EFFECTS OF DRUGS ON VERTEBRATE MECHANORECEPTORS

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I. INTRODUCTION

Recently Davis suggested that sensory receptors may be regarded as specialized dendritic poles of neurones (51). This implies the existence of a chemical mediator between the external stimulus and the production of a generator potential as suggested in the scheme outlined by Davis in Figure 3 of his review (51) and supported by Koelle (173, 174). So far it has not been possible to establish the existence of a chemical mediator at any vertebrate sensory ending. That acetylcholine might play a part in the normal initiation of sensory impulses has been considered in several reviews and dismissed as unlikely on the basis of existing physiological evidence (68, 74, 111, 112, 201, 252). The histochemical evidence also seems to be equivocal (99, 101, 121, 174, 213, 240). Further, electronmicroscopic studies have so far failed to reveal the presence of vesicle-like bodies, the possible stores of transmitter material, in juxtaposition to the endings (166, 226); this is what one would logically expect if the sensory endings were modified dendrites. Finally, as the present review will show, the generator region of the sensory ending usually has a low susceptibility to the influence of various chemical substances; in fact it is so low that various drugs produce marked effects on sensory receptors without producing any detectable effect on the generator region.

Since a great deal is now known about the neuropharmacology of invertebrate

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sensory cells, which have served as excellent tools for studying neurophysiological processes (48, 76, 77, 78, 83, 84, 89), this review is limited to the effects of drugs on vertebrate mechanoreceptors.

II. GENERAL ASPECTS

Functional parts of an ending. Functionally, a sensory ending consists of two parts, the generator region and the regenerative region (Fig. 1). The generator region is a specialized, terminal, non-medullated region producing graded potentials known as generator or receptor potentials in the case of mechanoreceptors (5, 51, 62, 64, 83, 84, 111, 115, 164, 205, 206, 207, 283, 323). The regenerative region as here defined is the initial part of the sensory nerve fibre where the propagated impulse is initiated; in the case of medullated fibres, it is the first node (51, 62, 63, 64, 205, 208, 209, 212, 214). In the case of non-medullated nerve fibres this region must be assumed to be a poorly defined central part of the nerve fibre (Fig. 1). Because of this difference in the regenerative regions it is considered desirable to describe the responses of endings with medullated and non-medullated nerve fibres separately.

Any drug may act at either one or both of these functional subdivisions of the ending and the responses observed in the nerve fibres centrally, therefore, must represent the net effect on both regions, in addition to any other effect on the more central part of the nerve fibre. Such net effects may be of the following types: 1) Stimulation: production of impulses in the absence of any added natural stimulus, *e.g.*, stimulation of pulmonary stretch receptors by veratrum alkaloids (57, 224, 252, 254). 2) Sensitization: increase in the frequency of discharge for a given natural stimulus, *e.g.*, sensitization of pulmonary stretch receptors by volatile anaesthetics (252, 254, 315, 316) (Fig. 2). 3) Stimulation and sensitization, *e.g.*, effect of phenyldiguanide on pulmonary deflation receptors (249, 253). 4) Stimulation and desensitization, *e.g.*, effect of veratrum alkaloids on pulmonary (Fig. 2) atrial and gastric stretch receptors (252, 254). 5) Finally, the endings may

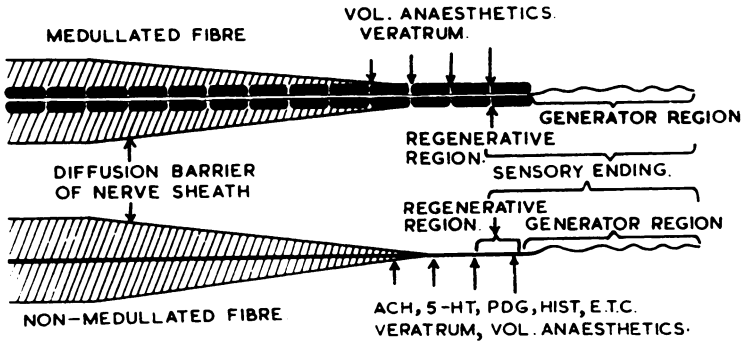

FIG. 1. Schematic diagrams of sensory endings of medullated and non-medullated nerve fibres showing the two parts of an ending and the probable site of action of drugs at the regenerative region, where there is no diffusion barrier.

A greater variety of drugs affects the endings of non-medullated fibres because the fibres themselves are more susceptible to these drugs.

be depressed. This may consist of reduction of the tonic discharge with or without sensitization or desensitization.

The above terminology describes how the total response of the ending is altered without any implication as to the way in which the effect is brought about. Along with information about changes in threshold it provides a satisfactory account of changes in the input into the central nervous system produced by a drug.

In describing the effect of a drug on an ending it is necessary to distinguish between primary effects and secondary effects due to changes in the tissue in which the endings lie and to which they are functionally connected. Examples of secondary effects are the excitation of carotid baroreceptors by topical application of adrenaline (132, 133, 190, 192), excitation of endings of muscle spindles by acetylcholine and succinylcholine (107, 109, 125, 137, 298, 310), and the excitation of pulmonary stretch receptors by adrenaline, histamine, and acetylcholine (318) and by pulmonary congestion (42, 219). When such secondary effects are excluded it follows that the drug must have a direct action on the ending.

It is conceivable that excitatory drugs may produce their effects by an action on the generator region as believed by Gray (111). Thus stimulation may be due to depolarization of the generator region; sensitization can be accounted for by an increase in the size of the generator potential for a given stimulus. Alternatively the drugs may act on the regenerative region; the latter may be depolarized by an excitatory drug to such an extent that it gives rise to repetitive activity in the presence of a constant generator potential. The threshold of the regenerative region may be lowered and its accommodation reduced; this would account for sensitization, or if the threshold is unchanged, as in the case of the effect of volatile anaesthetics on pulmonary stretch receptors (section III E), the sensitization may be due to enhanced recovery of the ending, as noted recently by Gill (102). Similarly, sensitization of endings of muscle spindles by adrenaline or sympathetic stimulation (139) could be due to the enhanced recovery of the ending that is known to occur initially (257).

What is enhanced recovery of the ending? Enhanced recovery of an ending means that a given natural stimulus is able to produce an impulse after a shorter delay following an antidromic impulse (257), or following an orthodromic impulse (36) since the effects of the latter are identical with those of an antidromic impulse in the presence of a constant discharge (256). This reduced stimulus-impulse latency increases the frequency of discharge.

The enhanced recovery of the ending could be due to increased recovery of either one or both of its functional segments. Thus, it could be due to enhanced recovery of the regenerative region; this might lead to a reduction in the relative refractory period, or, if this is unchanged, to a greater rate of recovery in the initial part of the recovery cycle; in either case threshold excitability of the regenerative region will be attained after a short interval following an antidromic impulse. Alternatively, enhanced recovery could be due to increased recovery of the generator region. The following account indicates the relative contribution by the two regions to the recovery of the ending.

Following an impulse, recovery in mammalian A fibres is complete by about

60 msec (97, 98). If this is also assumed to apply to the first node, then recovery of the first node will be an important factor in determining the time of initiation of the next impulse soon after the first, as in Pacinian corpuscles (113) and muscle stretch receptors (256). This will also determine the frequency of discharge of the ending at frequencies above 16/sec. It also follows, as shown by Hodgkin (134) in the crab axon and subsequently by others (37), that when the rhythmic discharge is of a low frequency the recovery of the fibre cannot be the determining factor. For example, Matthews (221) has shown that in the case of muscle stretch receptors firing rhythmically at about 7/sec, the arrival of an antidromic impulse at the end of an impulse cycle delays the appearance of the next impulse by a whole cycle, *i.e.*, by about 140 msec. No positive afterpotential is known to last so long in mammalian A fibres and it lasts much less in the case of the large fibres of muscle stretch receptors (138, 140). It must, therefore, be assumed that the threshold of the first node recovers fully long before 140 msec; this means that the generator region continues to be depressed for a considerable period after the first node has recovered. This becomes more convincing when one considers resetting of the rhythm in endings firing at about one to two impulses per second.

The conclusion that individual antidromic impulses depress the ending also by invasion of the generator region (or by some other effect on it) is therefore inescapable. This is an important point to be kept in mind when interpreting the effects of drugs, because if a drug acts by generating impulses at the first or second node, these impulses will depress the generator region and thus influence the response of the generator region to a natural stimulus. As shown in section III D this is probably the way in which veratrum desensitizes the ending and stimulates it simultaneously. In this connection it is well established that repetitive antidromic stimulation depresses the ending (34, 67). This depression depends on the frequency and duration of antidromic stimulation (257). It was suggested (257) that this depression was due to the production of the pronounced positive afterpotentials following repetitive stimulation (97) for which direct evidence has been provided by Loewenstein and Cohen (210, 211). Since the effect of orthodromic impulses is similar to that of antidromic ones, it follows that repetitive orthodromic stimulation will also depress the ending. However, in the latter case depression will be greater because of the depression produced by the added generator potentials themselves (35, 62, 158, 209); this latter factor will be absent in the case of a regular orthodromic discharge produced by a constant natural stimulus. Loewenstein and Cohen have shown clearly that repetitive orthodromic stimulation depresses the generator region as in the case of antidromic stimulation, but, curiously, in some experiments they observed facilitation (211). The authors provide different explanations for the facilitation and depression, but they do not say why they got depression in some experiments and facilitation in others.

The depression of the generator region by an impulse whether antidromic or orthodromic is well known (62, 84), although under certain circumstances it does not seem to occur (*cf.* Figs. 12 and 13 in 209). This depression could be a consequence of afterpotentials at the first node, but it would now seem from the

observations of Hunt and Takeuchi (142, 143) and Ozeki and Sato (242) that it may be due to actual invasion of the non-medullated generator region by an antidromic impulse. There is other evidence to show that antidromic impulses might invade the generator region normally and that this invasion ceases during the later stages of asphyxia (257). In this connection a point not stressed sufficiently in the original paper (257) is that the apparently increased recovery during asphyxia in some fibres occurred gradually in stages. This is shown in Figure 6 of that paper (257), where there is one point before the antidromically conditioned pull-impulse latency begins to run parallel with the pull-impulse latency. Other fibres show much better evidence of gradual increase in recovery. Such evidence, therefore, greatly favours the postulate that the antidromic impulse ceased to invade the non-medullated generator region and that this leads to enhanced recovery. If this was due to block of the antidromic impulse at the point of branching of the sensory fibre, the enhanced recovery would take place in one step and not in stages.

Site of action. The structure of the regenerative region of the ending is similar to that of the rest of the central nerve fibre (275). Therefore, since certain drugs have no effect on nerve fibres when injected into the circulation, but have an effect on the sensory ending, it is thought that the drug must be acting on a specialized region (the generator region) of the sensory ending (60, 69). While this is possible, it will become evident from the following section on local anaesthetics that it is more likely that injected drugs produce their effects by acting on the regenerative region of the ending. The differences in the response to drugs between the regenerative region and the central fibre are apparently due to differences in the diffusion barrier in the two cases (Fig. 1). This diffusion barrier is formed by the nerve sheath (46, 47, 86, 87, 183, 184, 185, 293, 294), whose structure is now well known (95, 267, 305). Thus, whereas the perineurium of a main nerve trunk may consist of 4 lamellae (Fig. 8 in 267), that of thin filaments consists of only one lamella (Fig. 10 in 227 and Fig. 7 in 267). It is possible that eventually as the fibres proceed alone to their terminations, they lose their sheath, or the sheath becomes so ineffective as to expose the fibre directly to the tissue fluid. As a matter of fact, Pease states that near the nerve terminals one does find naked nerve fibres but just when and where the perineurium drops off is not clear (266). This point urgently needs study.

III. ENDINGS WITH MEDULLATED FIBRES

A. Local anaesthetics

Procaine in vitro. Katz has shown that after soaking the isolated frog muscle spindle preparation (164) in 0.1% procaine for several minutes, only a single impulse can be produced by stretching the muscle, as compared to the prolonged train of impulses that is generated normally (165). With 0.2% he found evidence of a residual non-propagated spike and with higher concentrations all signs of excitatory activity usually became extinguished. On the other hand, the prolonged generator potential produced by a constant stretch was unaffected by concentrations up to 0.3%; with 0.4% to 0.5% it was somewhat reduced (165).

Similar observations have been made by Ottoson (241). It is clear from this that in order to affect the generator region one needs a concentration at least 4 times that needed to affect the regenerative region because, if 0.1% procaine permits the generation of only one impulse, owing to increased absolute refractory period (see below), then a much lower concentration will be required to reduce the peak frequency of discharge by only a small amount. Somewhat similar observations have been made on the Pacinian corpuscle (156). In the perfused preparation of the Pacinian corpuscle, Diamond *et al.* (63) found that while the impulse was abolished by procaine at a concentration of 0.013 to 0.075%, this concentration had practically no effect on the generator potential. Diamond *et al.* suggested that this difference between the generator region and the regenerative region is due to the non-medullated generator region lying in a non-vascular area. However, the first node is also intracorpuscular (275). Again this explanation cannot be applied to the endings of the muscle spindle, in which both the regenerative region (first node) and the generator region lie inside the capsule and therefore have a common diffusion barrier (225, 277, 278) to the solutions in the bath. Finally, the argument breaks down in the case of the crayfish stretch receptor, in which Eyzaguirre and Kuffler found that procaine abolishes the impulse in concentrations that leave the generator potential unaffected (83).

It should be pointed out that the difference in the relative susceptibilities of the generator and regenerative regions to procaine is so marked in sensory receptors that this property is used as a means of studying the generator potentials in isolation (62, 64, 84, 115, 156, 158, 209, 241). If this is the position concerning drugs that depress activity, as well as low sodium (63, 241), it follows that excitatory drugs should also be expected to show the same differential effect, *i.e.*, they should act first on the regenerative region, and in higher concentrations, or after action for a longer time, on the generator region.

Procaine in vivo. Intravenous injections of procaine (223, 264, 326) and similar local anaesthetics consistently reduce the tonic discharge where it exists and simultaneously desensitize the endings, *e.g.*, pulmonary stretch receptors (27, 181, 223, 264, 276) and presumably also Widdicombe's slowly adapting bronchial receptors (317), since these cannot be distinguished functionally from pulmonary stretch receptors (261). Other endings affected by local anaesthetics are systemic arterial baroreceptors (196, 329), cardiac receptors (6, 285, 332), intestinal receptors (15, 16, 222, 326), muscle stretch receptors (14, 196), and endings in teeth (311). These results leave no doubt that procaine (or other local anaesthetics) acts directly on the ending. Since the experiments *in vitro* discussed above show clearly that procaine has a selective action on the regenerative region, it follows that the same must be true with intravenous procaine. This means that procaine must reach an adequate concentration in the tissue fluid around the regenerative region for depressing this region. Since the usual dose adequate for depressing the pulmonary stretch receptors is about 10 mg/kg (223, 264), it is estimated that after dilution with blood the slug of procaine will be diluted to about 0.1 to 0.2%, in the blood of the capillaries and therefore in the tissue fluid for a short period of time. This is the concentration of procaine that

blocks the regenerative regions of sensory receptors *in vitro* (63, 165). As calculated by Wagers and Smith (311) the concentration will be much smaller after dilution in the tissue fluids.

During the period of action of procaine at the ending, conduction in the central part of the afferent fibre is unchanged (264). The observations of Wagers and Smith (311) would lead one to the same conclusion if one could be certain that their electrical stimulus stimulated the same structure (either ending or nerve fibre) each time. Since the concentration of procaine in the blood supplying the central part of the nerve fibre must be the same as that supplying the peripheral part, the question arises as to why procaine is able to act on the peripheral part of the sensory fibre, *i.e.*, the regenerative region, without affecting the central part. The reason for this is that, as already pointed out, the nerve sheath acts as a strong diffusion barrier, and therefore procaine does not reach an adequate concentration in the tissue fluid surrounding the nerve fibre in the main nerve trunk. In the periphery, the perineural sheath is very thin and the nerve fibre is, therefore, quickly exposed to the concentration of procaine in the blood. This difference in the diffusion barrier at the central and peripheral parts of the nerve fibre was excluded in recent experiments in which procaine was slowly infused into the arterial circulation. This helped to maintain a relatively constant concentration of procaine during study of the responses of the endings and conduction in the central and peripheral parts of their sensory nerve fibres (264). Under these conditions it was found, occasionally, that the endings continued to discharge impulses at a time when conduction in the central part of the sensory fibre was much impaired. In fact, in some experiments the discharge ceased simultaneously with occurrence of conduction block in the central part of the nerve fibre. The discharge reappeared as soon as the central block was overcome on stopping the infusion. The difference between the effect of an intravenous slug of procaine and of infusion is due to the greater amount of time available for diffusion of procaine as compared with that following injection of a slug of procaine.

The observations with procaine thus reveal the important new finding that drugs must reach higher and higher concentrations in the tissue fluid surrounding the nerve fibers as the periphery is approached because the diffusion barrier becomes weaker and weaker.

Two important conclusions now emerge. One is that nature has considered it desirable to leave the terminal portions of nerve fibres exposed to the action of substances in the blood. The other is that, unless otherwise proved, one would have to assume as a working hypothesis, that if a drug acts on a sensory ending, it does so by an action on the regenerative region. The juxta-regenerative region of the nerve fibre must be affected in the same way by the drugs, but since this region is beyond the influence of the generator potential, which is analogous to a test stimulus, the effect of the drug here cannot be revealed so readily.

Mode of action. The desensitization and the reduction in the resting discharge of various receptors by local anaesthetics (13, 14, 15, 16, 27, 120, 181, 241, 276, 327, 328, 329, 330, 331, 332, 333) can be explained on the basis of what is already known about the action of local anaesthetics on nerve fibres (40, 58, 65, 96, 182,

280, 291, 292, 295, 306, 309). Local anaesthetics raise the threshold of nerve fibres and, as shown by Tasaki *et al.* (303, 304), the maximal frequency of repetitive excitation of a narcotized nerve fibre depends on the rate at which the threshold of the fibre falls after an impulse, and on the rate at which the size of the action potential increases during the refractory period; when the size of the latter equals the threshold at that time, an impulse is generated. In the case of sensory endings the situation is different, because here the excitatory stimulus, *i.e.*, the generator potential responsible for producing the impulse, is unchanged (111, 165). Therefore, the frequency of discharge will be determined by the increase in threshold of the regenerative region (leading to an increased firing height of the generator potential) and by the amount of slowing of recovery of the first node and possibly the generator regions as well. That a rise in threshold of the first node must occur after procaine, is revealed by the fact that in the case of pulmonary stretch receptors the first impulse during inflation is initiated at a higher lung volume (264). Some direct evidence of rise in threshold in the Pacinian corpuscle also exists (64). However, this is not the first change to occur in all experiments, because in some instances the threshold remained unchanged, but the peak frequency of a train of impulses fell; this effect must be due to reduced rate of recovery of the first node (264). This situation will hold only if the concentration of procaine in the tissue fluid near the first node is greater than that at the more central nodes; and this is probably most often the case. Under these conditions the discharge produced by a natural stimulus will be regular but of a lower frequency. If the concentration of procaine is greater at the more central nodes, the discharge will become irregular, because post-impulse recovery of spike height and fall in threshold of these nodes cannot keep up with the impulses coming from the periphery.

Langrehr (196) found that 1 to 5 mg/kg Tessalon (benzonatate) paralyzed lung stretch receptors, baroreceptors, left and right atrial receptors, chemoreceptors, and primary and secondary muscle spindle endings. He also found some indication that the depression was greater in slowly adapting endings than in the rapidly adapting ones, and he said that similar observations have been made by Henatsch and Schulte on muscle stretch receptors. It would be interesting to know what the relative conduction velocities of the fibres of the slowly and rapidly adapting endings were, because, if procaine affects smaller fibres more than the faster ones, then it is conceivable that the fibres of the slowly adapting receptors may have had lower conduction velocities.

That procaine [like phenol (155, 234) and low sodium solutions (22, 236, 308)] affects the fibres of smaller diameter at a lower concentration than that which affects the larger ones is clear from the results of Nathan and Sears (235). Earlier, Everett and Goodsell (81) concluded that in the vagus there was no evidence of differential effect of local anaesthetics based on fibre size. In a subsequent paper, Everett and Toman (82) found that B fibres are the most sensitive and they consistently block first. By B fibres they probably meant fibres with B conduction velocity, *i.e.*, those conducting at less than 14 m/sec (116, 117). As stressed earlier by Erlanger and Gasser (80, 96), the compound action potential can be a mis-

leading index of changes in responses of groups of fibres. This point has recently been clearly demonstrated in experiments on differential block of nerve fibres by cold temperatures (262). It was shown that conduction in all medullated nerve fibres is blocked at about the same temperature, and that the reduction of the delta elevation of the compound action potential of the saphenous nerve before the alpha elevation is due not to block of the delta fibres at higher temperatures, but to the greater dispersion of the delta elevation, relative to the alpha elevation, owing to the much greater increase in conduction time of the delta fibres (262, 263). This defect in the compound action potential technique is not very troublesome while studying the differential effects of local anaesthetics, because the reduction of the conduction velocity by them is of a much lower order than that produced by cooling a 12 mm stretch of nerve (264). In recent experiments on single nerve fibres it has been confirmed that the slower fibres are more vulnerable to procaine than the faster ones. So far no evidence has been available to show that the endings of slower fibres are depressed more than those of faster fibres, but it is hoped that experiments now in progress will yield a firm answer. The conduction velocity of nerve fibres is related to their diameters (144). However, it must be pointed out that although one expects that the diameter of a fibre in the main nerve trunk should bear a relationship to the diameter of the first node, it is also clear that a fixed proportionality cannot exist, in view of recent observations on vagal afferent fibres. These have shown that the intrathoracic conduction velocity is reduced by a variable amount (usually less than 20%) in different fibres (259). In the case of sensory fibres of muscles, the conduction velocity of the fibres inside the muscles is unchanged (256). Another point to be kept in view is that the accommodation of fibres of different diameter is different (282).

There are many drugs with an action similar to that of procaine, some with more desirable effects than others, such as longer duration of action with small side-effects. For a proper description of these the reader should consult the original literature (13, 15, 16, 276, 325, 326, 327, 328, 329, 330, 331, 332, 333). Gamma-amino butyric acid also has a similar action (75).

B. Sympathetic stimulation and adrenaline

Moderate degrees of sympathetic stimulation or small doses of adrenaline cause sensitization and stimulation of sensory receptors and a reduction in the threshold of the endings (33, 79, 139, 203, 208). In several instances the excitatory effects are secondary, *e.g.*, in the case of mammalian cutaneous receptors the excitation is certainly secondary to contraction of the smooth muscles of the skin (69). Similarly, the effect of adrenaline on carotid baroreceptors is due to contraction of the smooth muscle in which the endings lie (60, 132, 133, 192, 320), leading to reduced distensibility of the vessel (189, 190). Apparently these effects of adrenaline are suppressed by adrenergic blocking agents, such as Dibenamine, Regitine (phentolamine), and dihydroergotamine (104, 132) so that it is difficult to find out if adrenaline has any primary excitatory effect on the baroreceptors as well.

The excitatory effect of adrenaline on atrial and ventricular receptors is also secondary to changes in vascular pressures and contractility of cardiac muscle (175, 194, 195, 196, 265). In the case of pulmonary stretch receptors, adrenaline reduces the discharge by reducing bronchial tone (318) or it has no effect (248). Adrenaline and noradrenaline have no effect on carotid chemoreceptors (320), which have medullated and non-medullated nerve fibres (85). This fits in with the interpretation that the increased chemoreceptor activity following sympathetic stimulation (90) is secondary to reduction in blood flow in the glomus (50).

Loewenstein (203) found that the tactile receptors of frog's skin, unlike the stretch receptors of the skin, are stimulated and sensitized and their threshold is lowered by sympathetic stimulation and small concentrations of adrenaline. Since the effective concentration of adrenaline was 0.01 μg/ml (203) this means that the amounts of adrenaline secreted by the adrenal medulla under physiological conditions would facilitate these tactile endings. These experiments of Loewenstein also show that the antidromic stimulation of cutaneous receptors observed by Habgood (119) is due to the simultaneous stimulation of sympathetic fibres. Catton's observations lead to a similar conclusion (35).

There is one preliminary communication by Loewenstein and Altamirano-Orrego (208) on the response of the Pacinian corpuscle to adrenaline. They found that after 1 to 10 μg/ml of adrenaline or noradrenaline the threshold of the ending fell by 10 to 30 % and the adaptation of the ending was reduced. That the ending was sensitized was also shown by the observation that after adrenaline it yielded a short train of impulses instead of the usual single impulse following the stimulus. Assuming that the drug acts on the first node, one can explain these changes by the known effects of adrenaline on nerve fibres, *i.e.*, reduction in threshold (30). However, in procainized preparations they also found that these concentrations of adrenaline and noradrenaline also increased the peak amplitude and rate of rise of the generator potential and sometimes it also increased the decay time of the generator potential. These observations need to be confirmed.

Effects on muscle stretch receptors. The endings of the muscle spindle (21, 33, 79, 139, 257, 270) and, possibly also to a lesser extent, the Golgi tendon organs (79, 272), are unique in that in addition to the excitation by adrenaline or sympathetic stimulation, they are also subsequently markedly depressed (21, 33, 79, 139, 257, 269, 270, 271, 272) and during the period of depression they may also show periods of stimulation (21, 257). These later effects are most probably due to asphyxia produced by vasoconstriction consequent to injections of larger doses of adrenaline (79, 257) or prolonged sympathetic stimulation (33, 79, 139). It is necessary, therefore, to describe the effects of asphyxia before discussing the effects of adrenaline further.

Effects of asphyxia. No sensory ending except the muscle stretch receptors is stimulated by asphyxia. Usually, as in the case of pulmonary stretch receptors described by Adrian (3) the first change is increase in threshold of the ending and soon this is accompanied by desensitization and increase in adaptation rate till all responses in the endings are abolished (3). Such changes have been observed consistently in arterial baroreceptors, type A and type B atrial receptors, ventricular receptors (264), and pressure-pain receptors of muscles (258).

In the case of muscle stretch receptors the events are as follows: on occluding the circulation (79, 221) or stopping respiration (257) the first change is a reduction in the frequency of the resting discharge without any significant initial enhancement (but see 79); soon after, the discharge ceases (221, 257). This period of silence is soon broken by a variable period of intense activity that is characteristic of the response of muscle stretch receptors to asphyxia. As shown by Matthews, such activity may be triggered by applying a brief natural stimulus, or by stimulating the muscle nerve so as to cause a contraction of the muscle (221). In fact, tetanization of the muscle nerve along with occlusion of the circulation causes the excitatory phenomenon to set in much sooner (221). However, this could be considered an effect of contraction of intrafusal muscles because Matthews used supramaximal stimuli while studying this phenomenon and he must, therefore, have stimulated the fusimotor fibres because their threshold is only 3 to 4 times the threshold of motor fibres (107, 198). It is conceivable, as suggested recently by the observations of Kidd (171), that tetanization of fusimotor fibres may have caused a persistent contraction of intrafusal fibres. However, this factor cannot play a part in experiments with occlusion of the circulation (221) or asphyxia (257) without stimulation of the muscle nerve, especially in experiments in which complete neuromuscular block was ensured (257).

It would now appear that this exclusive behaviour of muscle stretch receptors, especially of muscle spindle endings, is due to the diffusion barrier of the capsule within which the endings lie (12, 110, 166, 225). The fact that the capsule could act as a diffusion barrier has been stressed in several recent studies of the ultramicroscopic structure of the endings (225, 226, 267, 268, 277, 278). This being the case it is easy to understand that during stasis of the circulation accompanied by anoxia potassium will leak out of the intrafusal fibres as in the case of extrafusal fibres (43); the potassium will be largely retained within the capsule. This accumulated potassium will then lead to excitation of the first node, which also lies within the capsule (166, 225, 278). Brown and McIntosh have shown that potassium will stimulate nerve fibres in the absence of any added stimulus (25). However, the conditions in the muscle spindles are more favourable because of the static generator potential which must be assumed to be present since it was responsible for the initial resting discharge before onset of asphyxia. From the moment asphyxia starts and for a variable period thereafter, the recovery of the ending is greatly reduced (257).

In view of the above, it is now easy to understand that in the muscle spindles any factor that slows the circulation and causes stasis and anoxia, such as adrenaline or sympathetic stimulation, will produce depression followed by stimulation of the endings.

Sequence of events following adrenaline or sympathetic stimulation. On injection of adrenaline or sympathetic stimulation the first effect is an initial stimulation (21, 33, 41, 139, 257, 269, 270, 271, 272) accompanied by reduction in the threshold (33, 139) and enhanced recovery of the ending (257). Only this effect is produced by small doses of adrenaline (79) or by moderate stimulation of the sympathetic (139, 271). With larger doses, after this initial phase, which is over within a minute of injection, the ending shows marked depression, which consists

of abolition of the resting discharge (21, 33, 79, 139, 257, 269), rise in threshold of ending (33, 139) and greatly reduced recovery of the ending (257). Thereafter, presumably depending on the dose of adrenaline, there may be a period of marked stimulation similar to that produced by asphyxia (21, 257), during which recovery of the ending remains markedly reduced (257). Finally, the effects of the drug wear off gradually.

It is clear that since asphyxia does not produce an initial enhancement, this phase must be a direct effect of adrenaline or sympathetic stimulation. The question to be answered is: is the second phase of depression, with or without a period of stimulation, a direct effect of adrenaline and sympathetic stimulation (33, 139), or is it an effect of asphyxia (21, 79, 257)? Eldred *et al.* (79) and Calma and Kidd (33) found that the second phase (depression) occurred simultaneously with reduction in blood flow to the muscle (33, 79), following larger doses of adrenaline and longer periods of stimulation of the sympathetic. The depression (but not the initial excitation) and the reduction in blood flow could be prevented by prior administration of phenoxybenzamine (79). Calma and Kidd recorded the blood flow simultaneously with changes in the resting discharge and the threshold of the endings of muscle spindles. They found that the changes in the two ran parallel to each other following sympathetic stimulation or injections of adrenaline, *i.e.*, reduction in the resting discharge was always associated with reduction in blood flow (33). Similarly, Bhoola *et al.* (21) found that the effects of 10 to 20 μg of valine 5-angiotensin II were similar to those produced by 10 to 20 μg adrenaline and both produced marked vasoconstriction in the acutely denervated hind limb.

In some experiments in which rather large doses of adrenaline were used (257) the phase of depression set in without the initial phase of excitation. This shows that the depression is not merely post-excitatory, but, as pointed out above, a response to the asphyxia following vasoconstriction. This view is strongly supported by some recent observations of Bhoola *et al.* (21), who found that adrenaline did not give rise to the phase of depression in the isolated tenuissimus muscle of the kitten maintained in oxygenated Locke's solution. Evidence that drugs could enter the spindle in this preparation was obtained by showing that the endings responded in the characteristic manner to succinylcholine added to the bath. Corda and Staderini (41) observed that adding adrenaline to the bath stimulated primary and secondary endings without subsequent depression. Figure 1 of their paper shows that there was depression in the case of one secondary ending, but this could have been post-excitatory depression.

So far the only evidence suggesting that the second phase (depression) following sympathetic stimulation is not secondary to vasoconstriction is that provided by Hunt (139). He showed that the effects of sympathetic stimulation were present in endings of muscle spindles of the tenuissimus muscle *in situ* and suspended in liquid paraffin, but apparently devoid of circulation as revealed by microscopic observation. If this were actually so, the endings should have been showing the effects of circulatory occlusion and asphyxia (33, 79, 221, 257) even before sympathetic stimulation, especially since it is known that oxygen has to be

bubbled vigorously to maintain the resting potential of muscle fibres and prevent the efflux of potassium into the extracellular fluid (43, 44, 45). Even under the best conditions in thin slices of muscles it is not easy to maintain the resting potential of the deeper muscle fibres at a normal level (43, 45). It is conceivable, therefore, that in Hunt's experiments (139) sympathetic stimulation may have merely aggravated the already diminished blood supply.

The infusion experiments of Calma and Kidd (33) are noteworthy because they show that the spindle endings are stimulated and their threshold reduced when adrenaline is infused in amounts normally secreted by the adrenal medulla. However, so far no one has been able to ascribe a biological purpose to the effects of adrenaline or of sympathetic stimulation on muscle spindles (79, 139). In this connection it is necessary to explain the curious dependence of the response of the endings on a critical frequency of stimulation of the sympathetic (139) and a lack of relation between the amount of stimulation and the degree of acceleration of the sensory discharge (79, 139), assuming that acceleration is the significant effect of sympathetic stimulation. As pointed out already, the phase of depression is almost surely a secondary asphyxial effect of vasoconstriction. Terminations of sympathetic fibres have been observed by Barker in the muscle spindle (12), but it is possible that their main function is to innervate blood vessels.

It now remains to explain the initial excitatory action of adrenaline. Bülbring and Whitteridge (30) showed that adrenaline reduces the threshold of nerve fibres; there is also evidence that it might depolarize them (187, 197). Accordingly, it can be concluded that the initial excitation of the endings is due to depolarization and reduction in threshold of the regenerative region, *i.e.*, the first node; this is also accompanied by increased recovery of the first node (257). The second phase of depression is probably due to asphyxial effects on the first node; the subsequent phase of stimulation can be attributed to the accumulated potassium in the intracapsular space of the muscle spindle resulting from the efflux of potassium from the intrafusal muscles following anoxia (43, 44, 45) (see section on asphyxia above).

If the phase of depression is due to vasoconstriction, then it is just possible that the initial excitatory action of adrenaline or sympathetic stimulation might be due to vasodilatation, because it is known that small doses of adrenaline cause vasodilatation (11, 91), an effect that is due to a direct action on the muscle vessels (91) or indirectly through lactic acid production (217). However, one must keep in mind that the sympathetic nerve fibres concerned are apparently cholinergic and so it is remotely possible that the excitation of the sensory endings is due to acetylcholine, even though Eldred *et al.* (79) have shown that the excitatory effects of sympathetic stimulation survive after heavy doses of gallamine diethiodide. The question is, therefore, still open although the experiments of Corda and Staderini *in vitro* would seem to rule out the possibility (41).

C. Acetylcholine and substances with similar action

Effects on endings of muscle spindles. So far it has not been possible to establish whether acetylcholine and related substances act directly on the ending or in-

directly by causing contraction of intrafusal muscle fibres. Hunt (137) concluded that the excitatory effects of acetylcholine were secondary to contraction of intrafusal fibres because these effects were blocked by tubocurarine. So far the only suggestion that succinylcholine might have a dual effect, *i.e.*, also act directly on the endings in addition to excitation through intrafusal fibres, has come from Granit *et al.* (109). However, like other investigators (*e.g.*, 310), Granit *et al.* also noted that Golgi tendon organs were not stimulated by succinylcholine, which suggests that the entire action of this drug may be secondary to muscular contraction. Recently, Verhey and Voorhoeve (310) have shown that endings of group II fibres, *i.e.*, secondary endings, are also stimulated, but much less so than the primary endings. Since the main purpose of such studies (310) is to find out methods of providing selective kinds of sensory inputs to the central nervous system for the study of reflexes, they do not provide critical evidence of site of, or mode of action of, the various drugs tested, *e.g.*, succinylcholine (298, 299, 310).

Evidence for a dual mode of action of acetylcholine and succinylcholine on endings of frog's muscle spindles has been provided by Henatsch and Schulte (125), who found that the effects of both drugs persisted, though much reduced, after complete block of intrafusal neuromuscular junctions (124, 125). However, the concentrations of acetylcholine in the bath were rather high (100 to 300 μg/ml); that of succinylcholine was 1 mg/ml. It is, therefore, possible that the difference in the results of Hunt (137) and those of Henatsch and Schulte (125) may be attributed to the doses used; or it may be a species difference. However, the position is not quite so simple, because Ottoson (240) found that acetylcholine even in concentrations of 1 mg/ml did not excite the endings of the isolated spindle of the frog in which the intrafusal fibres were supposedly destroyed. Neither could Peruzzi and Corda get consistent effects (269). If this is true then it shows that the excitatory effects of acetylcholine (125, 137) are secondary to fusimotor contraction. Unfortunately, Ottoson could not establish the effectiveness of the destruction of the intrafusal fibres, *e.g.*, by stimulating the fusimotor nerve fibres, as he had to destroy the latter before recording the sensory impulses. Ottoson (240) also found that various anticholinesterases stimulated the endings markedly, but the concentrations he used were rather high; presumably, their excitatory action is non-specific.

That the excitatory effect of succinylcholine on mammalian muscle spindle endings may be directly due to intrafusal muscle contractions has been stressed by Smith *et al.*, who found that the effects of succinylcholine could be prevented by ryanodine, a substance that causes contracture of muscle fibres (300). However, such evidence cannot be regarded as conclusive.

Verhey and Voorhoeve (310) found that nicotine had an action like succinylcholine and acetylcholine apparently through a similar mechanism. On the other hand, close arterial injections of muscarine, methyl furmethide, barium chloride, and 5-hydroxytryptamine had no excitatory effect (310).

It is clear that at present there is no firm evidence favouring a direct action of acetylcholine on the endings of muscle spindles.

Cutaneous receptors. Acetylcholine and numerous other substances, some

related in their action to acetylcholine (*e.g.*, nicotine and lobeline) and others totally unrelated to acetylcholine, are known to stimulate cutaneous receptors (24, 28, 29, 69, 88, 150, 162, 273, 274, 321, 324). Atropine does not affect the responses to acetylcholine, but they are blocked by hexamethonium and tubocurarine (69, 111). That this may be a non-specific blocking effect is shown by the observation that effects of acetylcholine are blocked by adrenergic blocking agents such as Dibenamine, Regitine, or Priscoline (tolazoline) (104). The latter also stimulate the endings (104). In all these studies the impulses have been recorded from many fibres simultaneously and they therefore provide no information about the kinds of sensory endings affected. Most important of all, these studies have drawn no distinction between the endings of medullated and non-medullated fibres. Clearly, both types are involved, as revealed by records of sweeps (69) that show that impulses with spike durations of about 1 msec are more numerous than those with spike durations of 0.6 msec; this indicates that activity in non-medullated fibres was more prominent. That there is a pronounced discharge following acetylcholine from endings of non-medullated fibres in general was demonstrated conclusively by the ingenious occlusion technique of Douglas and Ritchie (70).

The relatively little excitation of endings of medullated cutaneous fibres by drugs has been suggested by the experiments of Fjällbrant and Iggo (88), who studied the effects of acetylcholine, histamine, and 5-hydroxytryptamine on the endings of both medullated and non-medullated fibres. They found that hair receptors, touch receptors, and insensitive (*i.e.*, high threshold) mechanoreceptors were unaffected by these drugs. The only ending that was stimulated and sensitized by acetylcholine, histamine, and 5-hydroxytryptamine was the slowly adapting pressure receptor. In this ending excitation was followed by a period of depression, which is a characteristic feature of excitation by drugs. So far no explanation is available to account for the exclusive response of the slowly adapting receptors to drugs. The responses of these endings to natural stimuli have been described by several groups of workers (88, 129, 130, 141, 154, 334, 335). There is no evidence to suggest that these endings are associated with some smooth muscle, nor is there evidence to the contrary. It is important to exclude the possibility that these endings may be excited by acetylcholine owing to a primary effect on smooth muscle, since these are the only cutaneous endings with medullated fibres that are so affected.

In the frog's skin, Jarrett (162) found that 10^{-4} g acetylcholine per ml produced a marked stimulation followed by inexcitability to just supraliminal mechanical stimuli. Perhaps because of this inexcitability, he used a lower concentration (10^{-6}) for studying the mechanism of action of acetylcholine. The largest change he observed was an 8 to 10 % lowering of the threshold of the ending in the best experiments; recovery or time course of excitation was unaffected. Jarrett also concluded that adaptation was increased because the critical slope of the stimulus required for stimulating the ending also increased. Unfortunately, one cannot be certain about this because he could not make control observations after recording the effects of acetylcholine owing to technical limitations. Jarrett concluded that

these results are best explained if it is assumed that the generator region is depolarized; he believes this accounts for the reduced threshold and also for the increased adaptation, which is actually small since a large part of it is accounted for by the rise in threshold. Since there is no resting discharge with 10^{-6} acetylcholine, this means either that the depolarization was subthreshold for producing a train of impulses or that the threshold (or accommodation) of the regenerative region had increased. In the latter case it is difficult to explain the generation of impulses by 10^{-4} acetylcholine. The alternative suggestion by Jarrett may, therefore, be more acceptable, namely, that acetylcholine 10^{-6} lowered the critical voltage at which propagation takes place, *i.e.*, reduced the threshold of the regenerative region. It is easy to understand that higher concentrations of acetylcholine (10^{-4}) will lower the threshold, further resulting in the production of a train of impulses by the existing static generator potential.

Mammalian thermal receptors of the tongue are apparently also stimulated and sensitized by acetylcholine and acetyl-β-methylcholine, but the excitatory responses are variable and at times inconsistent (66). More information is required before anything further can be said.

Visceral receptors. The pulmonary stretch receptors yield an increased discharge on intra-aortic injections of acetylcholine (318). As demonstrated by Widdicombe, this is accounted for entirely by the contraction of bronchial smooth muscle. In fact, after showing that the endings are not located in the visceral pleura as believed by some workers (313), Widdicombe used these responses to establish the location of the endings in relation to bronchial smooth muscles (318).

So far the only known visceral receptors with medullated fibres that are excited by acetylcholine and related drugs are the carotid chemoreceptors (191) and baroreceptors (60, 112, 193, 321). Diamond (60) concluded that acetylcholine and nicotine excited impulses in baroreceptor fibres by a direct action on a peripheral part of the sensory pathway, since he satisfactorily excluded the possibility of an effect due to stimulation of smooth muscle by showing that the response was not affected by atropine. Also, the latency for excitation was much smaller than that following adrenaline (60), which is known to stimulate baroreceptors by causing a contraction of the smooth muscle (132, 133). Diamond found that below 100 μg, the relationship of the peak frequency of discharge to the dose of acetylcholine was logarithmic (60). Presumably, above this dose the response is diminished and at still higher doses, as found by Landgren *et al.*, the resting discharge is abolished (193). However, there are some odd features, *e.g.*, the reduction of the resting discharge by small doses (*cf.* Fig. 2 in 193) in some experiments. So far there is no information about the effect of acetylcholine on the distensibility of the carotid sinus. This would be of considerable help in interpreting the changes in the responses of the carotid baroreceptors.

Gray (111) concluded that the most likely explanation of the action of acetylcholine is that it depolarizes the membrane of the terminal portions of the sensory nerve fibres and that this action is confined to those parts that take part in the generation of the receptor potential. This conclusion of Gray is based largely on

the belief that acetylcholine has no effect on nerve fibres themselves. This belief was based on the rather inadequate evidence that acetylcholine did not initiate any impulses, either in preganglionic fibres (25), or in those of the frog's skin (162). In both instances no suitable test stimulus was applied to the nerve fibres under the influence of acetylcholine. It is still possible that acetylcholine may have a significant action on the first node, which, by itself, may be inadequate to set off a train of impulses, but which may do so with the added stimulus from the generator potential.

The above view fits in with what has already been pointed out in connection with the relative susceptibility of the regenerative and generator regions to drugs (*cf.* section II, section III A).

D. Veratrum alkaloids

The alkaloids of veratrum noted for producing the Bezold-Jarisch effect (20, 160, 179) are apparently the only substances that can excite the sensory endings of all medullated fibres. So far all the endings tested have been stimulated, *i.e.*, endings of muscle spindles (196), although in this case an effect through intrafusal contraction has first to be excluded; cutaneous receptors (273, 322); pulmonary stretch receptors (13, 57, 178, 254, 318); carotid and aortic baroreceptors (159, 319); right and left ventricular pressure receptors (161, 237, 250); type A and type B left atrial receptors (237, 250, 254); and in larger doses, type A and type B right atrial receptors (237, 254). The rapidly adapting pulmonary receptors (172, 317) have not been tested.

Veratrine, a mixture of alkaloids (180), has been used most commonly and it is effective in intravenous doses of 50 to 200 μg (6, 161, 178, 285). Of the individual alkaloids, veratridine has been extensively used in several studies (*e.g.*, 10, 54, 237, 250, 254). The effective intravenous dose is 10 to 20 μg; much smaller amounts are needed when injected close to the location of the endings, of the order of 0.5 to 2 μg (53, 318). Other alkaloids, *e.g.*, germerine, germitrine, and germidine (92, 218), have been used less frequently (254).

In all cases, the characteristic response is stimulation plus desensitization of the ending, *e.g.*, in pulmonary stretch receptors (Fig. 2) (254), atrial receptors (254), and ventricular pressure receptors (250). Proof of desensitization during stimulation exists in the case of pulmonary stretch receptors, where the natural stimulus can be controlled (Fig. 2). Evidence in the case of atrial and ventricular receptors is also strong but of an indirect nature [reduction of peak frequency/lowest frequency ratio (250, 254)]. So far the only known exceptions are the endings of the sternocutaneous muscle of the frog, which are apparently sensitized by topical application of 1:40,000 veratrine (161). However, in this case, it is likely that the effects are also due to contraction of muscle fibres, both extra- and intra-fusal, that is known to be produced by veratrum [see review by Krayer and Acheson (180)].

Veratrum alkaloids are not known to lower the threshold of the endings to their natural stimuli (254). In the case of pulmonary stretch receptors the volume of the lungs at which an increase of the discharge occurs either remains unchanged

(Fig. 2) or is increased (see Fig. 2 in 224). This is an important point to bear in mind when considering the locus of action of the alkaloids and their mode of action.

Another important feature is that the adaptation rate of the endings, which consists of both mechanical and nervous components (114, 135, 186, 202, 204), is not reduced, in spite of the production of a continuous discharge (Fig. 2). In fact, in all instances where this point could be tested, *e.g.*, in pulmonary stretch receptors, the adaptation rate increases (161, 254). In these endings suitable doses of the alkaloids can convert a slowly adapting discharge into a rapidly adapting one. The atrial and ventricular receptors and carotid baroreceptors also respond in a similar way, but quantitative information in their case is not available, because it is not easy to ensure that the natural stimulus of atrial and ventricular receptors remains contant. This is possible in the case of carotid baroreceptors, but no work has been done on them to test this point.

If the quantity of alkaloid injected is large enough, the response of the endings to their natural stimuli is abolished for variable periods (254). As a rule this is not a total block, because a rapidly rising stimulus may yield a few impulses; this indicates that the central parts of the medullated nerve fibres are still conducting. The block is, therefore, a feature of the ending and has to be kept in mind while determining the mode of action of the alkaloids.

One of the most characteristic features of excitation by veratrum alkaloids is the occurrence of cyclical activity (254). This consists of periods of continuous activity followed by variable periods of silence which are in turn followed by activity again, and so on. The durations of the silent periods depend on several factors, such as presence of natural stimuli; in a fibre made silent by the alkaloids a burst of activity can be induced by the application of a natural stimulus (254). The above behaviour is reminiscent of the response of muscle stretch receptors during asphyxia (*cf.* section III B). That asphyxia has no excitatory effect on pulmonary stretch receptors is known (4) and it is, therefore, not surprising that the progress of excitation by veratrum alkaloids is not affected by asphyxia (254).

The latency between injection and the onset of stimulation may vary from 2.5 seconds to 3 minutes in pulmonary stretch receptors. The latency following veratridine is about 5 to 7 seconds in the case of ventricular pressure receptors; following Veriloid (Riker Laboratories) it is 8 to 15 seconds (250). In the case of left atrial receptors the latency following Veriloid is clearly longer, 19 to 70 seconds (250). The latency depends on the presence of activity in the endings normally, and, therefore, in the case of normally silent endings, the latency will depend on the moment of application of a natural stimulus or the occurrence of a period of rhythmic activity. However, in many endings, in spite of the presence of periodic activity, the latency was strikingly large (of the order of minutes); this goes to show that the drug has to have time to produce certain changes at the ending in order to stimulate it (250, 254).

Normally, reduction of calcium depolarizes nerve fibres (286, 301) and sensitizes sensory receptors (26, 202a), whereas increased calcium desensitizes them [*e.g.*, pulmonary stretch receptors (254), carotid baroreceptors and cuta-

neous mechanoreceptors (322), and endings of muscle spindles (26, 202a)]. However, when calcium is injected after the endings have been stimulated and desensitized by veratrum alkaloids, it restores their sensitivity to normal (254) simultaneously with the reduction of the steady discharge produced by the alkaloids (6, 159, 161, 254, 285, 322). On the other hand, sodium citrate, which acts by lowering the concentration of calcium (161) and which normally sensitizes carotid baroreceptors and stimulates them (322, 329), enhances the effects of the veratrum alkaloids (159, 161, 254). When given after the normal behaviour of the endings has been restored by calcium, sodium citrate precipitates the effects of the alkaloids (159, 161, 254, 329).

Local anaesthetics, *e.g.*, procaine (223, 224, 326), fagarin (an alkaloid of *Fagaro coco*) (223) and Tessalon (benzonatate) (196, 326), and several other substances (326, 327, 328), reduce or abolish the excitation produced by the alkaloids. Since procaine (and presumably other local anaesthetics) is known to act on the regenerative region (section III A), the alkaloids also may act on the regenerative region, *i.e.*, the first node.

One curious feature of stimulation by veratrum alkaloids is that the right atrial type A and type B endings require much larger doses than the left atrial ones to stimulate them (237, 254) although the endings in the two respective chambers are identical in nearly every way, *e.g.*, histologically (39, 238, 239). Also the conduction velocities of their fibres are similar (243, 245, 260, 261) and their responses to natural stimuli are identical apart from slight variability due to differences in venous filling of the two chambers (243, 260, 314). Also, the circulation in the walls of the two chambers is the same (312). So far the only explanation that can be advanced for the lower sensitivity of the right-sided endings to veratrum alkaloids is that, because they are mostly subendocardial (238, 239), they are also exposed to the higher PCO_2 of the mixed venous blood in addition to the tensions prevailing in the arterial blood. Increased CO_2 tensions are known to depress the endings of the Lorenzinian ampulla (128), which is possibly a mechanoreceptor capable of responding to small changes in temperature (126, 127, 207, 231, 232, 233). High CO_2 tensions also depress cold receptors of the tongue (23). A similar difference between the ventricular pressure receptors of the two sides does not exist, most probably because these endings are located within the thick walls of the ventricles (250); this prevents the endings from being influenced by the high PCO_2 in the right ventricle. However, these suggestions need experimental verification.

Site and mode of action. It was pointed out earlier (254) that the excitatory effect of veratrum alkaloids could not be due merely to an increase in the generator potential, because in several endings the excitation was clearly dependent on the production of impulses by the natural stimulus (254). The alternative suggestion that the alkaloids act on the regenerative region must therefore be favoured. There is now considerable indirect evidence in support of this conclusion based on a comparison of the concentrations of the alkaloids required to produce effects on nerve fibres with the concentrations required for stimulating the endings. Thus, Straub showed that 10^{-6} g of veratridine per ml will depolarize medullated

nerve fibres and a concentration of 10^{-5} g/ml will reduce the resting membrane potential by as much as 47 mV (302). Even smaller concentrations, *e.g.*, 10^{-7} g/ml, increase the negative afterpotential of medullated nerve fibres (290, 302). It follows that if about 20 μg of veratridine are needed for stimulating pulmonary and cardiovascular endings [*e.g.*, ventricular pressure receptors (250, 254)], the concentration in the plasma in the circulation near the endings will be greater than 10^{-6} mg/ml and the concentration in the tissue fluid will, therefore, approach this strength. And since the diffusion barrier appears to be absent near the ending (Fig. 2), the concentration of veratridine will be more than adequate to act on the distal part of the nerve fibre, *i.e.*, the regenerative region. It is, therefore, only necessary to assume that the alkaloids act on the first node; this is depolarized and the generator potential produced by the existing or applied natural stimulus starts off the repetitive activity, which becomes self-perpetuating owing to the gradual increase in the negative afterpotential (1). And if the depolarization proceeds far enough total block will occur (254). Then, when the depolarization falls to a critical level, repetitive activity will start at a high frequency as noted, and it will also cease suddenly when it increases once again beyond the critical level (254). The smooth increase in frequency produced by a natural stimulus during excitation by the alkaloids is also explained because the part affected is the ending itself, *i.e.*, the first node where the regenerative activity is produced. It is also easy to understand the actions of increased calcium, or reduced calcium following injections of sodium citrate, and also of the local anaesthetics, from what is already known about the effects of these substances on nerve fibres following the influence of veratrum alkaloids on them (1, 97, 105, 106, 131, 180, 215, 284, 290, 304).

Finally, now that it is known that orthodromic or antidromic impulses depress the ending, the degree of depression depending on the frequency of the impulses (257), it is easy to understand that the ending will be desensitized because of depression of the ending produced by the impulses initiated at the first node. Their frequency following veratrum alkaloids is far in excess of that generated normally by the existing amplitude of the generator potential.

There is, therefore, no need at all to postulate that the veratrum alkaloids have any action on the generator region since all the effects produced by them are explained by their action on the regenerative region.

It should be mentioned here that the fact that the concentrations of the alkaloids required to stimulate sensory receptors are much smaller than those needed for stimulating the nerve fibres themselves *in vivo*, gives one the impression that the alkaloids act on a part of the ending that is different from the nerve fibre. This erroneous impression is due to the diffusion barrier around the main nerve trunks that prevents the alkaloids from gaining access to the nerve fibres inside the nerve sheath (46, 47, 86, 87, 183, 184, 185, 293, 294). When this barrier is overcome by perfusion techniques (183) or by desheathing the nerve, it is found that the concentration of the alkaloids required for stimulating the endings is the same as that required for obviously influencing the nerve fibres of the same endings (264).

E. Volatile anaesthetics

In low concentrations volatile anaesthetics produce a remarkable sensitization without stimulation of sensory endings with medullated fibres, *e.g.*, pulmonary stretch receptors (Fig. 2) (254, 315, 316), carotid baroreceptors (279), and possibly muscle stretch receptors (221). The responses of other visceral and somatic sensory endings to these anaesthetics have not been studied so far.

As shown by Whitteridge and Bülbring (316), the various volatile anaesthetics such as ethyl ether, trichlorethylene, chloroform, ethyl chloride, and divinyl ether have similar effects. The initial effect is a slight increase in sensitivity; this becomes greater with longer exposure, and finally, the sensitivity declines before the endings are blocked (316). On withdrawal of the anaesthetic the sensitivity of the endings gradually returns; it comes back to normal after going through a peak (316). Similar responses have been obtained after halothane and carbon tetrachloride (315). In no case is the ending stimulated (254, 316), nor is the threshold reduced (Fig. 2). Adaptation is unchanged initially but it increases when the sensitivity falls with longer exposure before the ending is paralyzed (254, 316). The increased sensitivity cannot be considered secondary to broncho-constriction because it is present in atropinized cats (254, 316). Nor can it

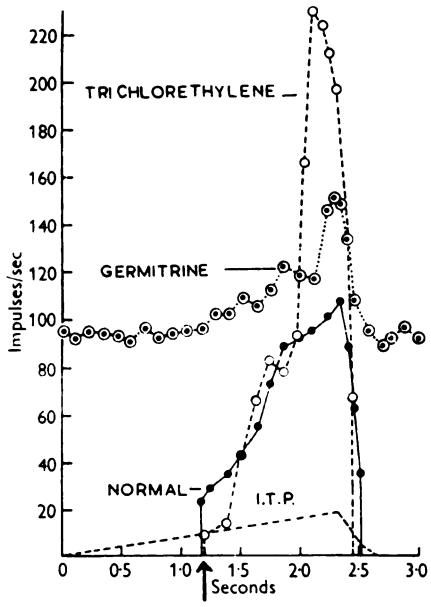

FIG. 2. Graphs showing contrasting effects of germitrine and trichlorethylene on a pulmonary stretch receptor of a cat.

Normal response of the receptor to artificial inflation of the lungs as indicated by the tracing of intratracheal pressure (i.t.p.) (●). Response 15 seconds after end of a period of administration of trichlorethylene showing the marked sensitization of the receptor (○). Response of the same receptor to inflation 3 minutes after injection of 26 μg germitrine, showing the marked stimulation and desensitization (⊙). Arrow indicates threshold of the ending; this is unchanged after both drugs. Chest was open (254).

be attributed to vascular changes because, as Whitteridge and Bülbring observed, there is either no change, or a slight *decrease* in the resistance of the lungs to inflation during the period of sensitization. It is known that marked congestion, enough to reduce the compliance of the lungs (136), produces only a small increase in the activity of pulmonary stretch receptors (42, 219).

Robertson *et al.* (279) have shown that the responses of the carotid and aortic baroreceptors are similar. The sensitization noted in intact preparations was also clearly demonstrated in experiments in which the carotid sinus was perfused; there can, therefore, be no doubt about the sensitization of the baroreceptors by the anaesthetics. This sensitization could last for as long as 15 minutes. Complete failure of the endings was noted after prolonged exposure to the anaesthetics as in the case of pulmonary stretch receptors. However, high concentrations produced rapid effects, *e.g.*, 4 % chloroform caused a reduction within 10 seconds and a similar effect by 3 to 4 % trichlorethylene was produced after 70 seconds of exposure (279). These phenomena resemble those observed by Liljestrand (200) and confirmed by Robertson *et al.* (279) who found only depression of the carotid baroreceptors following intracarotid injections of chloroform, most probably due to the relatively large concentrations of the anaesthetic injected.

The only information about the action of anaesthetics on muscle stretch receptors is the following extract from Matthews' paper (221): "In several preparations during induction of chloroform and other anaesthesia a rise of excitability was found indicated by a greater response to constant stretch." These observations were made on spinal or decerebrate cats. One can conclude that the endings were sensitized and not stimulated, because Matthews made the above remark in connection with the remarkable stimulation seen during occlusion of the circulation.

Two points deserve attention concerning the effects of the anaesthetic gases, cyclopropane and nitrous oxide (279, 315, 316). One is that, whereas even 50 % nitrous oxide or cyclopropane produces considerable sensitization of pulmonary stretch receptors, higher concentrations of these gases (even 100 % nitrous oxide) do not paralyze them (315, 316). The other point is that these gases have no effect, whatsoever, on baroreceptors (279). This will lead one to believe that there must be some specific difference between pulmonary stretch receptors and arterial baroreceptors, since it is known that the former, like the latter, are supplied by arterial blood (318) and both must, therefore, be exposed to the gases in the same way. However, in addition to the arterial channel, it has been found that, as in the case of deflation receptors (253), the volatile anaesthetics can gain access to some pulmonary stretch receptors directly through the airways as well. Proof of this has been obtained recently by the demonstration that sensitization and block of some of these endings occur on administration of ether after cardiac standstill and after the heart has been removed and the blood in the pulmonary veins drained out (Paintal, unpublished observations). This explains why the pulmonary stretch receptors are sensitized by the anaesthetic gases (315, 316) and the arterial baroreceptors are not (279).

Site and mode of action. Any explanation for the mode of action of volatile anaesthetics must take into account at least three factors: 1) sensitization, 2) absence of stimulation, and 3) unchanged threshold of the ending (Fig. 2).

In an earlier publication (254) it was suggested that the anaesthetics probably produce their effects by enhancing the recovery processes at the ending. An alternative but less favoured explanation suggested was that the amplitude of the generator potential produced by a certain natural stimulus may be increased after the anaesthetic (254). That this is very unlikely is shown by the unchanged threshold of the ending (Fig. 2); enhancement of the generator potential by a fixed stimulus should lead to a reduction in the threshold of the ending, which in turn would cause it to fire at a lower level of lung inflation. Recent observations by Lundy and Whitteridge (see Fig. 1 in 315) on the effects of cyclopropane also show that the threshold is not reduced at a time when the ending is greatly sensitized.

It follows that the anaesthetics must act on the regenerative region, and this is consistent with the mode of action of other drugs already discussed. It is unlikely that the anaesthetics act by lowering the threshold of the nerve fibre, although this is known to occur (17), because, as already pointed out, the threshold of the ending is not lowered at all (Fig. 2). Therefore the recovery at the first mode must be increased. This has been confirmed recently by Gill (102) who found that the antidromically conditioned stimulus-impulse latency (256) was clearly reduced after trichlorethylene, at a time when there was no change in the stimulus-impulse latency; the result shows in addition that the generator potential produced by the stimulus was unchanged by trichlorethylene (*cf.* 257).

Possibly, the initial enhancement of recovery is followed by depression till the ending is paralyzed, but it is also very likely that other changes in the first node occur simultaneously (*cf.* 122, 306) which contribute to the ending becoming totally unresponsive.

F. Miscellaneous substances

1. 5-Hydroxytryptamine. 5-Hydroxytryptamine (5-HT) does not stimulate or sensitize pulmonary stretch receptors, aortic baroreceptors, or right and left atrial receptors when it is injected intravenously in doses of 50 μg (230, 248). With doses of 50 to 100 μg/kg, however, Schneider and Yonkman (288, 289) observed a marked stimulation of pulmonary stretch receptors in cats and dogs, but in the rabbit there was no effect even in doses of 200 μg/kg. The excitatory effect takes a long time to begin (288). Because of this, and also because 100-μg doses produced equivocal effects (in fact, even depression of the discharge in some fibres), Kottegoda and Mott (177) concluded that the excitatory effect of 5-HT was secondary to bronchomotor changes. Neither bronchomotor changes nor increased transpulmonary pressure (*cf.* 52), however, can account for the pronounced stimulation, because histamine and acetylcholine, which are known to cause marked bronchoconstriction, produce only small changes in the discharge (318). It is, therefore, possible that in the large doses injected by Schneider and Yonkman (288, 289), 5-HT has an action similar to that of veratrum alkaloids

(*cf.* above). Fjällbrant and Iggo (88) have found that the only cutaneous receptor with medullated fibres that is affected by 5-HT is the slowly adapting pressure receptor. This is stimulated and sensitized initially. This action is followed by a period of depression, and, after this, the resting discharge is enhanced once again. The drug was injected close arterially in doses of 1 to 20 μg (88, 150).

There is some indirect evidence that 5-HT might stimulate carotid baroreceptors (103), but this needs confirmation by electrophysiological studies.

2. Histamine. Widdicombe (318) has shown that a 100- to 500-μg dose of histamine increases the resting discharge during expiration in some pulmonary stretch fibres, but reduces the peak frequency. During maintained inflation it causes a 60 to 80% increase in the impulse frequency. Since all these effects are accompanied by increase in bronchial tone, which can be quite marked in some experiments (318), it is difficult to state whether histamine has any direct effect on the endings.

Histamine is not known to excite atrial and ventricular receptors.

The only known cutaneous receptor with medullated fibre that is stimulated by histamine in doses of 6.6 to 66 μg injected close arterially is the slowly adapting pressure receptor (88). Fjällbrant and Iggo found that 10 μg were invariably effective, but the latency between injection and onset of stimulation was long (about 20 sec); maximal stimulation occurred within 1 to 3 minutes (88). The long latency is highly suggestive of indirect action on the ending, since cutaneous endings are known to be stimulated following much shorter latencies, *e.g.*, in 1 second by potassium chloride and certain drugs (24, 69). Brown and Gray (24) were apparently looking at these early effects when they concluded that even 1:1000 histamine had no effect on the endings.

It is noteworthy that in their single unit preparations, Fjällbrant and Iggo found that all the drugs tested, including acetylcholine, stimulated the endings after relatively long latencies, *e.g.*, 20 to 30 seconds, and none with shorter latencies of 1 to 2 seconds' duration. Fjällbrant and Iggo took care to point out the important fact that they injected the substances into the blood stream at a greater distance from the receptors; they believed that this procedure resulted in a more gradually rising concentration (88). This factor could account for minor differences in timing from what is already known about dispersion of substances in the circulation (176). In fact, the difference between the injection-response times of gastric stretch receptors following injections of drugs into the right atrium and into the aorta close to the endings is comparatively small (247).

While interpreting these results it is important to keep in mind the possibility of secondary action.

3. Bradykinin. In doses of 300 to 400 μg, impure bradykinin, injected close arterially, stimulates the slowly adapting pressure receptor of the skin (88), but again the latency is very long (20 sec) and indirect effects on the endings must, therefore, be ruled out.

4. Phenyldiguanide. Phenyldiguanide does not stimulate several mechanoreceptors of medullated fibres in doses adequate to excite the ending of non-medullated fibres (*cf.* below). Examples are pulmonary stretch receptors (56, 244, 248),

aortic baroreceptors, type A and type B atrial receptors (244), and stretch receptors of the muscles of the frog's toes (32). In view of the observations of Dawes *et al.* (55, 56), it can be assumed that other aromatic guanidines (*e.g.*, 2-α-naphthyl-ethylisothiourea) will also have no effect on these endings.

5. Hypertonic solutions. Hypertonic solutions (*e.g.*, 5% sodium chloride) have been used frequently for producing pain in different tissues (163, 167, 168, 169, 199) or for producing visceral effects (59) that may be partly reflex in origin, but no systematic studies of the effect of such solutions on the sensory endings themselves have been carried out. However, there exists a little information about the effects of such solutions on the endings and the nerve fibres of muscles. Injection of 5% sodium chloride solutions locally into a muscle gives rise to impulses in different kinds of large and small medullated nerve fibres (258), and also in non-medullated nerve fibres (152). While it is possible that the endings themselves, *e.g.*, pressure-pain receptors of group III nerve fibres, may be stimulated by such injections, it is equally possible that the nerve fibres themselves may be stimulated, since hypertonic solutions have profound effects on nerve fibres [*e.g.*, they reduce accommodation (281) and prolong the plateau of the spike (123) in addition to other effects (287, 291, 292)].

IV. ENDINGS WITH NON-MEDULLATED FIBRES

In their excellent reviews on endings of non-medullated nerve fibres Douglas and Ritchie (74) and Keele and Armstrong (169) have recently described the properties of non-medullated nerve fibres and the responses of their endings to natural stimuli and drugs. Further, the responses of cutaneous (72, 151, 167, 168, 169, 170, 220, 324, 335) and muscular endings (19, 152, 153) have been discussed. The following review will, therefore, be mostly concerned with the responses of visceral receptors to drugs. The Russian investigators have taken a keen interest in this field and although they have used drugs mostly for investigating visceral reflex effects, they have also provided general descriptions of the sensory discharges in multifibre preparations following the injections of drugs. For this information the reader should consult the highly informative monograph by Chernigovsky (38).

Visceral receptors. In view of the large number of non-medullated nerve fibres supplying the viscera (4, 49, 261) it would be expected that there should be a large variety of sensory endings. However, owing to the newness of this field, only the following types of sensory endings with non-medullated fibres have been identified so far.

a. Gastrointestinal receptors. Following recent histological (4, 49) and electrophysiological (148) evidence, it is now generally accepted (261) that the majority of vagal afferent fibres from the gastrointestinal tract are non-medullated. Possibly the same applies to the afferent fibres of sympathetic nerves (307). Currently the following types of gastrointestinal receptors are known: 1) gastric stretch receptors (247), synonymous with Iggo's tension receptors (145, 146); 2) intestinal distension-sensitive tension receptors (146); 3) gastric mucosal chemoreceptors (147); 4) gastric receptors not stimulated by distension (248); 5) disten-

sion-insensitive intestinal receptors, referred to as mucosal mechanoreceptors, whose functions are to signal the presence or movements of intestinal contents (255).

Recently (261), it has been shown satisfactorily that certain differences in conclusions advanced by Iggo (145) and myself (247) concerning the gastric stretch receptors are of a superficial nature and there is no doubt that the natural stimulus for these endings is the distension of the stomach that occurs when food or water enters the stomach (247). Once the distension has attained an adequate level, then, as shown by Iggo (145), gastric contractions do influence the activity of the endings. These points need consideration while interpreting the effects of drugs.

b. Pulmonary deflation receptors. Following recent measurements of conduction velocities, it now seems certain that most of these endings have non-medullated fibres, because the conduction velocities of most of their fibres are less than 2 to 3 m/sec, although there are clearly some fibres with conduction velocities between 2 and 6 m/sec (264). In agreement with earlier work (253), it has been confirmed that the endings must be located in a region where they can be reached through the pulmonary circulation, and also directly through the gas phase, as they are stimulated by volatile anaesthetics with latencies that are even shorter (264) than those already reported (253).

c. Ventricular receptors. Recently Sleight and Widdicombe (297) have described chemically evoked discharges from the epicardium and myocardium of the left ventricle. These endings could also be stimulated by certain mechanical procedures (*e.g.*, distension of the ventricle with a balloon) but not by asphyxia. The normal function of the endings has still to be determined.

A. Veratrum alkaloids

Veratrum alkaloids appear to have the same effect on endings of non-medullated fibres as they do on those of medullated fibres (section III D). The characteristic feature is a marked stimulation along with desensitization of the endings (254). The same missing of impulses and cyclical activity seen in endings of medullated fibres are also seen in gastric stretch receptors; asphyxia has no influence on the excitation by the alkaloids (254). It is noteworthy that the peak frequency of discharge at the height of stimulation never exceeds 70/sec; usually it is much less.

Other endings such as distension-sensitive intestinal receptors (13, 15, 16) and the unidentified ventricular receptors are also stimulated by the alkaloids (297).

In contrast, the deflation receptors are not stimulated by the alkaloids at all. Instead some depression follows their injection (253). While this is surprising, it is equally surprising that potassium chloride does not stimulate the endings either (253). This is perhaps the only exception to the rule that potassium chloride excites all sensory endings (69, 322) and nerve fibres, if given in adequate doses and in an appropriate manner (25). The effects of veratrum alkaloids are linked to potassium (*cf.* 180, 290). Thus Witzleb has found that the excitatory effects of veratrine are enhanced by potassium (322). In this connection it is worth keeping

in mind that the deflation receptors are unique in that they must be in equilibrium with mixed venous blood and not arterial blood, because they are accessible to drugs through the pulmonary circulation and not through the bronchial circulation, and they are stimulated by injections of drugs into the right atrium and pulmonary artery, but not by injections into the left ventricle (249, 253). These endings are, therefore, normally under the influence of a lower PO_2 and a higher PCO_2; this latter is known to have a stabilizing action on nerve membranes (188, 215, 228, 229) and a depressant effect on sensory endings (23, 128) other than the aortic and carotid chemoreceptors (132, 133). It is therefore possible that the negative response of the endings to veratrine and potassium chloride may have something to do with the fact that they are in equilibrium with mixed venous blood.

B. Phenyldiguanide

All varieties of gastrointestinal endings can be stimulated by phenyldiguanide in a consistent and remarkable manner. In fact, since it does no harm to the the animals in several repeated doses, it has been used as a reliable means for locating the endings of visceral afferent fibres (246). About 50 μg are adequate to produce an appreciable discharge of impulses if injected into the aorta (248); if injected intravenously, 80 μg yield a good response (146, 248), but 30 μg would probably be effective (248). Not all gastric stretch receptors, however, are stimulated by phenyldiguanide (248). The differences in the responses of the endings may be attributed to possible differences in the blood supply of different parts of the stomach, since the sensitivity of the endings to drugs is not related to the response of the endings to their natural stimulus, or to the location of the endings in particular parts of the stomach (248).

The latency between injection into the aorta and the onset of stimulation of gastric stretch receptors averages 1.5 seconds and the peak frequency attained varies from 20 to 40 impulses/sec (248). This is in keeping with the maximum frequency of discharge that can be aroused in these fibres (60 impulses/sec) (247). The evidence suggests that the excitatory action is a direct one on the endings (248). The endings are simultaneously sensitized to their natural stimulus.

The deflation receptors are stimulated and sensitized consistently by repeated intra-atrial injections of phenyldiguanide (249, 253). About 100 μg are adequate to stimulate the endings after an average latency of 1.7 seconds. This latency is approximately halved by increasing the concentration of the drug by 10 times, but then the stimulatory phase is followed by a period of depressed excitability, during which the response to a subsequent injection is either reduced or totally absent (253).

C. Miscellaneous drugs

Gastrointestinal receptors. 5-HT, nicotine, and lobeline produce responses in gastric stretch receptors similar to those produced by phenyldiguanide (248). Acetylcholine has not been tried, but it is possible that it may have similar effects. The quantities of 5-HT needed are about a fifth of those needed for excitation by phenyldiguanide. In the case of lobeline about 350 μg are necessary (248). Adren-

aline (20 to 50 μg) also stimulates gastric stretch receptors, the timing and pattern of the response being identical to those produced by phenyldiguanide, except that the duration of stimulation is sometimes considerably longer. Also, low frequency discharges persisting several minutes follow the initial marked stimulation (247, 248). Iggo (146) found that adrenaline could also stimulate the intestinal tension receptors (distension-sensitive).

The mucosal mechanoreceptors are also stimulated by 5-HT and nicotine (255). In addition, they are stimulated indirectly by a variety of substances introduced into the lumen (255). Possibly, this explains the observations of Sharma and Nasset (296). The intestinal receptors are also stimulated indirectly by acetylcholine (100).

Deflation receptors. Compared to phenyldiguanide, much smaller doses are required for stimulating the deflation endings by 5-HT, 6 μg/kg being adequate in some cases (249). The latency is similar to that following phenyldiguanide. The excitatory effect of 5-HT is not antagonized by Dibenzyline, which is known to antagonize the motor effects of 5-HT (94). Nicotine (175 μg) and urethane (225 mg) also stimulate and sensitize the endings in a similar manner. One important difference is that the latency between injection and stimulation is significantly less than that after phenyldiguanide, being about 1 second on the average. On the other hand, the latency after injection of acetylcholine is about 3 to 5 seconds (253). This is long, considering that it takes less than 1 second for the drugs to reach the pulmonary capillaries (251). Perhaps acetylcholine diffuses out more slowly than nicotine through the pulmonary capillaries. However, this cannot be the whole explanation, because the effects of acetylcholine are irreversibly abolished by 1 mg/kg atropine without affecting the responses of endings to other drugs such as nicotine, phenyldiguanide, urethane and volatile anaesthetics. This effect of atropine cannot, therefore, be attributed to its local anaesthetic actions (31). Some arguments favour the view that the excitatory effects of acetylcholine are not secondary to contraction of smooth muscle (253), and if this is true, then the curious block by atropine of the excitatory effects of acetylcholine without any alteration in the responses to nicotine needs to be explained.

Insufflation of the lungs with ether, trichlorethylene, or chloroform stimulates the endings with very short latencies; longer exposures paralyze the endings (253). Halothane has similar actions (264). The endings may be sensitized in addition to being stimulated, but so far, experiments to determine this specifically have not been done. The responses of the pulmonary stretch receptors, therefore, contrast with the responses of deflation receptors, because the former are not stimulated at all, in spite of considerable sensitization of the endings (Fig. 2).

Ventricular receptors. As shown by Sleight and Widdicombe (297), introduction of 50 μg nicotine into the pericardial sac apparently stimulated certain endings of the left ventricle. However, a direct action on the non-medullated nerve fibres themselves is not ruled out.

D. Site and mode of action

Three points must be kept in view when considering the mode of action of drugs on endings of non-medullated fibres. One is that the maximum frequency of dis-

charge that can be elicited by a drug in these endings is much lower than that produced in endings of medullated fibres. The other is that the endings of non-medullated fibres are excited by a variety of drugs that do not affect endings of medullated fibres in the same or even higher concentrations, *e.g.*, phenyldiguanide, 5-HT, and acetylcholine. Third, the diffusion barrier formed by the nerve sheath, and discussed already (section III, introduction), must be equally effective in the case of non-medullated fibres (Fig. 1).

It is well known that the maximum frequency of discharge in various endings of non-medullated fibres is very low. Thus, in the case of deflation receptors of the lungs, the usual peak frequency is of order of 10/sec (264), and the maximal that can be attained following phenyldiguanide is 60/sec (249, 253). The same is true of gastric stretch receptors and intestinal receptors (261) and of the various cutaneous mechanoreceptors with C fibres (74, 130, 149, 150, 151, 157, 324), apart from exceptional cases (151) [*cf.* discussion after Iggo's paper (150) in (324)]. In contrast the peak frequencies generated by endings of medullated fibres are of the order of 200 to 500 per second.

The absolute refractory period of non-medullated fibres lasts only 2 msec (118). Grundfest and Gasser (118) found that in the hypogastric nerve *in situ*, the excitability of the non-medullated fibres returns to normal at 14 msec. This is followed by a period of supernormality with a maximum at 25 msec which gives way to subnormality at 60 msec. Subnormality is maximal at 150 msec and it lasts over 600 msec (118). The corresponding figures for medullated fibres are: relative refractory period, 3 msec, supernormality between 3 and 15 msec with a maximum at 7 msec, subnormality between 15 and 70 msec with a maximum of 3% at 30 msec (97). According to Gasser and Grundfest (97), the periods of super- and subnormality correspond to the respective negative and positive afterpotentials.

The above differences between the return of excitability after a previous impulse in medullated and non-medullated fibres serve to show that the maximum frequency of discharge that can be generated in endings of non-medullated fibres is relatively low, probably because the recovery of excitability of the regenerative region is relatively slow. There is, therefore, no need to assume that the generator processes at endings of non-medullated fibres differ in any significant way from those taking place in endings of medullated fibres. What then is the reason for the greater susceptibility of endings of non-medullated fibres to various chemicals?

If it is assumed that the generator process is the same at the endings of both types of fibres, then it follows that the differences in the response to drugs must be due to differences in the properties of the regenerative region. This then boils down to the differences in the responses of medullated and non-medullated fibres themselves to certain drugs, *e.g.*, phenyldiguanide and acetylcholine. There is no information at all on the effects of phenyldiguanide on nerve fibres, but about acetylcholine there is now a good deal of information (*cf.* 74).

Whereas the evidence on the excitatory effects of acetylcholine on medullated nerve fibres is equivocal (25, 61, 162), that on non-medullated nerve fibres seems to be clear-cut. Armett and Ritchie found that application of acetylcholine in concentrations of about 10^{-4} (w/v) causes the resting potential of non-medullated

fibres to fall (7, 9); this leads to a fall in the amplitude of the spike, with slowing of the conduction velocity of the fibres. Concentrations of 10^{-3} block conduction in the fibres (7). These effects on the nerve fibres can also be produced by carbachol, nicotine, and tetramethylammonium, but very little or not at all by acetyl-β-methylcholine, bethanechol, pilocarpine, or arecoline (8). Armett and Ritchie (8) also found that hexamethonium and tubocurarine abolished the effects of acetylcholine, but these did not affect the conduction of electrically produced impulses (8).

The above characteristics of nerve fibres are similar to the responses of certain cutaneous endings of non-medullated fibres to acetylcholine (73) studied by the occlusion technique of Douglas and Ritchie (70, 72). In these experiments Douglas and Ritchie (73) found that the endings of non-medullated fibres could be stimulated by small doses of acetylcholine injected close arterially. This response was unaffected by atropine, but could be prevented by hexamethonium. As expected, the responses to natural stimuli were unaffected after hexamethonium. In view of the fact that these excitatory effects of acetylcholine are not secondary to other mechanical effects, *e.g.*, contraction of smooth muscle, Douglas and Ritchie (73) concluded that acetylcholine acted directly on the endings of non-medullated nerve fibres. These results could not be totally confirmed by Fjällbrant and Iggo (88), who studied the effect of acetylcholine on unitary discharges and who found that only one of the 4 units tested by them was excited by 30 μg acetylcholine. As pointed out by Douglas and Ritchie (74), the method of unitary analysis has certain limitations which are well known.

In view of the results of Douglas and Ritchie on vagal and cutaneous endings on the one hand (71, 73) and those of Armett and Ritchie on the other (7, 8), it is now easy to explain the excitatory effects of acetylcholine, phenyldiguanide, 5-hydroxytryptamine, and nicotine on the endings on non-medullated fibres by merely assuming that these drugs depolarize the regenerative region of the ending, and the existing generator potential, initially below critical firing level, now sets off the train of impulses. As in the case of endings of medullated fibres, there is no need to assume any action of the drugs on the generator region at a concentration that is adequate to stimulate and sensitize the endings. Surely, with higher concentrations, the generator region might well be affected as well, as shown by the effects of procaine on the Pacinian corpuscle and the muscle spindle (section III A).

This explanation is opposed to that of Armett and Ritchie (7) and Douglas and Ritchie (73), who suggested that acetylcholine acts on the generator region. Their conclusion is linked with the fact that, whereas acetylcholine injected into the circulation can produce visible effects on the non-medullated nerve fibres, yet it does not generate any impulses by itself (7). This is not surprising. After all, why should it, if there is no added stimulus, *e.g.*, something to take the place of the generator potential such as injury (2) or a constant or slowly rising current (18, 108)? It would be expected that a train of impulses would be aroused if a constant current normally subthreshold for the fibre were passed while acetylcholine was being injected.

V. CONCLUSIONS

By using the results of experiments *in vitro* on the effects of procaine on sensory endings for interpreting the effects of procaine *in vivo*, it has become clear that there is practically no diffusion barrier in the terminal parts of sensory nerve fibres. Nature has thereby exposed the regenerative region of the sensory ending to the influence of substances circulating in the blood stream. The generator region is probably equally exposed but is apparently more resistant to the effects of drugs. The central parts of the sensory fibres are not easily exposed to the drugs because of the protection afforded by the nerve sheath, which is known to act as a strong diffusion barrier. This barrier can be overcome (equilibrium approached) by infusion of drugs.

The effects of all intravenously injected drugs on sensory endings can be explained by their effects on the regenerative region, which has practically the same properties as the rest of the nerve fibre. Since non-medullated fibres are more susceptible to drugs than medullated fibres, it follows that the regenerative regions of the endings of non-medullated fibres must be more susceptible to drugs. This explains why the endings of non-medullated fibres are more readily stimulated by a variety of substances that leave the endings of medullated fibres unaffected.

The effects of local anaesthetics have revealed that only in higher doses, or after longer action, do such drugs act on the generator region, but when this occurs, the regenerative region is already totally blocked. It may be assumed that the same applies to other drugs.

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