. they do not as a rule have a cardiac rhythm) presumably because pulsations in pulmonary capillary pressure do not produce corresponding pulsations in interstitial pressure or volume. The absence of excitation by histamine indicates that these endings are not associated with the smooth muscle of respiratory bronchioles and alveolar ducts (Alcock, Berry, Daly & Narayana, 1937; Colebatch, Olsen & Nadel, 1966). As shown by Colebatch *et al.* (1966) contraction of smooth muscle in the region of the alveolor ducts sets in within 2·8 sec of histamine injection into the right ventricle or pulmonary artery. It is therefore certain that contraction of this smooth muscle does not stimulate the endings. The periodic discharges seen during pulmonary congestion (Figs. 5*B*, 7 and 8) cannot therefore be due to the contraction and relaxation of this smooth muscle.

Physiological role. It is to be expected that the endings will be stimulated under any physiological condition that leads to an increase in pulmonary capillary pressure, the greater the increase, the greater the stimulation. From the evidence available, one can now be certain that an increase in pulmonary capillary pressure occurs during exercise. This is obvious in subjects living at an altitude of 10–15 thousand feet in whom the rise in pulmonary artery pressures during even moderate exercise is quite marked. Thus Vogel, Weaver, Rose, Blount & Grover (1963) found that during moderate exercise at Leadville (10, 150 ft.), the mean pulmonary artery pressure rose to 54 mm Hg (average in twenty-eight normal residents) from a resting level of 25 mm Hg; the corresponding figures obtained in thirty-five normal subjects at Morococha (14,900 ft.) by Peñaloza, Sime, Banchero & Gamboa (1963) were 60 and 29 mm Hg respectively. The subjects of these two studies did not develop pulmonary oedema but apparently many of the 332 soldiers studied by Singh, Kapila, Khanna,

Nanda & Rao (1965) developed pulmonary oedema on account of exertion at an altitude of 11,000–15,000 ft. In fact some of them developed pulmonary oedema during exercise and died within 1 hr of onset (I. Singh, personal communication, 1969). Increase in mean pulmonary artery pressures has also been recorded during moderate or severe exercise at sea level (Donald, Bishop, Cumming & Wade, 1955; Freedman, Snider, Brostoff, Kimelblot & Katz, 1955; Bevegård, Holmgren & Jonsson, 1963). Moreover, Bevegård *et al.* (1963) found that the pulmonary capillary pressure increased to two to three times the resting value during heavy exercise in some subjects. It is to be expected that the activity of type J receptors will increase under such conditions.

Reflex effects. Following upon earlier observations of Dawes, Mott & Widdicombe (1951), it was shown that stimulation of type J receptors produces reflex bradycardia and apnoea (Fig. 1*B*) followed by tachypnoea (Paintal, 1955, 1957*a*) the latter being the dominant feature if the endings are weakly stimulated (Paintal, 1955). Tachypnoea is a prominent feature of phosgene inhalation (Whitteridge, 1948; Banister, Fegler & Hebb, 1949) which also leads to the appearance of pulmonary oedema in some cats (Whitteridge, 1948). And since the endings are markedly stimulated during pulmonary congestion preceding and during pulmonary oedema (Figs. 5–7), it is almost certain that they would be stimulated during phosgene inhalation.

Since the available evidence indicates that a rise in pulmonary capillary pressure (which stimulates the endings) occurs during exercise, it is important to note that stimulation of these endings (by 2α-naphthyl isothiourea or phenyl diguanide) does not produce a reflex fall in pulmonary artery pressure (Dawes *et al.* 1951) or a reduction in pulmonary vascular resistance (Barer & Nüsser, 1958). In the absence of such reflex cardiovascular adjustments, it is therefore postulated that stimulation of the endings by exercise might cause reflex inhibition of the exercise itself.

There is evidence that stimulation of chemoreceptors, and endings in the chest wall and lungs can produce sensations of dyspnoea (Howell & Campbell, 1966). Recently, it has been argued that type J endings are probably an important source of dyspnoeic sensations arising from the lungs (Paintal, 1968). The present results showing that pulmonary congestion is the natural stimulus can only strongly support such arguments. They are of particular relevance in diseases in which pulmonary capillary pressure is raised. In such cases a marked rise in pulmonary artery pressure often occurs during mild exercise enough to produce marked dyspnoea (Hickam & Cargill, 1948; Blount, 1959; Ferrer & Harvey, 1959). It is no wonder therefore that in some of these diseases a significant relief from the unpleasant sensations of dyspnoea can be achieved by vagal block (Guz,

1966; J. Eisele & S. K. Jain, 1968, personal communication). In this connexion it would be desirable to know whether the increased breath-holding time during vagal block (Guz, Noble, Widdicombe, Trenchard, Mushin & Makey, 1966) is due to the elimination of the resting discharge in type J receptors.

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