IMPULSES IN VAGAL AFFERENT FIBRES FROM SPECIFIC PULMONARY DEFLATION RECEPTORS. THE RESPONSE OF THESE RECEPTORS TO PHENYL DIGUANIDE, POTATO STARCH, 5-HYDROXYTRYPTAMINE AND NICOTINE, AND THEIR RÔLE IN RESPIRATORY AND CARDIOVASCULAR REFLEXES.

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RAPID shallow breathing (tachypnœa) in animals can be produced experimentally by multiple pulmonary emboli, pulmonary congestion and phosgene inhalation (for references see reviews by Christie, 1938, and Whitteridge, 1950). The remarkable feature common to all these is the abolition of the tachypnœa by bilateral vagotomy; this establishes the rôle of reflex pathways in the vagi.

Christie [1938] suggested that the tachypnœa due to pulmonary congestion, starch embolism, phosgene inhalation and the dyspnœa accompanying many pathological conditions were always due to stimulation or sensitization of pulmonary stretch receptors. Christie's suggestions aroused considerable interest, but Bülbring and Whitteridge [1943] were unable to show that congestion of the lungs is accompanied by an increased sensitivity of the pulmonary stretch receptors. They concluded that there must be a second set of afferent fibres in the vagus, capable of accelerating the respiration. Neither Walsh [1947] nor Whitteridge [1948] could provide any evidence of increased activity in pulmonary stretch fibres following starch embolism and phosgene inhalation respectively. Torrance and Whitteridge [1947] showed that the tachypnœa of starch embolism persists after cooling of the vagi to 6° C., which indicates that vagal afferent fibres of small diameter were concerned.

Dawes, Mott and Widdicombe [1951] showed that rapid shallow breathing could be produced by injecting derivatives of guanidine and isothiourea into the right atrium but not into the left. In an attempt to identify the mechanism concerned, Paintal [1953 *a*] studied the effects of phenyl diguanide on various pulmonary and cardiovascular receptors, and found that phenyl diguanide produced activity in previously inactive afferent fibres of small conduction velocity. It turned out later [Paintal, 1954 *a*] that most of these fibres came from the stomach and intestines. However, in a recent investigation on gastric stretch

receptors [Paintal, 1954 *c*], two vagal afferent fibres that yielded a discharge of impulses with an unusually short injection-response time were observed. These probably came from receptors in the lungs. This interesting observation led to the present investigation, in which it will be shown that some receptors sensitive to phenyl diguanide are definitely located in the lungs and, since they are sensitized by deflation of the lungs, they have been termed pulmonary deflation receptors. The text will show that these deflation receptors have not been described before, and they bear no resemblance to the deflation receptors described by Adrian [1933].

Methods

Thirty-one adult cats weighing 1·4–4·3 kg. were used in this investigation; they were all anæsthetized with ether in a box followed by intravenous chloralose 70 mg./kg.

The method of dissecting minute strands of the vagus and recording their action potentials has been described earlier [Paintal, 1953 *b*]. A balloon inserted through the mouth could distend the stomach when required. The intrapleural pressure was recorded through a wide bore needle connected to a mirror membrane manometer. In a few experiments the intragastric balloon was connected to this manometer and served as a satisfactory respiratory signal, a fact confirmed by comparing the record with the activity in pulmonary stretch fibres.

In all experiments a semi-rigid catheter (No. 6 U.S.A. cardiac catheter) about 21 cm. long was inserted into the right atrium through the right external jugular vein. In two experiments a similar catheter was inserted through the left common carotid artery as far as the left ventricle. The position of these catheters was confirmed post-mortem. In one experiment after opening the chest, the catheter was inserted into the left atrium through the left ventricle, and in another into the pulmonary artery through the right ventricle. In some experiments a catheter was inserted into the abdominal aorta so that its tip lay about 2·5 cm. above the diaphragm. The dead space of all these catheters was 0·25 ml., and they were all provided with leak-proof taps. An allowance for the dead space was made in estimating the quantity of the drug injected.

Injections were made with a 2·5 ml. syringe. The beginning and duration of the injection was signalled by pressing a foot switch connected to a 2·5 V bulb. The error involved in this was reckoned to be less than 0·1 sec. This system of signalling was preferred to an electrical contact on the plunger of the syringe, as very often the contact was made before the fluid left the syringe. The beginning of the injection was taken as the reference point in determining the various injection response times. The duration of 68 injections of phenyl diguanide was

$1{\cdot}0 \pm 0{\cdot}2$ sec.; in one case the duration was 1·5 sec. The quantity of the solution injected was 2–2·5 ml.; the rate of injection therefore corresponds to the rapid injection of Gray and Paton [1949].

Artificial respiration was at first applied by a pump. Later, this was carried out by an assistant blowing through a tube connected to the tracheal cannula. This afforded quick and effective control of pulmonary inflation, an advantage that was necessary in carrying out the experimental manœuvres after opening the chest. Since the volume of air required to inflate the cat's lungs was about 50–100 ml., most of the air exhaled by the assistant consisted of air from his own dead space. Analysis of such air collected in a balloon showed about 20 per cent oxygen and 1 per cent CO_2. This did not affect the results of the experiments, as the activity of pulmonary deflation receptors is not affected by anoxia or CO_2 excess (see below).

The drugs were dissolved in 0·9 per cent NaCl (w/v). The concentration of phenyl diguanide, 5-hydroxytryptamine (HT) and nicotine sulphate was 100 μg./ml. The suspension of potato starch was prepared by filtering peeled minced potato through four layers of surgical gauze [Walsh, 1947]. The filtrate was then diluted with nine times its volume of 0·9 per cent NaCl (w/v). The solutions were injected at room temperature, which was 38°–39° C. The doses of HT were estimated in terms of the base by dividing the weight of the salt by 2·3.

Results

Of the many types of vagal afferent fibres the pulmonary deflation fibres are the most difficult to isolate. Records of only 17 strands containing these fibres have been obtained in 14 out of 28 cats. Many other strands containing similar fibres were encountered, but their activity was studied on the cathode ray tube only without taking permanent photographic records.

Isolation and Identification

Experiments were always started with the animals' chest intact. Vagal strands were dissected and hooked on the recording electrodes one by one. If the strand from which impulses were being recorded did not contain more than two or three active pulmonary or cardiovascular afferent fibres, phenyl diguanide (about 200 μg.) was injected rapidly into the right atrium. If this produced a sudden burst of impulses in afferent fibres within 3 seconds, it was concluded that the fibres came from pulmonary deflation receptors (fig. 1). Apart from negative evidence, this was the only positive criterion for identifying these fibres in the first 9 strands. In 6 out of the remaining 8 strands, each containing at least two fibres, it was found after opening the chest

that the receptors were markedly sensitized to phenyl diguanide by collapse of the lungs and desensitized by inflating them (figs. 2, 6, 7, 8). Since these 6 strands showed a pattern of behaviour similar in all respects to the 9 strands examined earlier, it was concluded that all the 17 strands contained afferent fibres from similar pulmonary deflation receptors. They were distinguished from other pulmonary and cardiovascular afferent fibres by the pattern of normal activity and by the fact that injection of phenyl diguanide did not increase activity in the latter [Paintal, 1953 *a*, 1954 *c*]. Distinction from gastric and intestinal receptors sensitive to phenyl diguanide was achieved by two criteria: (1) that the injection-discharge time following injection of phenyl diguanide is more than 3·5 sec. [Paintal, 1954 *c*], and (2) that an intra-aortic injection of phenyl diguanide is followed by activity in the gastro-intestinal fibres and not in pulmonary fibres. As a rule, the difference in the injection-discharge time between the two sets of receptors was so marked that this criterion alone was sufficient to distinguish the two sets of receptors. However, sometimes difficulty was encountered in the absence of an aortic catheter; in such cases the gastric stretch fibres were identified by their characteristic response to distension of the stomach.

Localization

Localization of the receptors was carried out along lines described already [Paintal, 1954 *a*].

It became clear early in the investigation that the receptors were not located in the left ventricle or downstream from it, as no response was observed in strands 2, 3 and 4 following injection of phenyl diguanide into the left ventricle whereas a right atrial injection gave a clear response. Twice in another experiment no response could be obtained following an injection into the right atrium after occluding the pulmonary artery, and it was concluded that the receptors were located somewhere downstream from the pulmonary artery (fig. 2A). In this cat a catheter was then inserted through the right ventricle as far as the bifurcation of the pulmonary artery. Since the injection-discharge time following injections of phenyl diguanide through this catheter was 1·4 sec. and those after injection into the right atrium varied from 1·3 to 2·0 sec. in the same strand, it was concluded that the receptors were not located in the pulmonary artery or its bigger branches in the lungs. In the subsequent experiment, left atrial injection of phenyl diguanide did not stimulate the receptors (fig. 2C), and so the receptors were definitely located in the lungs. Right atrial injections of phenyl diguanide, after clamping the root of the left lung and the roots of the upper two lobes of the right lung, yielded a discharge of impulses in the same strand (fig. 2F). Lobar localization of pulmonary vascular deflation receptors can therefore be done without much difficulty.

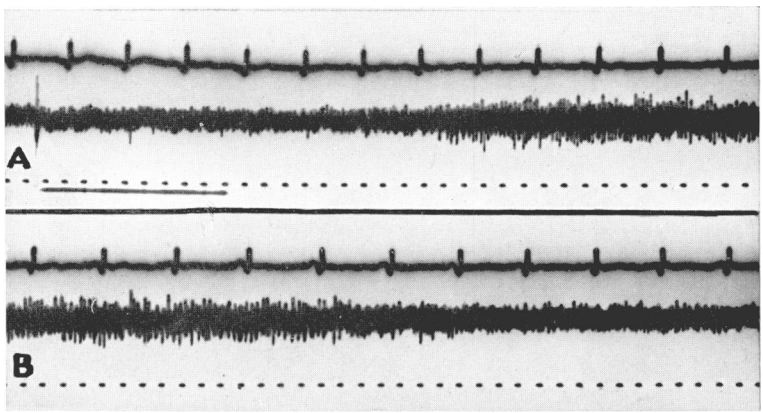

FIG. 1.—Impulses in deflation fibres. Injection of 175 μg. phenyl diguanide into the right atrium of a cat with intact chest at signal in A produces a discharge of impulses; injection-discharge time is 2 sec. The discharge ends in B although the increased base-line noise persists. From above downwards in each record: e.c.g.; impulses in deflation fibres; time in 1/10 sec. and injection signal in A. A and B are continuous records. Slowing of the heart starts 2·7 sec. after injection.

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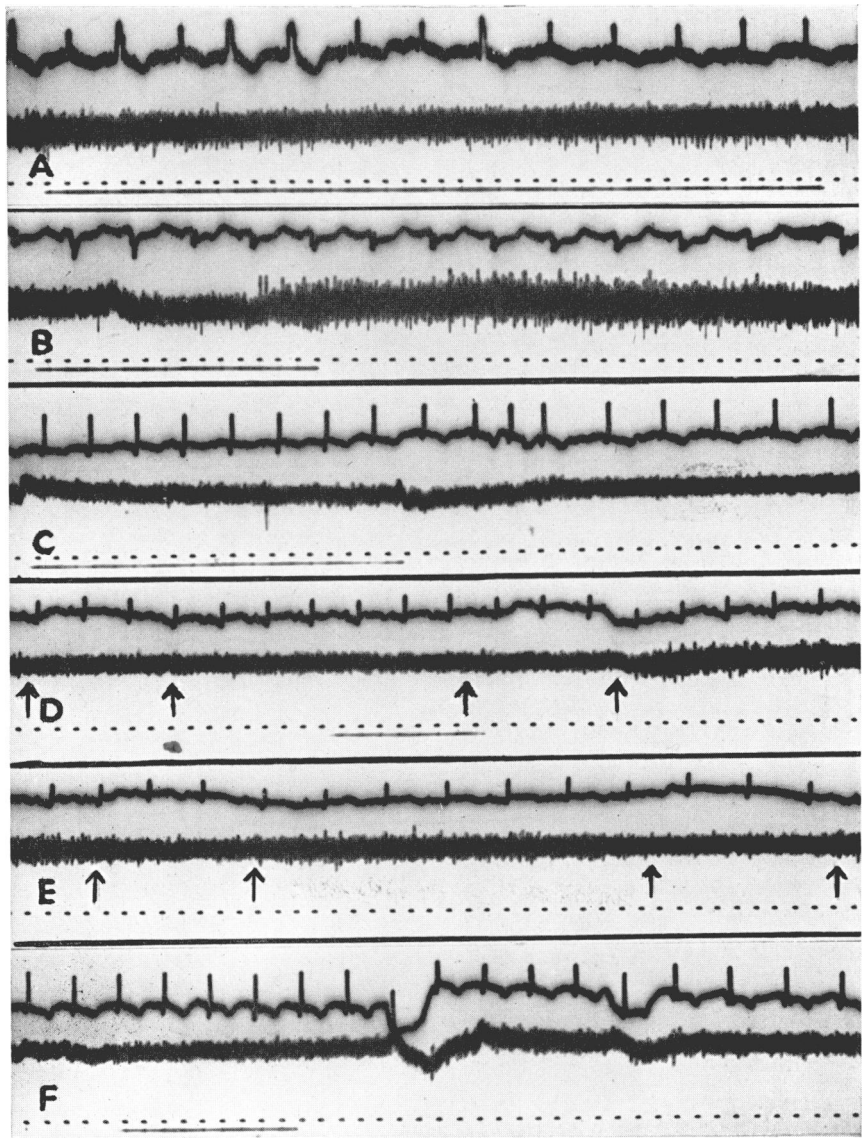

FIG. 2.—Localization of deflation receptors in cats with open chests and artificial ventilation. In A, 225 μg. phenyl diguanide was injected into the right atrium while occluding the pulmonary artery; there is no response. In B, a similar injection was given without occluding the pulmonary artery. The injection-discharge time for the fibre with the largest action potential (plotted in fig. 5A) is greater than that in some of the other fibres. Note that whereas the activity in some of the fibres with larger potentials has ceased before B ends, the base-line noise is still greatly enhanced. A and B together show that the receptors are located downstream from the pulmonary artery. C to F are records of activity in another strand. In C and D, phenyl diguanide was injected into the left and right atria respectively. D and E are continuous records. In E, the activity in deflation fibres is abolished during inflation (at arrows) of the lungs. In F, phenyl diguanide was injected after clamping the roots of the left lung and the upper two lobes of the right lung.

Characteristics of Pulmonary Deflation Afferent Fibres

The action potentials of these afferent fibres were of smaller amplitude than those of any other fibres known to exist in the vagus. Rarely they exceeded 25 μv., as compared to the 50–100 μv. spikes of pulmonary stretch fibres in the same strands. In fact, the amplitude of the majority, of which little account has been taken in this investigation, barely exceeded the base-line noise level. It must therefore be remembered that the characteristics of pulmonary deflation fibres described here, such as adaptation, duration of discharge, apply chiefly to the largest fibres of this group.

There were many opportunities of comparing the action potentials of these deflation fibres with those of gastric stretch fibres in the same strand, and without exception those of the latter were much larger. Since the conduction velocity of the gastric afferent fibres ranges from 6 to 13 m./sec. [Paintal, 1954 *b*), the conduction velocities of the majority of deflation fibres would probably be less than 6 m./sec.; there would also be a wide range of conduction velocities, as in other types of vagal afferent fibres [Paintal, 1953 *b*].

Whereas it is easy to obtain by repeated subdivisions a strand containing a single active unit of pulmonary stretch or cardiovascular afferent fibres, it was possible in only one case to obtain a single fibre from a pulmonary deflation receptor. The majority of the other 16 strands contained at least two or three deflation fibres, although by subdivision the size of the strands had been reduced to about 40 μ in many instances. Further subdivision invariably destroyed the fibres. In 8 cats the fibres were isolated from the first bundle dissected off the vagus. In the remaining 6 they were obtained from the third or fourth bundle, and in 14 cats all attempts at isolating them failed. It seemed, therefore, that if these fibres were not encountered early in the experiment the chance of finding them later on was small. The above facts explain some of the difficulties associated with isolating these fibres.

In 4 cats the first bundle yielded by subsequent subdivision respectively 7, 4, 12 and 5 strands each containing exclusively two or more pulmonary deflation fibres. It is therefore certain that in many cats these fibres must be grouped together in bundles in the cervical vagus.

The presence of any spontaneous activity was looked for in 9 strands in 9 cats. In spite of prior injections of phenyl diguanide, which were unavoidable, no spontaneous activity was found in eleven *fibres* in cats with intact chest or in cats with open chests where artificial ventilation of a moderate degree was carried out. In the other strands it was difficult to be certain one way or the other, owing to the presence of other fibres or their action potentials being too small.

Inflation.—Large rapid inflations of the lungs in cats with intact or open chest did not produce any activity in any of the deflation fibres.

On the other hand, as will be shown later (figs. 2E, 6, 7), this procedure always abolished the activity that was produced by injection of drugs.

Deflation.—Suction of air from the trachea, if rapid and especially immediately after inflation of the lungs, did yield a short burst of impulses of low frequency. Fig. 3A shows a very rapidly adapting response. With open chests it was sometimes possible to produce a couple of impulses if the lungs were allowed to collapse rapidly after an inflation (fig. 3B). In most fibres, however, this was not so. Artificial pneumothorax was carried out in 2 cats by injecting 80 ml. of air rapidly into the right side of the chest. In one case a burst of impulses lasting 0·6 sec. appeared; in the other there was no response. Since all these observations were made after prior injections of phenyl diguanide, an element of sensitization may be involved. However, the effects of phenyl diguanide probably wear off after five to ten minutes, and so the foregoing observations can apply to normal conditions.

Anoxia.—The receptors are apparently unaffected by reduced oxygen content or CO_2 excess, as rebreathing from a small rubber balloon did not produce any activity in these fibres although it resulted in marked hyperventilation and cyanosis (fig. 4). Further, stopping the artificial ventilation did not arouse any activity in the fibres. The receptors are therefore not chemoreceptors.

Pulmonary Congestion.—The activity in 3 strands in 3 cats following occlusion of the left auriculo-ventricular junction for about 15 sec. was observed. This produced distension of the left auricle followed by distension of the right auricle, thus ensuring that pressures in the pulmonary vascular bed had risen considerably above normal. In one strand, whereas there was previously no activity, during the occlusion occasional impulses were observed. In another strand no activity was produced, and in the third the occlusion sensitized the receptors to collapse of the lungs. It is therefore likely that congestion of the lungs may enhance the activity of pulmonary deflation receptors and may even stimulate them. The evidence would suggest, however, that they are not pressure receptors responding to changes in pulmonary vascular pressures.

Responses to Drugs

Phenyl Diguanide.—In cats with intact chests the pulmonary deflation receptors responded characteristically to injections of phenyl diguanide into the right atrium (fig. 1). A discharge of impulses appeared within 1·1 to 2·7 sec. (mean 1·9 sec.) after the beginning of injection (injection-discharge time) and lasted from 0·4 to 16 sec. The injection-discharge time for different fibres sometimes varied considerably, and the activity in some of the fibres dropped off before others. These variations are not unexpected. The pattern of discharge when plotted as the frequency of impulses was characteristically

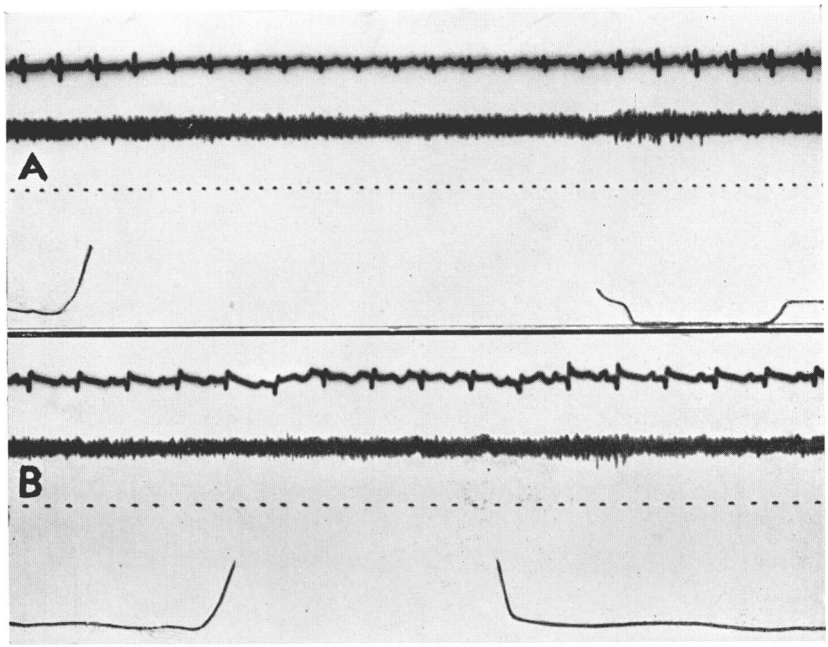

FIG. 3.—Impulses in deflation fibres. In A (intact chest) a rapidly adapting discharge of impulses is produced by suction of air from the trachea immediately after inflating the lungs. In B (open chest), collapse of the lungs after inflation produces only two impulses. From above downwards: e.c.g.; impulses in fibres; time in 1/10 sec. and intratracheal pressure, inflation upwards.

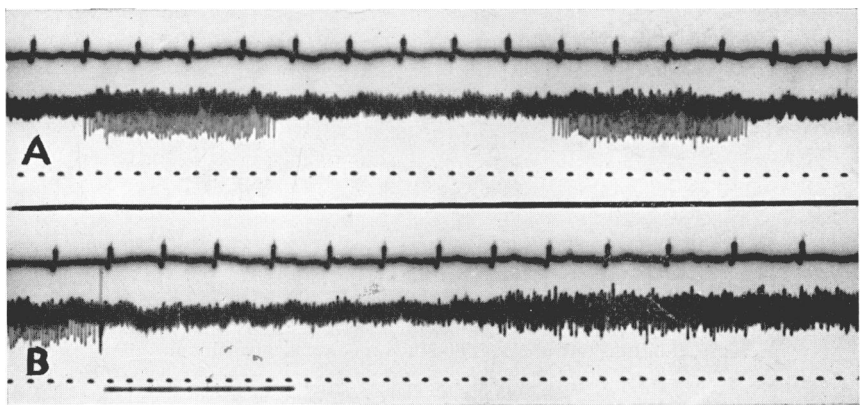

FIG. 4.—Records of activity in deflation fibres. Injection of 175 μg. phenyl diguanide in B is followed by a clear discharge of impulses in deflation fibres, whereas rebreathing from a small rubber bag for about 2 min. has no effect on them in A, although the respiratory rate had doubled and the cat was cyanosed. From above downwards in each record: e.c.g.; impulses in fibres; time in 1/10 sec. and injection signal in B. The monophasic downward spikes are from pulmonary stretch fibres.

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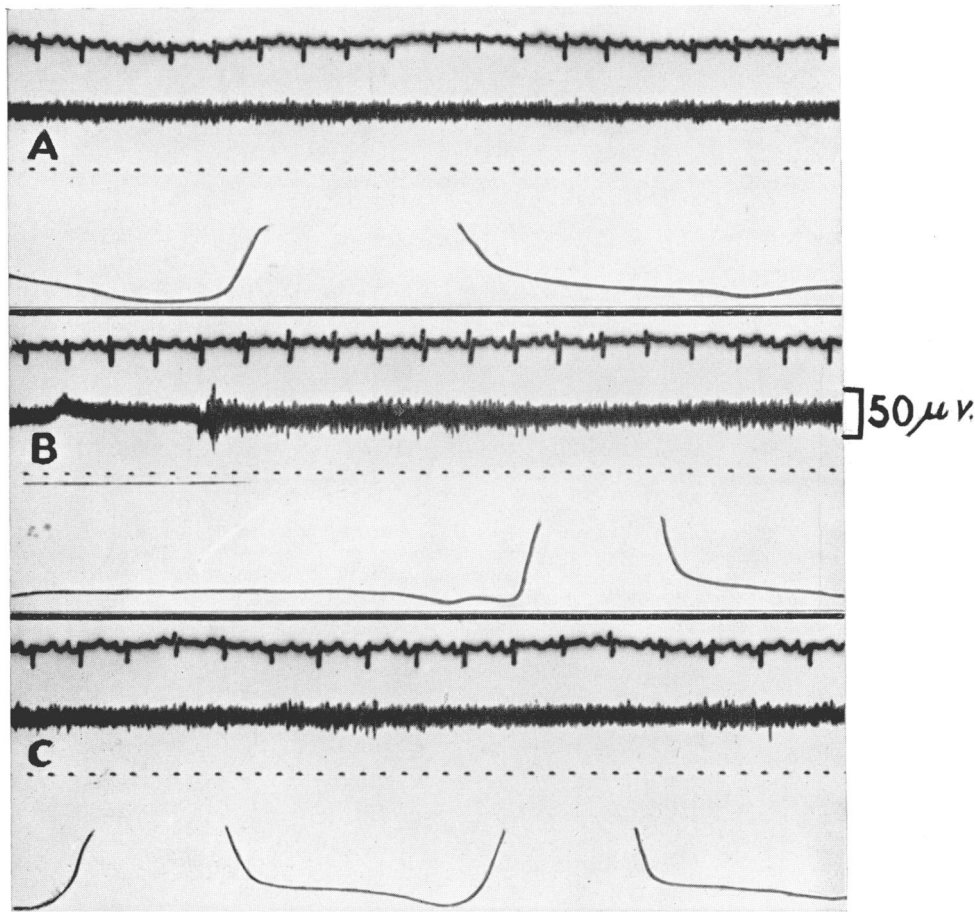

FIG. 6.—Effect of inflation and collapse of the lungs on the activity of deflation fibres in a cat with open chest. A, B and C are respectively records before and after injection of phenyl diguanide at signal in B. Collapse of the lung is not accompanied by impulses in A. From above downwards in each record: e.c.g.; impulses in deflation fibres; time in 1/10 sec.; injection signal in B and intratracheal pressure, inflation upwards. The three records are continuous.

irregular (fig. 5B). It is important to point out here that the respiratory inhibition which set in after the injection always outlasted the discharge in the fibres, and therefore the respiratory fluctuations seen with open chests (see below) were not observed here.

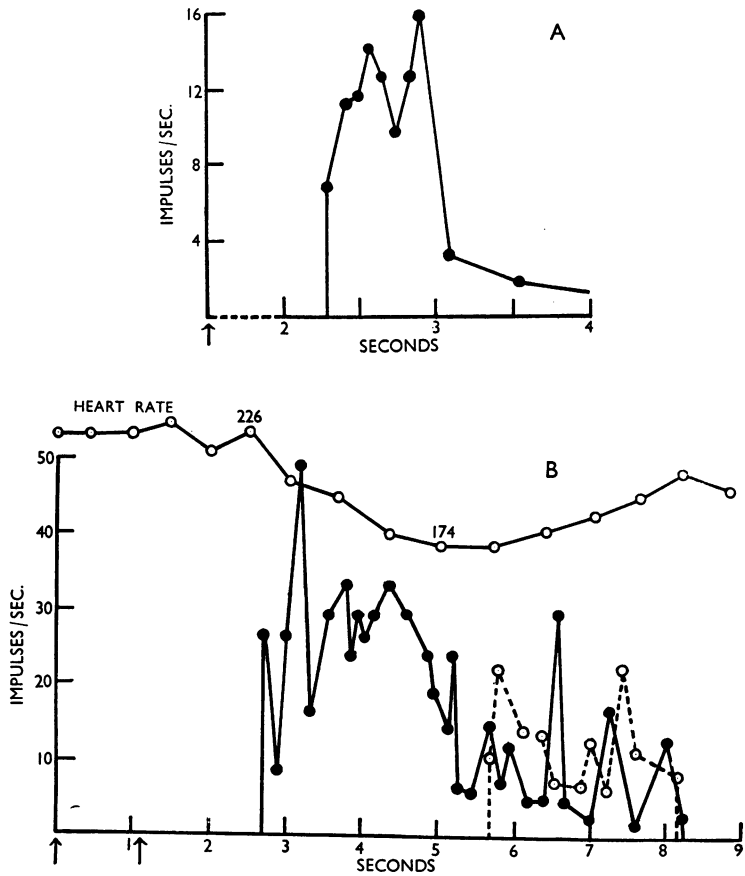

FIG. 5.—Activity in two deflation fibres following injection of phenyl diguanide at arrows into the right atrium. A shows the frequency of impulses in the fibre with the largest potential in fig. 2, B (open chest). B (intact chest) shows the difference in the injection-discharge time between a deflation fibre —●—●— and a gastric stretch fibre - - ⊙ - - ⊙ - - recorded simultaneously. The activity in deflation fibres is accompanied by a fall in the heart rate. The number of points plotted in B have been reduced to half for the sake of clarity.

The peak frequency of impulses was 10–50/sec. In fibres encountered later in an experiment, *i.e.* after several injections of phenyl diguanide had been given, the intensity of discharge following phenyl diguanide was not less than in those encountered initially in other cats. The problem of tachyphylaxis is, therefore, not of much importance in some of these receptors.

Many fibres were observed which yielded the typical discharge of impulses after the first injection of phenyl diguanide but failed to respond following a second injection given a few minutes later. It was obviously not possible to take photographic records of these and they were therefore not studied further. The description given in this paper therefore applies only to those fibres with receptors that do not show appreciable tachyphylaxis. There are definitely other receptors that do exhibit this phenomenon towards phenyl diguanide; perhaps in other respects they may have similar properties.

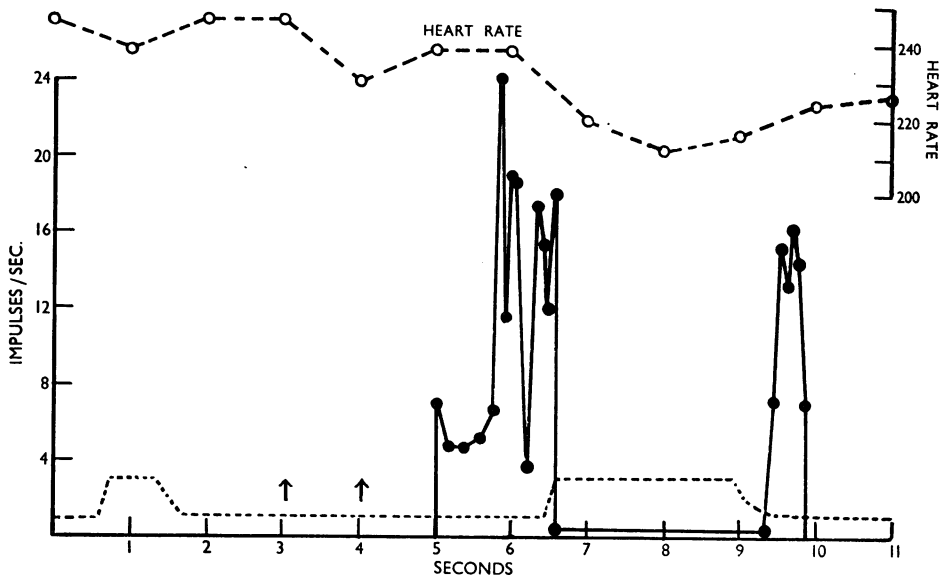

FIG. 7.—Frequency of discharge in a deflation fibre —●—●— after injection of phenyl diguanide between arrows during collapse of the lungs in a cat with open chest. Note the effect on the discharge of inflation and collapse of the lungs indicated by the interrupted line, inflation upwards.

Of greater interest are the responses in the fibres in cats with open chests (figs. 2, 5A, 6, 7). When the drug was injected while the lungs were collapsed the injection-discharge time was reduced significantly (Table I), the mean in 7 strands being 1·2 sec. The intensity of the discharge was also greater. The most significant observation was that, when the lungs were inflated during fibre activity, the discharge ceased instantaneously and no further impulses appeared till the lungs were allowed to collapse (figs. 6 and 7). In some fibres the discharge then continued for a few seconds until the lungs were inflated again (fig. 2E). In most others the discharge adapted rapidly in spite of being sensitized by the drug—the fibres then being inactive during the rest of the period of collapse (figs. 6 and 7). Activity in the latter fibres reappeared after the subsequent inflation, and so on till the fibres were no longer sensitized.

Various grades of activity were observed between these two extremes. The sensitization of the receptors by phenyl diguanide lasted 7–21 sec. (average 12·6 sec.).

TABLE I.—SUMMARY OF RESPONSES FOLLOWING INJECTIONS OF 175–225 μg. PHENYL DIGUANIDE INTO THE RIGHT ATRIUM

	No. of observations	Range sec.	Mean sec.	S.D. sec.
Injection-discharge time in deflation fibres:				
Intact chest	15 strands	1·1– 2·7	1·9	0·5
Open chest (lungs collapsed)	7 strands	0·9– 1·5	1·2	0·16
Injection-reflex time:				
Respiratory inhibition	14 cats	1·3– 2·5	1·9	0·41
Bradycardia	16 cats	1·7– 4·3	2·9	0·67
Duration of discharge in deflation fibres (intact chest)	14 strands	0·4–16·0	5·7	3·9
Duration of sensitization in deflation fibres (open chest)	5 strands	7·0–21·0	12·6	4·7
Duration of respiratory inhibition	17 cats	4·0–22·0	11·6	4·8

TABLE II.—EFFECT OF INFLATION OF THE LUNGS ON THE RESPONSES IN 4 STRANDS CONTAINING PULMONARY DEFLATION FIBRES FOLLOWING INJECTION OF 175–275 μg. PHENYL DIGUANIDE INTO THE RIGHT ATRIUM OF 4 CATS WITH OPEN CHESTS.

Serial no. of strand	Injection-discharge time in deflation fibres. Drug injected during:		Injection-reflex time (bradycardia). Drug injected during:	
	Collapse	Inflation	Collapse	Inflation
11	1·5 sec.	3·3 sec.	2·4 sec.	5·2 sec.
12	1·2 ,,	5·0 ,,	1·7 ,,	5·4 ,,
13	1·2 ,,	2·3 ,,	2·3 ,,	4·5 ,,
17	0·9 ,,	3·3 ,,	3·3* ,,	No bradycardia

* Weak response.

When phenyl diguanide was injected during a maintained inflation of the lungs no activity in the fibres appeared until the lungs were allowed to collapse (fig. 8), so that the injection-discharge time could be varied within reasonable limits (Table II). The resulting duration and intensity of the discharge was also considerably reduced. The threshold of deflation at which different fibres discharged impulses varied somewhat, this no doubt depending partly on the concentration of the drug

reaching the receptors, which in turn is determined by the varying vascularity of different parts of the lung [Wearn, Ernstene, Bromer, Barr, German and Zschieche, 1934].

The degree of pulmonary collapse or inflation appeared to be the only factor which consistently modified the activity of the deflation receptors. The effect was primarily mechanical and was not secondary to vascular changes. These receptors are therefore *true* deflation receptors and, as

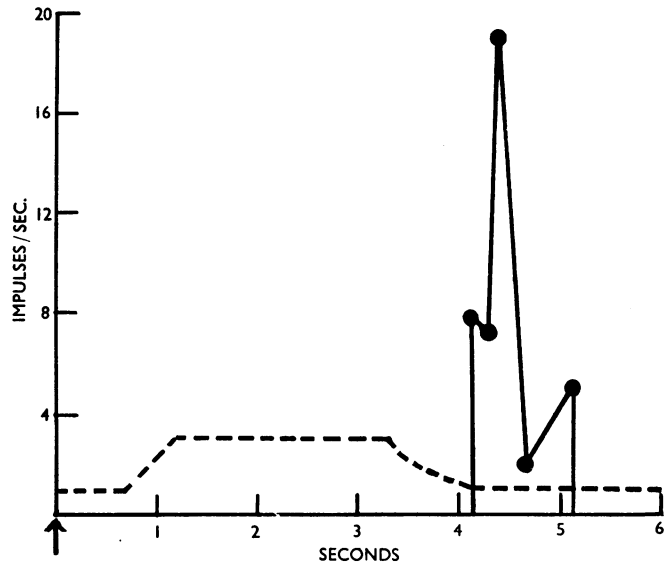

FIG. 8.—Frequency of discharge —●—●— in the same fibre as illustrated in fig. 7. Inflation of the lungs - - - - - increases injection-discharge latency and reduces the intensity and duration of discharge as compared with fig. 7. Injection of phenyl diguanide is shown by the arrow.

will be shown, are quite different from those described previously [Adrian, 1933; Paintal, 1953 *b*].

Starch.—The effect of injecting 2·5–4 ml. of starch on the activity in 3 strands each containing at least two pulmonary deflation fibres was observed; in all, a clear discharge of impulses appeared (fig. 9C, D). The injection-discharge times were longer than those following phenyl diguanide (Table III), but not the durations of the discharges. As in the case of phenyl diguanide, the discharge following starch was also inhibited by inflation of the lungs.

Repeated injections of starch usually produced responses in the same fibres, except in one strand in which some injections failed to produce a discharge of impulse while others did. This behaviour could not be correlated with anything.

It should be stressed that the starch granules in suspension may not be responsible for stimulating the receptors, but instead one or more of

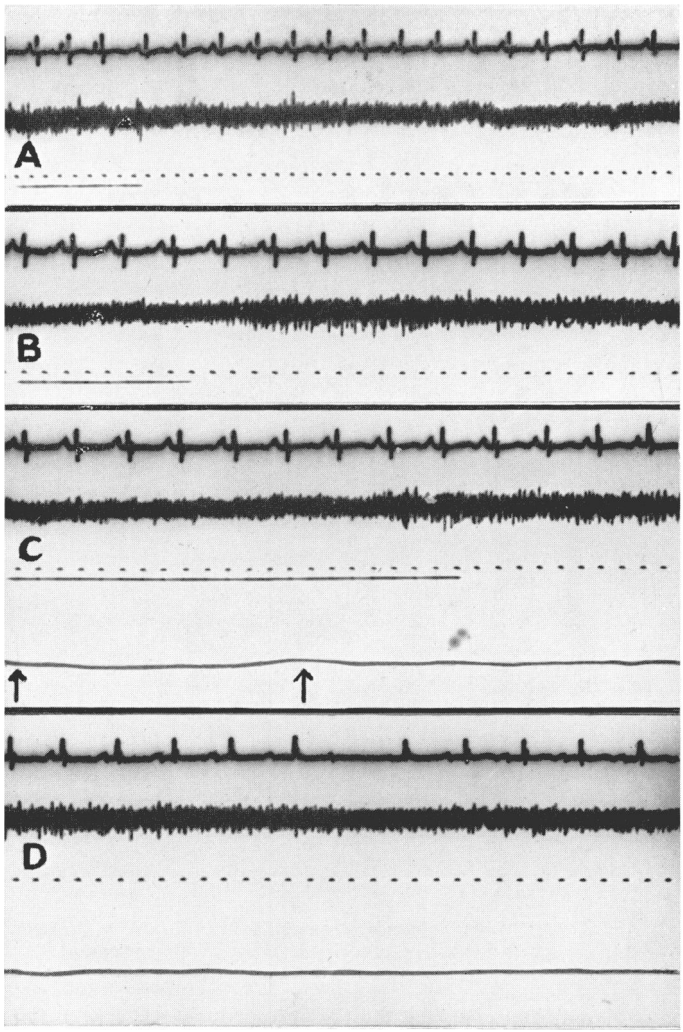

FIG. 9.—Effect of starch and phenyl diguanide on the activity of deflation fibres in the same strand. In A, B and C, 2·5 ml. saline, 175 μg. phenyl diguanide and 4 ml. starch were injected respectively into the right atrium. C and D are continuous. Note that the two drugs stimulate similar receptors. From above downwards in each record: e.c.g.; impulses in fibres; time in 1/10 sec.; injection signal; and in C and D respiratory signal, inspiration (at arrows) upwards. Injection of starch is followed by apnœa.

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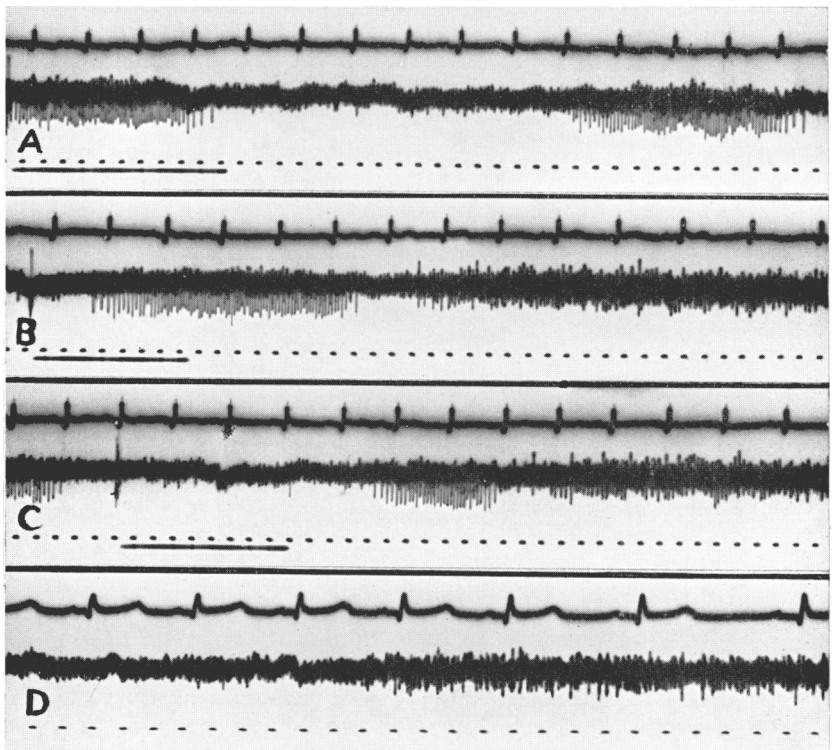

FIG. 10.—Action of HT on deflation receptors. 2·5 ml. saline, 175 μg. phenyl diguanide and 75 μg. HT were injected in A, B and C respectively. Activity is produced in deflation fibres in B and C; the pulmonary stretch fibre, downward monophasic spike, is unaffected. D shows the response in another strand following injection of 20 μg. HT (6 μg./kg.) into the right atrium. Slowing of the heart is clearly seen in B and D.

the soluble substances present in potato extract. This is supported by the fact that the filtrate of the suspension passed through an Eaton-Dikeman (U.S.A.) filter paper No. 613 produced in one cat the same respiratory effects as the suspension itself.

5-Hydroxytryptamine (HT).—Since HT produces reflex responses similar to those of phenyl diguanide [Mott and Paintal, 1953], its effects on the activity in two strands were determined (Table III). In both a discharge of impulses appeared, similar to that produced by phenyl

TABLE III.—RESPONSES OF SOME PULMONARY DEFLATION RECEPTORS TO STARCH, NICOTINE, HT AND PHENYL DIGUANIDE IN CATS WITH INTACT CHESTS

Weight of cat in kg.	Serial no. of strand	Drug	Dose	Injection-discharge time in fibres in sec.	Duration of discharge in sec.	Injection-reflex time	
						Respiratory responses in sec.	Bradycardia in sec.
1·4	5	Phenyl diguanide	225 μg.	2·6	0·4	A 2·7	No bradycardia
		Nicotine	175 μg.	1·0	2·8	A 2·5	,, ,,
2·1	6	Phenyl diguanide	175 μg.	2·0	3·2	I < 2·4	2·5
		HT	75 μg.	2·3	1·8	I < 1·9	3·5
		Nicotine	75 μg.	1·4	0 6	I < 1·7	2·7
3·6	13	Phenyl diguanide	225 μg.	1·6	> 6·0	I 1·7	2·3
		Nicotine	225 μg.	1·4 *	1·6 *	*	2·3 *
		Starch	2·5 ml.	4·1	2·2	I 2·5	4·5
3·6	14	Phenyl diguanide	225 μg.	1·7	2·6	I 1·7	2·7
		Starch	2·5 ml.	3·9	1·8	I > 3·5, < 5·0	5·0
3·6	15	HT	20 μg.	3·0	2·2	I 3·0	3·3
1·9	17	Phenyl diguanide	175 μg.	1·1	1·6	I 1·3	3·1
		Starch	4·0 ml.	1·8	4·2	I < 2·6, > 1·6	3·7

* Recorded with open chest, therefore not comparable.

A, respiratory acceleration; I, respiratory inhibition.

diguanide. Fig. 10D shows that 6 μg./kg. HT can produce a large burst of impulses, so much smaller doses would probably sensitize the receptors, even if they did not stimulate them. The effects of repeated injections were not studied.

Nicotine.—It was shown earlier [Paintal, 1954 *c*] that nicotine stimulates pulmonary phenyl diguanide sensitive receptors—the deflation receptors described here. To confirm this observation the effects of nicotine on the activity of deflation fibres in three strands were determined (Table III). In all a discharge of impulses was produced, and the injection-discharge times following nicotine were much smaller in strands Nos. 5 and 6 than after phenyl diguanide. In one of the strands described previously [Paintal, 1954 *c*] the injection-discharge times following phenyl diguanide and nicotine were respectively 1·7 and 1·2 sec., thus adding weight to the possible significance in the different injection-discharge times.

Reflex Respiratory and Cardiac Responses to Drugs

Respiratory and cardiac reflex responses were recorded simultaneously with the observations of impulse activity in deflation fibres. Additional observations were made separately on cats in which no deflation fibres could be isolated. All these have been put down in Tables I to IV.

Respiratory Responses

The method used in recording respiratory movements permitted only two aspects of these responses to be studied: the injection-reflex time, *i.e.* the interval between the beginning of the injection and the

Table IV.—A Comparison of the Reflex Effects of Starch and Nicotine with those of Phenyl Diguanide

Serial no. of cat	Weight of cat in kg.	Drug	Quantity injected	Injection-reflex time in sec.	
				Respiratory	Bradycardia
2	3·2	Phenyl diguanide	175 μg.	I > 1·1, < 2·5	No bradycardia
		Nicotine	75 μg.	I > 1·0, < 2·5	,, ,,
3*	1·4	Phenyl diguanide	175 μg.	A 1·9	,, ,,
		Nicotine	175 μg.	A 1·6	,, ,,
6	3·1	Phenyl diguanide	175 μg.	I 1·3	2·2
		Nicotine	75 μg.	I 1·1	1·8
7	3·1	Phenyl diguanide	175 μg.	I 2·0	3·3
		Nicotine	75 μg.	I < 2·6	3·7
8	2·8	Phenyl diguanide	175 μg.	I > 1·3, < 2·4	4·3
		Nicotine	75 μg.	I 1·7	No bradycardia
9	2·4	Phenyl diguanide	175 μg.	I 2·0	,, ,,
		Nicotine	75 μg.	I 2·1	,, ,,
11	2·4	Phenyl diguanide	225 μg.	I 2·1	3·9
		Nicotine	75 μg.	I 2·1	3·7
25	3·6	Phenyl diguanide	225 μg.	I 1·7	2·3
		Starch	2·5 ml.	I > 3·5, < 5·0	5·0
		Phenyl diguanide	20 μg.	A 3·2	No bradycardia
		Starch	0·2 ml.	A 3·8	,, ,,
26	3·5	Phenyl diguanide	175 μg.	I 2·5	3·3
		Starch	2·5 ml.	I 4·0	?
		Phenyl diguanide	75 μg.	A 3·5	No bradycardia
29	1·7	Phenyl diguanide	225 μg.	A 2·0	2·3
		Starch	2·5 ml.	A 2·2	No bradycardia

* A clear respiratory inhibition was obtained by 125 μg. phenyl diguanide earlier in the experiment.

I, respiratory inhibition; A, respiratory acceleration.

beginning of the reflex respiratory response of inhibition or acceleration, and the nature of the response (inhibition or acceleration). Unfortunately, it was not possible to study the changes in the functional residual air.

Measurements of the injection-reflex time when the initial response was respiratory acceleration was easy and accurate, as the moment when respiratory acceleration set in could be easily reckoned. This was not so when the initial response was respiratory inhibition, as it is not easy to determine with a single injection the exact moment when respiratory inhibition sets in, unless, of course, the discharges in phrenic motoneurones are recorded simultaneously. Thus, if the respiratory rate is 20/min. and the drug is injected at the beginning of an inspiration, then if the next breath does not appear, it will only be possible to conclude that the injection-reflex time is less than 3 sec. This difficulty was overcome by injecting the drug during different phases of respiration and narrowing down the limits of probability within which respiratory inhibition could have set in. Often, by injecting the drug just before the cat took a breath, it was possible to determine accurately within 0·1 sec. the moment when respiratory inhibition set in, by observing the earliest change in the shape and depth of that breath. In arriving at the statistics of Table I it was possible to obtain such evidence in 12 out of 14 cats. In 2 cats (Nos. 2 and 8, Table III) the average interval between the upper and lower limits was taken as the average injection-reflex time.

Phrenic motoneurone activity was recorded in 1 cat, and in this the moment of respiratory inhibition following phenyl diguanide was accurately determined; the injection-reflex time was 1·7 sec.

Phenyl Diguanide.—The reflex respiratory responses following injection of phenyl diguanide are partly summarized in Table I. The average injection-reflex time was 1·9 sec. agreeing well with the observations of Dawes *et al.* [1951] with 2-α-naphthyl ethyl isothiourea. Under the conditions of the experiment the duration of respiratory inhibition was 4–22 sec. (average 11·6 sec.). It is noteworthy that the figures concerning reflex respiratory responses (Table I) correspond closely to those of activity in deflation fibres.

As a rule, injection of about 200 μg. phenyl diguanide was followed by early respiratory inhibition, and after the apnœa, which lasted 4–22 sec., rapid shallow breathing set in. These observations in general are in agreement with those of Dawes *et al.* [1951]. However, in some cats, *e.g.* Nos. 3 and 29 (Table IV), rapid shallow respiration started from the very beginning with the same dose. This is of course uncommon, but with smaller doses of about 20–40 μg. initial acceleration of respiration is more commonly observed. It is therefore rather interesting that the same drug should produce respiratory acceleration in small doses and inhibition in the expiratory position in larger ones.

When the frequency of respiration was plotted as the reciprocal of the interval between two respiratory cycles the graph shown in fig. 11 was obtained. The same graph also illustrates clearly the phenomenon of tachyphylaxis.

It was possible to produce initial respiratory acceleration even when large doses (500 μg.) of phenyl diguanide were given provided the injection was given slowly. There is thus sufficient evidence to show that the drug under suitable conditions, *e.g.* of dosage and rate of injection, does produce an initial respiratory acceleration instead of the usual inhibition. This fact, not observed by Dawes *et al.* [1951], is of considerable importance (see below).

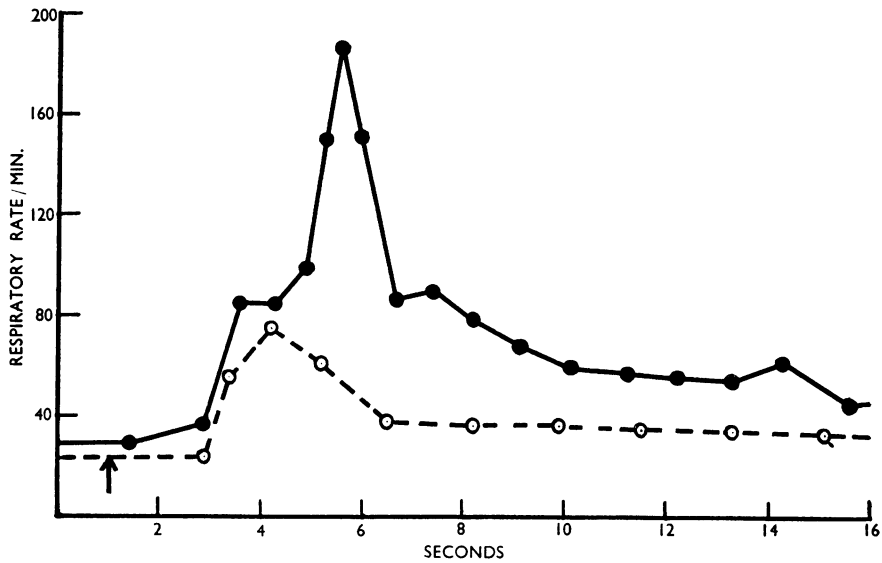

FIG. 11.—Graph of frequency of respiration following injections of phenyl diguanide at arrow. When 225 μg. of the drug was injected about 5 min. after a previous injection, the response shown by - - ⊙ - - ⊙ - - appeared. Injection of the same dose 30 min. after a preceding injection produced a much greater response —●—●—. The graph shows clearly that tachyphylaxis occurs with phenyl diguanide, and that the drug can produce marked respiratory acceleration without a preceding period of apnœa.

Respiratory Responses Following Starch and Nicotine.—It is evident from Table IV that when starch and nicotine are injected in suitable doses, reflex respiratory responses similar to those of phenyl diguanide are produced. In this respect it would seem that 2·5 ml. starch and 75 μg. nicotine are equivalent to about 200 μg. phenyl diguanide. Thus, if phenyl diguanide produced an initial respiratory inhibition in cats Nos. 2, 6, 7, 8, 9, 11 (Table IV), so did nicotine; if acceleration, as in cat No. 3, so did nicotine. A similar parallelism was observed between starch and phenyl diguanide (see cats Nos. 25, 26 and 29 in Table IV).

However, whereas after both phenyl diguanide and starch tachypnœa followed the period of apnœa, after nicotine there was invariably

hyperpnœa instead. Further, with nicotine the duration of apnœa was not greater than 6·0 sec, as compared to that of 4–22 sec. following phenyl diguanide. This inhibition was probably cut short by the respiratory stimulation produced by the action of nicotine on the aortic and carotid chemoreceptors.

An interesting point is the increased injection-reflex time after starch (Tables III and IV), which is probably related to the increased injection-discharge time in the fibres (Table III).

The responses produced by HT have already been shown to be similar to those produced by phenyl diguanide [Mott and Paintal, 1953].

Reflex Bradycardia.—Reflex bradycardia set in about 2·9 sec. (mean of 16 cats) after the beginning of an injection of about 200 μg. phenyl diguanide. This injection-reflex time is longer than the mean injection-reflex time for respiratory inhibition and the mean injection-discharge time in deflation fibres (Table I) by about one second.

Bradycardia also occurred after injection of nicotine or starch. As seen in Tables III and IV the injection-reflex times (bradycardia) after nicotine correspond to those following phenyl diguanide. The injection-reflex times after starch, however, are much greater. It is therefore probable that the increased delay in both reflex respiratory and cardiac responses following starch is due to a common factor—possibly the increased injection-discharge time in the pulmonary deflation fibres.

Like the injection-discharge time in the fibres, the injection-reflex time (bradycardia) was increased by injecting phenyl diguanide during a maintained inflation (Table II). There is no doubt, too, that under the same conditions the degree of bradycardia is reduced and may be abolished altogether. It is therefore certain that at least some of the receptors which produce reflex bradycardia are desensitized by inflating the lungs, and since the deflation fibres described here are similarly affected, it is probable that reflex bradycardia must, at least partly, be produced by them.

It was observed that reflex bradycardia was a weaker response than the reflex respiratory responses produced by phenyl diguanide (Table IV). It often failed to appear although reflex respiratory responses were clearly visible.

Effects of Adrenaline, Glucose and DL-Amphetamine.—In an earlier investigation [Paintal, 1954 *c*] it was shown that adrenaline, glucose and amphetamine did not stimulate pulmonary phenyl diguanide receptors, *i.e.* the deflation receptors described here, and although the respiration and e.c.g. were recorded simultaneously they were not studied in detail. These records have now been closely examined. Six injections of about 100 μg. adrenaline into the right atrium of 4 cats produced no early respiratory responses or early bradycardia. Six injections of 50 per cent glucose 3–5 ml. in 4 cats did not produce an early bradycardia or reflex respiratory responses except in one case in which respiratory inhibition

occurred after three seconds. Finally, three injections of 4 mg. amphetamine in 2 cats also had no effect. The doses of adrenaline and glucose, however, were sufficient to arouse activity in certain gastric stretch receptors [see Table I of Paintal, 1954 *c*]. It is therefore certain that the receptors responsible for producing reflex respiratory and cardiac responses following phenyl diguanide are not stimulated by adrenaline, glucose and amphetamine.

Discussion

Location of Receptors

Since injections of phenyl diguanide into the left atrium or left ventricle do not stimulate the deflation receptors, the possibility of the latter being located anywhere in or in tissues supplied by the bronchial arterial system and broncho-pulmonary shunt is excluded. In this respect the site of the pulmonary deflation receptors is therefore quite different from that of the pulmonary stretch receptors, which have been shown to lie in the intrapulmonary bronchi [Widdicombe, 1954 *b*]. The stretch receptors are more easily stimulated by veratridine when injected into the bronchial arteries than into the external jugular vein.

Since the injection of phenyl diguanide directly into the bifurcation of the pulmonary artery does not alter significantly the nature of the response or the injection-discharge time, the receptors are not likely to be situated at the bifurcation of the pulmonary artery near the arterial ligament, or in the walls of the pulmonary artery near the hilum. The fact that the discharges in the deflation receptors do not show a cardiac rhythm makes this possibility still less likely. The deflation receptors cannot therefore be identified with those described by Larsell [1922] in the pulmonary artery, or with those of Nonidez [1941] and Takino and Watanbe [1937] in the arterial ligament.

After making due allowances for the saline to travel from the femoral vein to the right atrium and from the left atrium to the carotid artery in the figures of Gray and Paton [1949], it is estimated that the pulmonary circulation time, *i.e.* time taken for saline to travel from the right ventricle to the left auricle in the cat, would amount to about 2·5 sec. if the saline were injected rapidly. Since the greatest delay is likely to occur in the pulmonary capillaries, it is likely that by 1·2 sec. the drug will have reached the capillaries, where it could stimulate the deflation receptors near the alveoli. Such receptors have been described by Okamura [1930], Miller [1950], and earlier by Berkley [1893]. It is also conceivable that intense pulmonary congestion leading to capillary distension could stimulate the receptors in this region, thus explaining the occurrence of occasional impulses and sensitization of the deflation receptors in the cat following occlusion of the left a–v junction.

There are two possible explanations for the respiratory fluctuations in the discharge of impulses following phenyl diguanide in cats with open chests. It is possible that respiratory movements by producing fluctuations in pulmonary blood flow or pressure may exert a mechanical influence on the receptors. In the closed chest it is known that increased pulmonary arterial pressure and flow occur during inspiration [Pearce and Whitteridge, 1951; Baxter and Pearce, 1951] but no significant changes have been reported with the open chest. Pulmonary congestion can lead to feeble responses in the receptors and can sensitize them also, but the responses are not comparable in magnitude to those seen during collapse and inflation of the lungs. The more likely explanation, therefore, is that the receptors are stimulated by mechanical deformation produced by collapse of the lungs. Just as the pulmonary stretch receptors signal the state of inflation of the lung, the deflation receptors could serve to signal deflation; but in the cat this cannot be carried out satisfactorily, as the discharges in the receptors adapt rapidly and it is possible to stimulate the receptors only by rapid and complete collapse.

That deflation of the lungs sensitizes the receptors satisfactorily explains the marked difference in the mean injection-discharge times with open chests and closed chests (Table I). The open-chest measurements were all made while the lungs were collapsed. With intact chests the lungs are normally always partially distended, having a certain functional residual capacity. If, therefore, it is borne in mind that there is probably an inverse relationship between the degree of pulmonary collapse and the concentration of the drug required to stimulate the receptors, and that the concentration of the drug at a particular point of the circulation gradually rises to a peak [Gray and Paton, 1949; Pearce, Lewis and Kaplan, 1952], the difference in the mean injection-discharge times is explained. Hence, the shortest injection-discharge time would be obtained by timing the injection such that the drug reaches the receptors at a moment when they are maximally sensitized by a rapid collapse following upon a previous inflation.

Different fibres in the same strand have different injection-discharge times (fig. 2B). This is explained chiefly by the differing blood flow in different parts of the pulmonary circulation, for which there is much evidence [Wearn *et al.*, 1934]. Perhaps small differences in the magnitude of distension of different parts of the lungs may also play a part.

The deflation receptors described in this paper bear no relation to the so-called deflation receptors described earlier [Paintal, 1953 *b*]. Some of the latter appear to be more closely related to the slowly adapting bronchial receptors described by Widdicombe [1954 *a*]. In the present investigation a gastric stretch fibre which at one time became active during expiration was encountered while the stomach had been partially distended. Gastric stretch fibres which show a

respiratory rhythm are no doubt rare [Paintal, 1954 *b*], but one wonders now whether the so-called deflation fibres which become active during expiration and were illustrated in one of the earlier publications [Paintal, 1953 *b*; fig. 9C] were not, in fact, gastric stretch fibres!

The majority of the fibres firing on suction of air from the trachea described by Adrian in the cat [1933] were not rapidly adapting, and further, since there was a cardiac rhythm in their impulses, his fibres bear no resemblance to those described in this paper. Perhaps, as pointed out by Widdicombe [1954 *a*], Adrian's deflation endings were really slowly adapting bronchial receptors.

Rôle of Deflation Receptors in Respiratory and Cardiac Reflexes

The results of this investigation and others [Dawes *et al.*, 1951; Mott and Paintal, 1953] suggest that the afferent mechanism(s) responsible for producing early reflex respiratory inhibition by drugs should satisfy the following conditions. (1) Many of the receptors should be stimulated within 1·9 sec. following injections of phenyl diguanide—this being the average injection-reflex time. (2) That the afferent fibres connected to the endings should be of small diameter, as the reflex is not blocked by cooling the vagi to as low as 3° C. [Dawes *et al.*, 1951]. (3) That, in addition to phenyl diguanide, HT, nicotine and potato starch should stimulate the receptors, since all four of them produce early respiratory inhibition. (It would be unwise to assume as many different receptors as there are drugs that produce respiratory inhibition!) (4) That adrenaline, glucose and amphetamine should not stimulate the receptors since they do not produce early reflex respiratory inhibition.

The pulmonary deflation receptors satisfy these conditions perfectly. They are of small diameter, and since they have a mean injection-discharge time of 1·9 sec., it is evident that many fibres will be active by that time; phenyl diguanide, HT, nicotine and starch stimulate these receptors and, as shown before, adrenaline, glucose and amphetamine do not do so [Paintal, 1954 *c*]. Further evidence in support is that the increased injection-discharge time in the deflation fibres following starch is accompanied by an increased injection-reflex time (Table III). Gastric and intestinal receptors which are stimulated by phenyl diguanide [Paintal, 1954 *c*] probably play no part in this reflex, as injection of the drug into the left atrium does not produce the reflex [Dawes *et al.*, 1951]. On the other hand, other pulmonary receptors yet unknown but sensitive to phenyl diguanide may be concerned.

Since smaller doses of the drugs (phenyl diguanide, etc.) produce early respiratory acceleration instead of inhibition, it is reasonable to conclude that the receptors produce respiratory acceleration when they are less active. This view also explains the later rapid shallow breathing

following starch, phenyl diguanide and HT which occurs at a time when the receptors are considerably sensitized (Table I). The same table shows, however, that the discharge in the deflation fibres studied with intact chests lasts on an average for 5·7 sec. although the mean duration of respiratory inhibition is 11·6 sec. Undoubtedly this is not in keeping with the hypothesis regarding the cause of the rapid shallow breathing. However, the increased base-line noise which continues for longer intervals, and which in fact constitutes evidence for the largest number of deflation fibres encountered, provides support for the hypothesis. Again, one would expect that respiratory acceleration should precede the inhibition (which is observed but rarely) following a rapid injection of phenyl diguanide. This discrepancy is explained by the fact that the activity in the fibres rises to a sudden peak (figs. 5, 7, 8); the respiratory centre is therefore suddenly flooded with impulses in a fraction of a second whereas it was receiving few, if any, impulses before that. If, however, the receptors are gradually stimulated by a slow injection, then the initial response *is* acceleration even if the quantity of the drug injected is large.

It is therefore suggested that the deflation receptors are primarily responsible for producing reflex respiratory acceleration, and that this response becomes an inhibition when the receptors are greatly active. Since rapid breathing above a certain rate must occur at the expense of depth, rapid shallow breathing results. However, the reflex is essentially inhibitory in nature.

Reflex Bradycardia

Dawes *et al.* [1951] showed that the bradycardia following phenyl diguanide is of reflex origin. Since the early bradycardia produced by nicotine, HT and starch is similar to that of phenyl diguanide, it is assumed that the bradycardia of the latter drugs is also probably of reflex origin. These studies of reflex responses reveal that the afferent mechanism responsible for reflex bradycardia should have the following features. (1) The receptors should be stimulated by phenyl diguanide before 2·9 sec., this being the average injection-reflex time for bradycardia. Dawes *et al.*]1951] found the injection-reflex time ranged from 1·9 to 2·5 sec. (2) The receptors should be stimulated by phenyl diguanide, nicotine, HT and starch. (3) The receptors should not be stimulated by adrenaline, glucose and amphetamine as these drugs do not produce *early* reflex bradycardia. (4) The afferent fibres concerned should be blocked gradually between 10°–2·5° C. as would be expected from the observations of Dawes *et al.* [1951]. (5) The receptors should be desensitized by inflation of the lungs, as injection of the drug during inflation increases the injection-reflex time (Table II) or abolishes the response.

Once again the deflation receptors seem to satisfy all these requirements, and we are therefore forced to the conclusion that the same afferent mechanism is responsible for producing both respiratory and cardiac reflexes. This conclusion is contrary to that of Dawes *et al.* [1951], who felt that two sets of afferent fibres were involved because (1) the two reflexes can be dissociated by selective cooling of the vagi, (2) they differ in their relative size from time to time in the same animal, and (3) various active amidines differ greatly in their ability to elicit the two types of reflex responses.

It is known that the different types of afferent fibres in the vagus have a wide range of conduction velocity [Paintal, 1953 *b*], and probably the same is true for the deflation fibres. The results of this investigation have shown that reflex bradycardia is a weaker response than the reflex respiratory responses, and if we believe that one afferent mechanism is largely responsible for both reflexes, it is now possible to give another explanation for the dissociation of the two reflexes by selective cooling of the vagi: progressive cooling would block more and more fibres until at about 3° C. the number of unblocked fibres would only be sufficient to produce the respiratory reflexes and not bradycardia.

The second point has been confirmed in this investigation. Tables III and IV show with one exception that when a drug produces an early respiratory acceleration instead of inhibition there is no bradycardia; and that there may be no bradycardia in spite of respiratory inhibition being present. These facts are conveniently explained on the basis that it requires a greater amount of activity to produce reflex bradycardia than reflex respiratory responses. It is therefore understandable if phenyl diguanide produces an early reflex respiratory response and not a reflex bradycardia, but the reverse is not! Fig. 9 of Dawes *et al.* [1951] shows that the latter phenomenon, *i.e.* bradycardia without a respiratory response, can occur following phenyl diguanide. Since I had never come across this, I re-examined all my previous records, and in none of the 45 injections of phenyl diguanide in 19 cats was this phenomenon observed. As shown by Dawes and Mott [1950], depth of anæsthesia plays an important part in the production of these reflexes.

There is thus much evidence in favour of the view that the deflation receptors are largely responsible for the reflex respiratory responses and the reflex bradycardia following injection of phenyl diguanide. Other types of receptors may no doubt be concerned. Reflex vasomotor activity was not studied in this investigation, but since Dawes *et al.* [1951] have shown that this is closely related to reflex bradycardia, it is possible that the deflation receptors play some part in producing vasomotor reflexes as well.

Like many other types of pulmonary receptors [Knowlton and Larrabee, 1946; Widdicombe, 1954 *a*], the pulmonary deflation receptors also play no part in eupnœic breathing, but it is possible that a

few impulses may be produced in hypernœa when the lungs are deflated more rapidly. On the other hand, the receptors may well play a dominant rôle in certain pathological states accompanied by collapse and/or congestion of the lungs. Several people from time to time have been forced to postulate the existence of reflex mechanisms to explain the dyspnœa in pathological states [for a comprehensive list of references see Christie, 1938; Altschule, 1950]. Since the possibility of the pulmonary stretch receptors [Adrian, 1933] playing a significant rôle in this has been largely ruled out [Bülbring and Whitteridge, 1943; Walsh, 1947; Whitteridge, 1948], the deflation receptors are in an advantageous position in this respect.

A point to be borne in mind is that the receptors are stimulated by small quantities of HT and that they will be sensitized by much smaller quantities, and since it is now known that HT is a normal constituent of the blood [Gaddum, Hebb, Silver and Swan, 1953; Bigelow, 1954], it may be worth while to study the concentration of HT in various pathological states accompanied by dyspnœa.

Starch Embolism.—Torrence and Whitteridge [1947] showed that the rapid shallow breathing of starch embolism survives cooling of the vagi to 6° C. The deflation receptors are clearly stimulated by injection of potato starch, and since these fibres will surely survive cooling to 6° C., we now have at least one set of receptors to explain the phenomenon. There may be others. The initial respiratory inhibition following a rapid injection (this will not occur with a slow injection of even large quantities of starch) can be explained by the sudden outburst of impulses in the deflation fibres, and the much reduced activity later on will explain the rapid shallow breathing. If pulmonary congestion also occurs, the rapid shallow respiration will last longer owing to the sensitization of the receptors by the congestion. In this connection it would appear that there are other receptors in the pulmonary vascular bed which may also be involved, since raising the pulmonary arterial pressure in the dog leads to tachypnœa [Aviado *et al.*, 1951]. Perhaps the pulmonary arterial pressure receptors recently found by Swan and Whitteridge [1953, personal communication] may be directly concerned.

It is not always safe to apply the results obtained in one animal to another, but the likelihood of the deflation receptors described here in the cat existing also in the rabbit is great, as indeed also in other mammals. If it is assumed that phenyl diguanide exerts its reflex effects by stimulating these receptors in the rabbit, then certain differences in the organization of the respiratory centre are brought about [see Dawes *et al.*, 1951]. Whereas the activity in deflation fibres produces arrest of respiration in the expiratory position in the cat, the arrest occurs in the inspiratory position in the rabbit. On the other hand, functionally different afferent fibres, such as the excito-inspiratory

ones, may be predominantly concerned, or it is possible that several different types of fibres are involved; undoubtedly exhaustive experiments on rabbits will be necessary to clear up these points.

Summary

1. The endings of certain vagal afferent fibres have been located in the lungs, using the method of locating visceral receptors described recently [Paintal, 1954 *a*). These receptors were sensitized specifically by pulmonary deflation.

2. The fibres were found to be normally inactive. With the cats' chest intact it was sometimes possible to evoke a rapidly adapting discharge of impulses by suction of air from the trachea or by collapse of the lungs with open chest. The receptors were unaffected by anoxia but they could be sensitized by congestion of the lungs.

3. The action potentials of these fibres were the smallest yet observed in vagal afferent fibres; in most deflation fibres the potentials barely exceeded the base-line noise level. It is estimated that the conduction velocities of the majority of the fibres are below 6 m./sec.

4. The receptors were stimulated by injection of phenyl diguanide, starch, nicotine and 5-hydroxytryptamine. Some of the receptors yielded considerably reduced responses following subsequent injections of phenyl diguanide, but the majority of them were little affected.

5. The injection-discharge time following rapid injections of phenyl diguanide into the right atrium of cats with intact chest ranged from 0·9 to 2·7 sec. With open chests the injection-discharge time could be varied by injecting the drug during different phases of artificial respiration; the values were increased when the drug was injected during inflation of the lungs. The drug sensitized the receptors from 7 to 21 sec.

6. Apart from the usual response of respiratory inhibition, phenyl diguanide on many occasions gave rise to respiratory acceleration without the initial period of apnœa. This response could be elicited more frequently by small doses of phenyl diguanide, but it could also be produced by large doses injected slowly.

7. Nicotine, starch and HT gave rise to early reflex respiratory and cardiac responses identical with those following phenyl diguanide.

8. It is suggested that the deflation receptors are primarily responsible for producing reflex respiratory acceleration (rapid shallow breathing) and that they cause respiratory inhibition when greatly stimulated by drugs. They may also take part in the reflex bradycardia following injections of the drugs used in this investigation.

9. The receptors are not connected with the bronchial circulation or with any part of the broncho-pulmonary shunt, but with the pulmonary circulation. They are probably situated near the alveoli.

10. In many cats the deflation fibres were encountered grouped in bundles. At present the only way of isolating them is by injecting drugs which stimulate them.

11. These deflation receptors are quite different from the so-called deflation receptors described previously [Adrian, 1933; Paintal, 1953 *b*].

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